THE USE OF TECHNETIUM 99m HEXA-METHYL PROPYLENE AMINE OXIME SPECT SCANNING IN ACUTE STROKE MANAGEMENT

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A short report submitted to the Faculty of Medicine, University of the Witwatersrand in partial fulfillment of the requirements for the degree of Master of Medicine in Nuclear Medicine

Johannesburg 1991

DECLARATION

I declare that this dissertation is my own work. It has not been previously submitted for any degree or examination in any other University.

The research protocol was approved by the Human Ethics Research Committee, University of the Witwatersrand with a clearance number of 7/8/86.

Ruth Winterton

15th August 1991

ACKNOWLEDGEMENTS

My gr· eful thanks are extended to Professor J Esser for his supervision of this study, to the Department of Neurology and the staff of the Nuclear Medicine Department, without whom this study would not have been possible.

Special thanks to Dr R Hassoun and UCB for their invaluable assistance.

DEDICATION

To my husband and children for their wonderful support

SUMMARY

19 patients were selected, from the patients screened, for investigation within 48 hours of the onset of an ischaemic cerebrovascular accident. Clinical neurological scoring, computerized tomography (CT) scans and single photon emission computed tomography (SPECT) scans were performed on day 1, day 10 and day 30.

SPECT scan data was analysed by 5 semi-quantitative methods, and findings were compared with neurological clinical scores on each respective day.

It was found that day 1 SPECT scans are of value for early localization of the acute ischaemic infarction.

A multiple regression model was developed using both the day 30 Defect Volume index and segmental analysis score which related to the day 30 clinical scores. The day 1 model was unsatisfactory and no such model was found relating day 10 SPECT semi-quantitative methods to day 10 clinical scoring. Changes in semi-quantitative scores from day 1 to day 30 did not correlate with clinical changes. Longer follow up may be required for there to be value in performing SPECT scans in stroke trials.

A prognostic equation was derived by multiple regression analysis of day 1 SPECT scan scores and day 30 clinical scores.

CONTENTS

CHAPTER 1

INTRODUCTION

INTRODUCTION

"Stroke" is a term used to describe any sudden paralysis resulting from a vascular disturbance in the brain due, most commonly, to thrombosis, embolism or haemorrhage (1, 2).

The importance of stroke and it's complications is demonstrated by the fact that it is the third highest cause of death (in adults) in North America and causes even more physical disability which is expensive for both the state and the individual (3, 4, 5). Rehabilitation of stroke patients can be highly labour intensive and so resources should be applied to those most likely to derive maximum benefit from such therapy (6).

Early localization and definition of stroke pathology is advised because of the value of various therapeutic measures, such as anticoagulant therapy in progressing stroke, surgical intervention with endarterectomy and extracranial-intracranial bypass surgery (4, 7, 8, 9, 10). Based on the timing of maximum cerebral oedema (i.e. 2 to 4 days post-ictus) medical therapy aimed at minimizing the amount of infarction should be started within 24 to 48 hours of the ischaemic event (11).

Computerized axial tomography (CT scan) and magnetic resonance imaging (MRI) both play an important role in the diagnosis of cerebrovascular disease (12, 13), but functional studies should be considered so as to better understand the pathophysiologic basis of stroke evolution. CT scans may often be negative in the first 24 to 48 hours after the acute onset of cerebral infarction (14, 15, 16, 17), whereas single photon emission tomography (SPECT) with cerebral perfusion agents and MRI are usually positive at this time (14, 18, 19, 20).

Interventional treatment could be more fully evaluated following functional studies, while cerebral perfusion imaging may also have a place in determining the therapeutic value of such treatment, particularly in regard to objective clinical stroke trials (8, 21).

Essential to the management of acute stroke is the knowledge of whether the involved brain tissue is reversibly or irreversibly damaged (12, 22). Early restoration of blood flow in acute stroke patients may improve recovery, especially in the ischaemic penumbra (peri-infarct area) (23, 24). Any interventional therapeutic study in acute brain infarction is based on the assumption that the ischaemic insult is reversible in some of the affected neurons.

Physiological patterns that characterise viable tissue may be identified by correlating acute changes in cerebral blood flow and metabolism with the clinical course of the patient. Therapeutic measures that alter impaired tissue function and subsequently improve clinical outcome or shorten hospital stay may then be investigated (25).

Positron emission tomography (PET) may be used for investigating the changes in cerebral oxygen metabolic rate and glucose utilization, which accompany changes in structural brain neuronal function (12, 25, 26, 27). PET is, however, expensive and is limited to a few research centres, although it permits reliable quantitative measurements of cerebral physiology over a wide range of circumstances (27, 28). In more general use, SPECT imaging may demonstrate regional cerebral blood flow changes seen in acute ischaemic cerebral infarction.

