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Semi-quantitative SPECT scanning in acute ischaemic stroke

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ABSTRACT. We performed semi-quantitative SPECT scans using ^{99m}Tcm-HMPAO on 34 elderly subjects 10–15 days after ischaemic stroke. Each cerebral hemisphere was divided into five regions of interest. Asymmetry scores were determined for ten slices in each region using activity ratios to the other hemisphere and to the ipsilateral cerebellum. Outcome was assessed by maximal Barthel ADL score during the first two months after stroke. Asymmetry scores in the hemisphere involved by the stroke event were much higher than those in the opposite hemisphere. Subjects with poor outcome (maximal Barthel 0–12) had significantly higher asymmetry scores than those with good outcome (Barthel 13–20). The total asymmetry score (both hemispheres) and the score of the involved hemisphere predicted Barthel ADL score in a general linear model. Total asymmetry score remained a significant predictor of maximal Barthel score in multivariate models. Thus semi-quantitative SPECT scanning is of value in predicting functional recovery after stroke.

Key words: cerebral ischaemia, cerebrovascular disorders, tomography emission computed.

Stroke is the third leading cause of death in New Zealand. Among survivors stroke is a major cause of disability, leading to institutionalisation in up to 30%. Although stroke rehabilitation units hasten functional recovery after stroke, 23% of stroke survivors aged 60 or over from Waikato Hospital remain so severely dependent that they require long-term geriatric hospital care.

There have been many previous studies of predictors of functional outcome after stroke. Most have examined only clinical variables such as motor loss, age and homonymous hemianopia (16–19). Others have examined lesion volume on CT scan (1, 3, 11) or SPECT scan (2, 11) as predictors of stroke outcome without adjustment for the effects of clinical variables as predictors. Few studies of lesion volume on CT scan have used multivariate modelling to assess the relative contributions of clinical variables and scan findings in predicting functional outcome (9). No such studies exist for SPECT scanning.

Most studies of semi-quantitative SPECT scanning have used the hemisphere opposite to the stroke lesion as the reference standard, calculating an activity ratio of affected to non-affected hemisphere or region within the hemisphere (2). Unfortunately flow to the contralateral hemisphere is often reduced following stroke (14). Others have suggested that the ipsilateral cerebellum is a superior reference standard for two reasons. First, prior stroke is less likely in the cerebellum than in the opposite cerebral hemisphere. Second, following cerebral infarction blood flow to the contralateral cerebellar hemisphere is reduced more than that to the ipsilateral cerebellum (12). Accordingly we decided to compare regions in the affected hemisphere to both the opposite cerebral hemisphere and to the ipsilateral cerebellum.

We tested three hypotheses in this study:

1. The cerebral hemisphere involved by the stroke event would have significantly higher asymmetry scores than the opposite hemisphere.
2. Asymmetry scores based on cortical/cerebellar ratios would be more closely related to current functional state and functional outcome than scores based on cortical/cortical ratios (left/right).
3. Asymmetry in the involved cerebral hemisphere would be associated with poor functional outcome after stroke whereas asymmetry in the opposite hemisphere would not be related to functional outcome.

MATERIALS AND METHODS

Inclusion criteria for this study were:

1. Age 60 or above
2. Admitted to Waikato Hospital with acute hemiplegia or

bilateral limb weakness due to non-lacunar hemispheric stroke (cerebral infarction or intracerebral haematoma)

Exclusion criteria were:

1. Previous hemispheric stroke
2. Lacunar stroke syndrome, bilateral cortical stroke or cerebellar stroke
3. Not ambulatory prior to stroke
4. Moderate or severe dependency prior to stroke (Barthel score $\leqslant 15$)
5. Lower extremity amputation prior to stroke
6. Other illness precluding rehabilitation
7. SPECT scan not performed between days 10 and 15 or technically inadequate

Semi-quantitative SPECT using HM-PAO were performed 10–15 days post-stroke. HM-PAO kits were reconstituted with 740 MBq of pertechnetate which was eluted less than 2 hours previously from an Amersham generator which had been eluted within 24 hours. Staff explained the procedure to each subject to allay any possible anxiety. Following intravenous injection of HM-PAO within 5–10 minutes of reconstitution imaging was performed using 6° (64-step) 360° acquisition. All patients were imaged in the same anatomical position with their eyes open. Room lighting was moderate and the noise level was low. None of the patients were agitated or required sedation. Imaging commenced 10–30 minutes post-injection. Scan time was approximately 32 minutes. Nuclear Diagnostics SPECTS Tomographic Reconstruction Software was used with a PDP/73 TSX+ operating system.

Each cerebral hemisphere was divided into five regions of interest as shown in Fig. 1: frontal, fronto-parietal, parietal, posterior parietal and occipital. Regions of interest were zoomed to fit the image and were of similar but not identical size. Regions of interest contained primarily cerebral cortex. Semi-quantitative analysis involved linearization and comparison of activity ratios in five regions of interest in the affected cerebral hemisphere to that of the ipsilateral cerebellum and the contralateral cerebral hemisphere (10, 20). Images from 10 consecutive transaxial reconstructions were analyzed using the defined regions of interest bilaterally. Counts from each of these regions of interest were averaged prior to calculating ratios compared to the ipsilateral cerebellum and opposite cerebral hemisphere. For comparison to the opposite cerebral counts were normalized according to the size of each region. Each reconstructed section had a thickness of 6.4 mm.

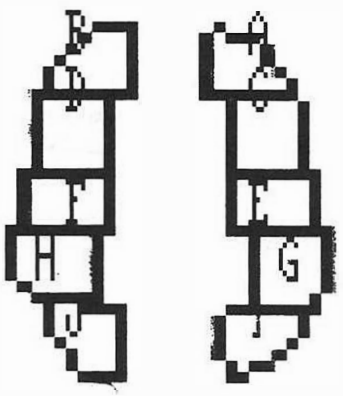

Fig. 1. The five cortical regions of interest: Frontal (A and B), fronto-parietal (C and D), parietal (E and F), posterior parietal (G and H) and occipital (I and J).

A cortical asymmetry ratio was calculated for each of the 50 areas by dividing the activity in the left hemisphere area by that of the corresponding right hemisphere. Ratios between 0.85 and 1.15 were defined as normal; ratios below 0.85 were scored as left-sided asymmetry whereas ratios above 1.15 were scored as right-sided asymmetry. These norms were adapted from a study of 17 normal subjects by Giubelei et al. (6) who found that 12% asymmetry represented the normal range (two standard deviations above or below the mean). Thus for the 10 slices involving each region the number of abnormal scores could range from 0 to 10; some of the abnormal scores could indicate left-sided asymmetry whereas others might indicate right-sided asymmetry. Adding all 50 scores for each hemisphere yielded a left hemisphere score (0–50), a right hemisphere score (0–50) and a total cortical score (0–50) reflecting asymmetry in either hemisphere.

Each cerebellar hemisphere was counted as an additional region and ratios were obtained comparing each area in the cortex with the ipsilateral cerebellar hemisphere. These ratios were not normalized for the size of the regions. We defined cortex/cerebellar ratios above 0.55 as normal based on a study of seven normal subjects (8) and results from ten pilot scans.

SPECT scans using ^{99m}Tcm-HMPAO were read conventionally and subsequently compared to simultaneous non-contrast CT brain scans.

The following scores were obtained:

1. Total cortical score: the sum of all abnormal cortical ratio scores (range 0–50).
2. Ipsilateral cortical score: the sum of all abnormal scores in the hemisphere related to the current stroke event (range 0–50).
3. Contralateral cortical score: the sum of all abnormal scores in the hemisphere opposite to the current stroke event (range 0–50). This can represent either luxury perfusion in the involved hemisphere or a prior ischaemic event in the opposite hemisphere.
4. Total cortex/cerebellar score: the sum of all abnormal scores for cortex/cerebellar ratios (range 0–50).
5. Ipsilateral cortex/cerebellar score: the sum of all abnormal scores for the cerebral hemisphere involved in the current stroke event (range 0–50).
6. Contralateral cortex/cerebellar score: the sum of all abnormal scores for the cerebral hemisphere contralateral to the current stroke event (range 0–50).