Several lipophilic cerebral perfusion agents that cross the normal blood-brain barrier to produce tomographic blood flow maps have been produced. In current use for this purpose are Iodine-123

iodoamphetamine (8, 17, 20, 29, 30, 31, 32), Iodine-123 propanediamine (HIPDM) (29, 30, 33), Thallium-201 diethyl dithio-carbamate (30, 31, 34. 35), Technetium-99m DMG-ZMP (a boronic acid adduct of technetium oxime, SQ 32 097) (36, 37), Technetium-99m amino-alkyl diaminodithiol derivatives such as NEP-DADT (38), Technetium ethyl cysteinate dimer (39, 40, 41, 42, 43, 44, 45, 46, 47, 48) and Technetium hexa-methyl propylene amine oxime (21, 49, 50, 51).

Xenon-133 has been used for the measurement of cerebral perfusion but purpose built equipment is required. The 81 KeV photon emitted makes the discrimination of scattered radiation a problem, yielding poor spatial resolution and considerable crosstalk from background radioactivity (12, 30, 32).

Objective comparison of serial SPECT scans performed in order to evaluate therapeutic measures and possibly to develop a prognostic index for acute ischaemic infarction would be facilitated by a reliable semi-quantitative method to determine cerebral blood flow changes. The various analytical techniques of evaluation of cerebral blood flow changes in acute ischaemic infarction should, therefore, be correlated with a selected clinical scoring system (the Canadian Neurological scale being used in this thesis).

Predicting the functional outcome following a stroke remains a problem to which there is not yet a satisfactory solution. Clinical prognostic indicators have not proved useful and are only used to describe in general terms those patients that will improve or deteriorate (6). The improvement of prognostic assessment in cerebrovascular disease is urgently required (52).

In this thesis an attempt has been made to determine whether clinical outcome can be predicted early in the course of the ischaemic infarction by using the semi-quantification of the decrease in regional cerebral blood flow found in this pathology. Five methods of semi-quantification of regional cerebral blood flow defects were investigated, in patients presenting with acute ischaemic infarction. An assessment of the role of cerebral perfusion imaging with Technetium-99m Hexa-methyl propylene amine oxime (HMPAO) in clinical stroke management was undertaken.

In this pilot study of 19 patients, (who met the trial criteria, out of more than 100 patients screened) only trends and suggestions for further study could be deduced. Other centres have had similar problems in recruiting into acute stroke trials, using only 7,4 - 10,2% of patients screened (53).

CHAPTFR 2

OBJECTIVES

OBJECTIVES

The aims of this thesis are as follows:-

1. To determine the place of SPECT cerebral perfusion studies in the management of cerebral infarction, and hence their value in stroke trials.

2. To investigate five methods of semi-quantification of cerebral perfusion lesions in acute ischaemic cerebral infarction and to determine which, if any, of these methods correlates with clinical findings and would be of clinical value.

   The methods of semi-quantification investigated were :-

   i) Defect volume index (DV index) as described by Launes et al (24).
   ii) Side to side comparative region of interest (ROI) ratios based on counts/voxel seen in a small area (33, 35, 54, 55).
   iii) Comparison of counts/voxel of a small area in the affected region to the counts/pixel in the ipsilateral cerebellum, expressed as a percentage (56, 57).
   iv) Thirty degree segmental analysis of the average counts per segment (8, 58).
   v) The area of the lesion as compared with the area of the ipsilateral cerebral hemispheric area expressed as a percentage.

3. To determine whether there is any prognostic value in the use of semi-quantification of cerebral perfusion defects with regard to stroke management.

CHAPTER 3

PATIENTS, MATERIALS AND METHODS

A. PATIENT POPULATION
   - INCLUSION CRITERIA
   - EXCLUSION CRITERIA

B. RADIOPHARMACEUTICAL

C. CT SCANS

D. SPECT SCANS

E. VISUAL ANALYSIS

F. SEMI-QUANTITATIVE ANALYSIS OF SPECT SCANS

PATIENTS, MATERIALS AND METHODS

A. PATIENT POPULATION

Nineteen patients presenting with an acute ischaemic cerebral infarct were selected from more than one hundred acute stroke patients investigated at the Johannesburg hospital, over a two year period, for entry into the study.