Arm and leg power on the affected side were measured on the MRC scale (0–5). Homonymous hemianopia was assessed by confrontation field testing. Mini-Mental State Examination score was obtained as soon as the patient was able to perform the test (5).

The modified Barthel ADL score was the principal indicator of functional outcome (19). Barthel scores range from 0 (totally dependent and doubly incontinent) to 20 (independent self-care activities). Barthel scores were measured at days 7, 30 and 60 post-stroke and at hospital discharge. Pre-stroke Barthel score was determined from reports by family or friends. The day 7 score was used as the measure of functional state at the time of SPECT scanning. The highest Barthel score during the two months after stroke was recorded as maximum Barthel score; this served as a time-independent index of functional outcome.

Table I. *Asymmetry scores according to cortical/cortical ratios and cortical cerebellar ratios*

Scores in one hemisphere can range from 0 (no asymmetry) to 50 (all regions asymmetric). Total score for both hemispheres scores can range from 0 to 50.

Region	Cortical/cortical	Cortical/cerebellar
Both hemispheres	15.7±11.5	17.4±15.7
Involved hemisphere	10.5±11.6	13.2±12.5
Opposite hemisphere	5.2±6.7	4.2±5.4

The SAS Statistical Package, version 6.04, was used for all data analysis. Exploratory data analysis began with the SAS PROC NORMAL UNIVARIATE procedure, which demonstrated that none of the variables were normally distributed. Hence, non-parametric statistical tests were used for further analyses. These procedures included Spearman rank correlations and the Wilcoxon rank sum test. General linear models were created using PROC GLM. P values were taken from the type III sum of squares.

RESULTS

Thirty-four subjects, 16 men and 18 women, were evaluated. All 34 subjects had ischaemic stroke; none had intracerebral haematoma on CT scan. Their mean age was 75.5 years. Prior to the current stroke 31 subjects lived at home and three lived in rest homes. Their mean Barthel ADL score prior to stroke (19.8 out of a possible 20, range 18–20) indicated that subjects could perform self-care activities prior to stroke.

SPECT scanning was performed on average 12.4 days after stroke. Asymmetry scores are shown in Table I. The hemisphere affected by the stroke event accounted for 67% of the total cortical asymmetry score and 76% of the total cortical/cerebellar asymmetry score. The cortical/cerebellar asymmetry score for the involved hemisphere was significantly higher than that of the opposite hemisphere ($p=0.0001$); for cortical asymmetry scores this difference did not reach statistical significance ($p=0.065$).

Asymmetry scores derived from cortical/cortical ratios were higher than those derived from cortical/cerebellar ratios in four out of five regions of interest (Table II). In the frontal regions, however, scores based on cortical/cerebellar ratios were higher. Sections low in the frontal regions often included significant amounts of bone, leading to lower counts than other regions; comparison to the cerebellum, which has greater blood flow than the cerebral hemisphere, may have created artefactually high cortical/cerebellar asymmetry scores in the frontal regions. The mean of the ten correlation coefficients between cortical/cortical and cortical/cerebellar scores was 0.35; five of the ten were significant at the $p<0.05$ level. The weakest correlations were seen in the posterior parietal regions; the strongest were seen in the parietal regions (Table II).

Six subjects had major postischaemic hyperaemia on SPECT scanning. In every case this was accompanied by a zone of subtle increased attenuation at the margins of the infarct on the unenhanced CT scan. Hyperaemia leads to "ischaemia" on cortical/cortical ratios in the region opposite to the true ischaemic injury.

Table III shows the Spearman rank correlations between different variables. Total cortical score was

Table II. *Cortical/cortical and cortical/cerebellar asymmetry scores according to region of interest*

Cortical/cortical scores were higher than corresponding cortical/cerebellar scores except in the frontal regions. Correlations represent Spearman rank correlations between cortical/cortical and cortical/cerebellar scores. *p*-values denote the significance of these correlations.

Region	Side	Cortical/Cortical	Cortical/Cerebellar	Correlation	*p*
Frontal	Right	1.38	3.56	0.25	NS
	Left	1.09	4.12	0.40	0.019
Fronto-parietal	Right	1.82	0.62	0.45	0.0084
	Left	1.15	0.47	0.25	NS
Parietal	Right	1.71	0.50	0.55	0.0007
	Left	1.94	1.29	0.44	0.0086
Posterior parietal	Right	1.97	1.91	0.08	NS
	Left	1.76	2.97	0.26	NS
Occipital	Right	1.65	0.56	0.30	NS
	Left	1.85	1.67	0.49	0.003

Table III. *Spearman rank correlation matrix: 34 subjects*
Bold correlations are significant ($p < 0.05$).

Variable	1	2	3	4	5	6	7	8	9
1. Total cortical score	—								
2. Cortical score of involved hemisphere	**0.73**	—							
3. Cortical score of opposite hemisphere	0.32	−0.26	—						
4. Total cortex/cerebellar score	0.17	**0.39**	−0.27	—					
5. Cortex/cerebellar score of involved hemisphere	0.28	**0.49**	−0.21	**0.96**	—				
6. Cortex/cerebellar score of opposite hemisphere	−0.29	−0.19	−0.18	**0.58**	**0.37**	—			
7. Age	−0.09	0.05	−0.02	**0.35**	**0.34**	0.22	—		
8. Arm power	−0.26	−0.22	−0.06	0.21	0.19	0.28	**0.38**	—	
9. Leg power	−0.32	**−0.39**	0.07	−0.07	−0.13	0.15	0.10	**0.72**	—
10. Day 7 Barthel ADL	**−0.50**	**−0.66**	0.14	**−0.42**	**−0.51**	0.10	−0.34	**0.38**	**0.57**

significantly correlated with cortical score for the involved hemisphere, the major component of total cortical score, and Barthel ADL score at day 7. Cortical score for the involved hemisphere was more closely related to clinical variables than was total cortical score; it was significantly correlated with leg power and Barthel ADL score at day 7. Cortical score for the opposite hemisphere was not correlated with any of the variables in Table III.

Total cortex/cerebellar score was correlated with scores for the involved and uninvolved hemispheres, age and Barthel ADL at day 7. Cortex/cerebellar score for the involved hemisphere was correlated with that of the opposite hemisphere, age and Barthel ADL score at day 7 (Table III).

We divided subjects into two groups according to functional recovery. Poor outcome was defined as maximal Barthel score 0–12 during the first two months after stroke; good outcome as a score of 13–20. The group with poor outcome was on average 5 years older than those with good outcome (p = NS, Table IV). They had significantly lower leg power scores and a higher prevalence of homonymous hemianopia.

Total cortical score and score for the involved hemisphere were significantly lower in the group with poor outcome versus those with good outcome (Table IV). Likewise total cortex/cerebellar score and score for the involved hemisphere were also significantly lower in those with poor outcome. Cortical or cortex/cerebellar scores for the opposite hemisphere were not significantly different in the two groups.

Using a general linear model we sought predictors of maximal Barthel ADL. The strongest predictor was Barthel score at day 7 followed by total cortical score, cortical score for the involved hemisphere, age, leg power, homonymous hemianopia and cortex/cerebellar score for the involved hemisphere (Table V). Using

Table IV. *Comparison of the 24 subjects with good outcome (maximum Barthel ADL score 13–20) with the 10 subjects with poor outcome (maximum Barthel ADL 0–12)*