INCLUSION CRITERIA

1. Caucasian patients between the ages of 45 to 80 years presenting with an occlusive cerebrovascular accident (CVA) within a maximum of 48 hours of the vent.
2. Patients with a previous acute cerebrovascular accident were only included if no consequent motor or intellectual deficit or sequelae remained following that previous incident.

EXCLUSION CRITERIA

1. Any patient where there was full recovery within 72 hours. This was to exclude any spontaneous clinical evolution or other pathology such as a transient ischaemic attack.
2. Patients with reversible ischaemic neurological deficit (RIND) were excluded when the diagnosis had been established (either on day 1, or on day 10 having confirmed RIND using the CT scan).
3. Cerebral or subarachnoid haemorrhage (excluded by CT scan on day 1).
4. Patients presenting in a stage IV coma.
5. Patients with a CVA of other vascular origin (e.g. aneurysm, vertebro-basilar CVA), or post-traumatic CVA.

6. Tumours involving the brain or other sites.
7. Degenerative disease of the CNS such as Huntingtons disease, Parkinsons or Alzheimers disease.
8. Severely psychotic patients on previous or current treatment with antidepressants or neuroleptics.
9. Severe associated medical problems such as serious cardiac, renal, hepatic, respiratory dysfunction or severe psychosis.

Patient ages ranged from 51 years to 77 years with a mean age of 65 years. Nine males and ten females were included. The distribution of cerebral ischaemic infarcts was as follows :-

- 9 right middle cerebral artery territory lesions.
- 1 right anterior cerebral artery territory lesion.
- 1 right posterior cerebral artery territory lesion.
- 1 patient with multiple small infarcts as confirmed with MRI although clinically presented with left middle cerebral artery pathology.
- 7 left middle cerebral artery territory lesions (one of which was lacunar in nature and one with a small lesion in the left posterior internal capsule).

See Fig 1.

Two patients died during the trial period, that is, on day 4 and on day 23 (from unrelated problems). One patient had another cerebrovascular accident on day 19.

FIG. 1 PATIENT CHARACTERISTICS

PATIENT NO.	AGE	SEX	SITE OF LESION	OTHER
1	56	M	Right MCA	Died on day 4
2	74	F	Multiple small infarcts	Clinically Right MCA
3	55	F	Right MCA	
4	61	M	Left MCA	
5	69	M	Left MCA	Posterior left internal capsule
6	69	M	Left MCA	Small lacunar infarct
7	71	F	Left MCA	
8	72	F	Left MCA	
9	65	M	Right MCA	Repeat CVA day 19
10	58	F	Right MCA	
11	74	M	Right MCA	Died day 23
12	53	M	Right PCA	
13	51	M	Left MCA	
14	67	M	Right MCA	
15	63	F	Left MCA	
16	76	F	Right ACA	
17	52	F	Right MCA	
18	77	F	Right MCA	
19	73	F	Right MCA	

ACA - Anterior cerebral artery territory
MCA - Middle cerebral artery territory
PCA - Posterior cerebral artery territory

B. RADIOPHARMACEUTICAL

The radiopharmaceutical used for this study was Technetium-99m hexa-methyl propylene amine oxime (HMPAO) which is a lipophilic cereb.al perfusion agent that crosses the normal blood brain barrier.

HMPAO was supplied in single dose vials by Amersham Corporation. Each vial was reconstituted with 500 MBq of Technetium-99m in 5ml of normal saline, and the total injected intravenously within half an hour of preparation. This was repeated for each scan.

C. CT SCANS

CT scans were performed on day one in every case, and on days ten and thirty where possible, in order to verify brain infarction and to exclude intra-cranial haemorrhage. Both pre- and post-contrast (Conrav 420) injection scans were performed using a Phillips 310 Tomoscanner.

D. SPECT SCANS

SPECT scans were performed on days one, ten and thirty (where possible) after the acute onset of cerebral infarction using an Elscint Apex-415 ECT gamma camera fitted with a general, all-purpose, low energy parallel hole collimator and a dedicated computer. The patients eyes were shielded, with only the hum of the equipment remaining as background noise.

Cerebral SPECT scans were performed twenty minutes after the injection of 500 MBq of Tc-99m HMPAO. The data was acquired using a 360 degrees rotation, and an angle step of two degrees (180 projections), over a period of 20 minutes. A matrix size of 64 x 64 pixels was used.

The raw data was normalized so as to correct for imperfections in the acquired data, such as, flood non-uniformity, centre of rotation misalignment, and decay of the radiopharmaceutical between the start and end of the SPECT acquisition.

Transaxial images of the normalized raw data was reconstructed by the standard back projection method. Ramp filtering removed blurring of the image due to simple back projection, but also increased the noise present in the projections. The noise factor was reduced by the use of a Hanning filter.