	Poor outcome	Good outcome	p
n (% Male)	10 (60%)	24 (42%)	NS
Age	79.1 ± 7.2	73.9 ± 8.0	NS
Pre-stroke Barthel ADL	19.6 ± 0.8	19.9 ± 0.4	NS
Prior residence in rest home	1/10 (10%)	2/24 (8%)	NS
Arm power	0.70 ± 1.49	1.73 ± 1.90	NS
Leg power	1.00 ± 1.63	2.87 ± 1.75	0.009
Homonymous hemianopia	6/10 (60%)	4/23 (17%)	0.014
Mini-Mental State Score	17.4 ± 9.6	20.8 ± 5.8	NS
Total cortical score	25.7 ± 11.3	11.5 ± 8.9	0.0033
Cortical score of involved hemisphere	19.9 ± 14.8	6.6 ± 7.2	0.0064
Cortical score of opposite hemisphere	5.8 ± 6.5	4.9 ± 6.9	NS
Total cortical/cerebellar score	26.0 ± 18.9	13.8 ± 13.1	0.043
Cortical/cerebellar score of involved hemisphere	21.7 ± 14.4	9.7 ± 9.9	0.015
Cortical/cerebellar score of opposite hemisphere	4.3 ± 6.8	4.1 ± 4.8	NS

Table V. *Predictors of maximum Barthel ADL score among 34 subjects ranked according to F values from a general linear model*

All predictors had one degree of freedom.

Variable	F	*p*
Barthel ADL score at day 7	41.2	0.0001
Total cortical score	10.5	0.0028
Cortical score of involved hemisphere	8.8	0.0057
Age	7.7	0.0090
Leg power	7.2	0.011
Homonymous hemianopia	6.0	0.020
Cortical/cerebellar score of involved hemisphere	4.8	0.036

these significant predictors we created multivariate general linear models of maximum Barthel score. Because total cortical score was highly correlated with cortical score for the involved hemisphere (Spearman $r=0.73$), these two variables could not be included in the same model. Total cortical score was used because it was a stronger predictor of maximal Barthel ADL score. One successful multivariate model included Barthel ADL at day 7 ($p=0.0025$), age ($p=0.0097$) and total cortical score ($p=0.023$). The use of Barthel ADL score at day 7 to predict maximum Barthel score during the first two months after stroke may be questioned on the grounds that the score at day 7 could represent the maximal value. Among multivariate models excluding Barthel ADL at day 7, the most successful model included age ($p=0.0001$) and total cortical score ($p=0.001$).

DISCUSSION

In this study of 34 elderly subjects with acute ischaemic stroke, semi-quantitative SPECT scanning showed that approximately 70% of asymmetric areas were in the hemisphere involved in the current stroke event, as assessed by clinical signs such as hemiplegia.

Current functional state and functional outcome following stroke were significantly correlated with total asymmetry scores (both hemispheres) and asymmetry scores of the involved hemisphere. Asymmetry scores from the cerebral hemisphere opposite to the current stroke event were not correlated with current functional state, functional outcome or any clinical parameters measured. This supports the experimental hypothesis that ischaemia in the hemisphere affected by stroke is related to current stroke deficit and functional outcome whereas ischaemia in the opposite hemisphere is not.

Cortical/cerebellar asymmetry scores were less strongly correlated with current functional state and functional outcome than were cortical/cortical scores. Rank correlations between these two sets of scores by region of interest were modest. Although cortical/cortical scores of the involved hemisphere were significantly correlated with cortical/cerebellar scores for the involved hemisphere, total scores were not significantly correlated. Cortical/cortical scores exceeded cortical/cerebellar scores in four of the five regions of interest whereas in the frontal regions cortical/cerebellar scores were higher. This may be explained by two factors. First, the frontal region of interest was the smallest of the five regions. Cortical ratios were normalized by area of each region of interest cortical/cerebellar ratios were not. This may have created artefactual ischaemia in the frontal regions according to cortical/cerebellar ratios. Second, due to constraints of reconstruction angle in the SPECT software used, lower sections through the frontal regions contained significant amounts of bone. When activity ratios through these sections were compared to those of the contralateral cortex the presence of bone on both sides would not alter left/right ratios greatly. In contrast the comparison of low frontal cortex sections with bone to cerebellar sections free of bone would yield "ischaemic" cortical/cerebellar ratios.