A matrix size of 128 x 128 pixels with a zoom factor of two was used to create eight transaxial slices from the superior aspect of the cerebral hemispheres to the cerebellum. Each slice had a thickness of 2,07cm (3 pixel thickness).

Thinner slices were reconstructed to determine the exact site of the lesion, if the lesion was not visualized when using a 3 pixel slice thickness.

The average number of counts obtained per scan was 3,8 megacounts per scan, while the average count per central slice in the reconstructed transaxial images was 486 kilocounts.

Coronal slices were obtained from the transaxial reconstruction, and displayed from anterior to posterior in the cerebral hemispheres with a slice thickness of 4 pixels on a 64 x 64 matrix.

E. VISUAL ANALYSIS

The area of decreased isotope uptake on the HMPAO SPECT scan was visually assessed and subjectively scored as being :-

0 - not visualized
1 - defect less than 1/4 of the ipsilateral cerebral hemisphere in size.
2 - 1/4 to 1/2 of the ipsilateral cerebral hemisphere in size.
3 - more than 1/2 of the ipsilateral cerebral hemisphere in size.

F. SEMI-QUANTITATIVE ANALYSIS OF SPECT SCANS

Once transaxial and coronal images had been reconstructed and stored, semi-quantitative analysis was performed on each scan.

At the start of this study only the side to side comparisons had been described. As further methods were reported in literature these were added to the study, using the same data.

i) Defect Volume index (DV index)

Launes et al in 1989 found that the perfusion defect volume, estimated from transversal and coronal slices on SPECT scans performed one to

forty six days after the onset of neurological symptoms of a CVA, correlated with presenting clinical findings and outcome (24).

In this method the volume of the perfusion defect relative to the brain volume was measured.

The perfusion defect was identified on the images obtained, and it's size was measured from the transverse and coronal slices in which the defect appeared largest.

The perfusion defect volume (DV) index was calculated according to the formula :-

$$DV = l/L + w/W + h/H$$

where :-

L = maximal length of the transversal slice in the fronto-occipital projection.

l = maximal length of the defect in the above slice.

W = maximal width of the transversal slice.

w = maximal width of the defect in the above slice.

H = maximal height of the supratentorial part of the brain in the coronal slice.

h = maximal height of the defect in the above slice.

See fig. 2.

Where no visible defects were seen a DV index of 0 was given. This method has the advantage that the decrease in blood flow in the defect area was not semi-quantitated relative to any brain area that has been assumed normal.