Our choice of 0.55 as the cutoff for cortical/cerebellar ratios was based on a study of seven normal subjects (8) using ^{123}IMP SPECT and the results of ten pilot scans; these norms may be inappropriate for ^{99m}Tcm-HMPAO SPECT. Perhaps a better cutoff would have yielded scores more predictive of current functional state and functional recovery. In any event study results do not support the experimental hypoth-

esis that asymmetry scores based on cortical/cerebellar ratios would be more related to functional state and functional outcome than scores based on cortical/cortical ratios.

In multivariate models containing other powerful predictors of functional outcome such as Barthel score at day 7 and age, total cortical asymmetry score remained a significant predictor of functional outcome. Hence total cortical asymmetry score was an independent predictor of outcome.

Eighteen per cent of our subjects had major postischaemic hyperaemia on SPECT scanning. Such hyperaemia confounds semi-quantitative scan analysis by creating false "ischaemia" in the opposite cortex on left/right cortical ratios.

Left/right cortical ratios were derived from primarily cortical regions of interest. Analysis based on such ratios may miss important subcortical ischaemia.

Bushell et al. (2) studied 14 subjects with first-ever stroke 4–30 days post-stroke using ^{123}IMP SPECT. Five of seven subjects with good recovery had ischaemia involving less than 10% of the affected hemisphere whereas five of six with poor recovery had ischaemia involving greater than 25% of the affected hemisphere. In our study the average subject with good and poor outcomes had ischaemia involving 13% and 40% of the affected hemisphere respectively. Direct comparison to Bushell and coworkers' study is not possible because we measured ischaemia in a different manner.

Raynaud et al. (15) studied 17 subjects with ^{123}IMP SPECT more than 90 days post-stroke. Lesion volume predicted current functional status.

Lee et al. (11) performed CT and ^{123}IMP SPECT scans in 16 subjects within seven days of stroke. Lesion volume on CT but not SPECT was related to outcome assessed subjectively by a physician. Subjects with severe initial deficits from stroke had higher lesion volumes on CT and SPECT than those with less severe deficits.

Mountz et al. (13) used the ratio of lesion volume on HM-PAO SPECT divided by lesion volume on CT to predict functional outcome one year after stroke. Subjects whose ratios were close to 1.0 had the least recovery. The higher the ratio the greater the recovery. However, only 6 of 27 subjects were scanned within one month of stroke. Hence much of their recovery would have occurred before they were scanned.

Hayman et al. (7) performed ^{123}IMP SPECT scans and CT scans on day 0–5 and again on day 5–17 post-stroke. Lesion size on SPECT and CT scans were graded rather than measured. Reduction in lesion size from the first to the second scan did not predict clinical improvement.

Giubilei et al. (6) performed HM-PAO SPECT scans on 32 subjects within 6 hours of ischaemic stroke and again at days 7 and 30. They calculated an asymmetry index as the activity ratio in one of three regions of interest compared to the contralateral region. Ratios of 40% or greater were classified as severe ischaemia. Of 12 subjects with severe ischaemia in one region on admission scan, 92% had poor functional outcome at 30 days compared to 45% of the 20 subjects with mild ischaemia. Asymmetry ratios improved significantly between day 0 and day 7 irrespective of whether clinical improvement occurred. The authors suggested that early SPECT scanning, prior to onset of luxury perfusion, is superior to later scanning (day 7) in predicting stroke outcome.

From reviewing these articles one cannot draw firm conclusions about the timing for SPECT scanning after stroke. Postischaemic hyperaemia, seen in nearly one out of five of our subjects, complicates interpretation of scan results. Ideally scanning should be performed before this is likely to develop (i.e. within 48 hours of stroke onset).

The preferred method for semi-quantitative analysis of SPECT scanning is unknown. The five regions of interest we selected in each cerebral hemisphere were largely cortical. Hence we may have missed important subcortical ischaemia. We are currently repeating this study using a sixth region of interest to detect and measure subcortical ischaemia. Our method for obtaining cortical/cerebellar ratios was unsatisfactory.

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