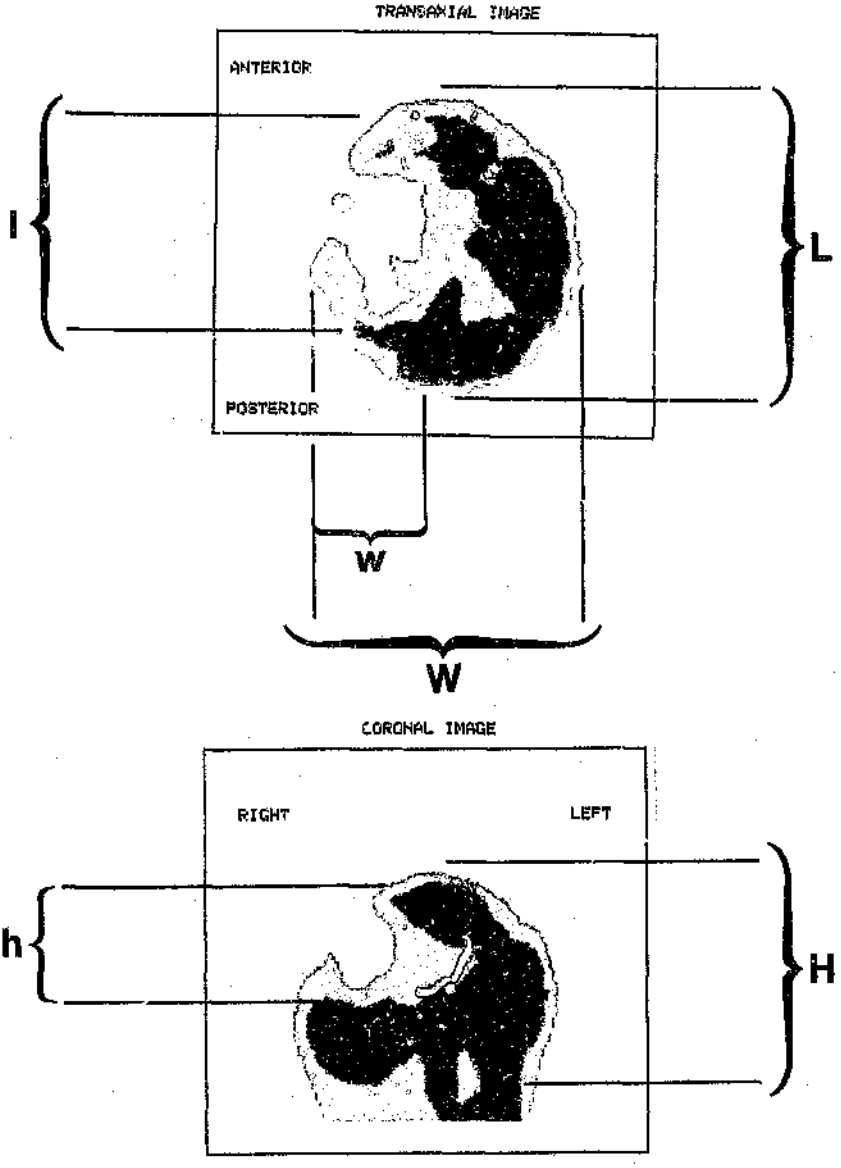


Fig 2. Method of Defect Volume Measurement

W = width of brain

w = width of the defect

L = length of the brain in the anteroposterior projection

l = length of the defect

H = height of the brain

h = height of the defect

In this trial the same method was used for subsequent scans on days 10 and 30.

ii) Side to side comparison of count density

Small circular regions of interest (ROI) were drawn in the affected area using the reconstructed transaxial images. A mirror ROI was drawn on the normal side.

Counts per voxel were determined in the ROI on the assumed normal side and on the side of the lesion. The counts per voxel of the affected side were expressed as a percentage of the normal side. The ratio of count density of the low uptake area relative to the contralateral area was calculated.

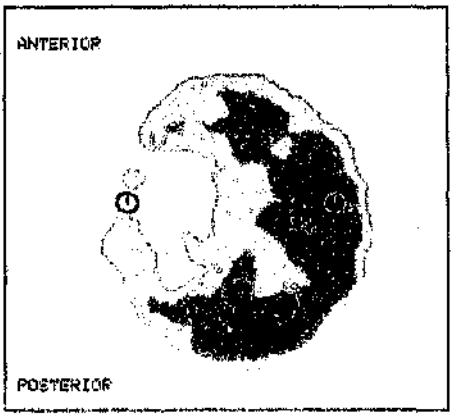
$$\text{Ratio} = \frac{\text{count density of low uptake area}}{\text{count density of the contralateral normal side}} \times 100\%$$

The same slice and method was used for subsequent scans.
See fig. 3.

This method has been used previously by Leonard et al who used five symmetrical ROIs drawn on two middle transverse slices, to calculate right to left ratios and to compare HMPAO with I-123 HIPDM (33).

Other authors have also employed variations of this method, such as Buell et al, Podreka et al and Van Royen using the same principle (35, 54, 59, 60).

Lesion ROI



Normal contralateral ROI

Fig 3. Regions of interest used for side to side comparison of counts per voxel

Semi-quantitation of I-123 IMP SPECT imaging was obtained by Knapp et al by side to side comparison of segments containing territories affected by cerebrovascular disease (61).

Lee et al performed semi-quantitative assessments of regional cerebral blood flow defects on I-123 IMP SPECT images by drawing a region of interest around the lesion and comparing the count density of the lesion with that of a similar normal contralateral area (62).

iii) Ratio of lesion count density to cerebellar count density

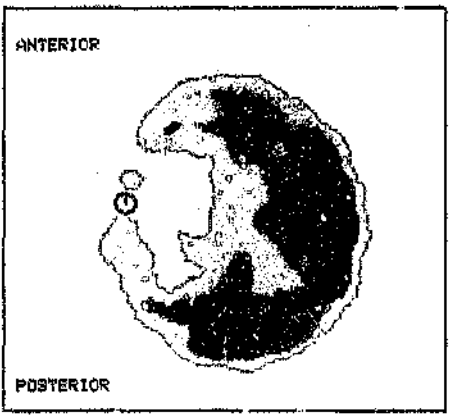
A small circular ROI was drawn in the affected area on the transaxial image where the lesion was most clearly seen. The counts per voxel for this ROI were obtained.

A similar circular ROI was placed over the ipsilateral cerebellar hemisphere on the appropriate transaxial image and the count per voxel for the cerebellum was obtained. The cerebellar hemisphere with the highest count density was used if diaschisis was present.

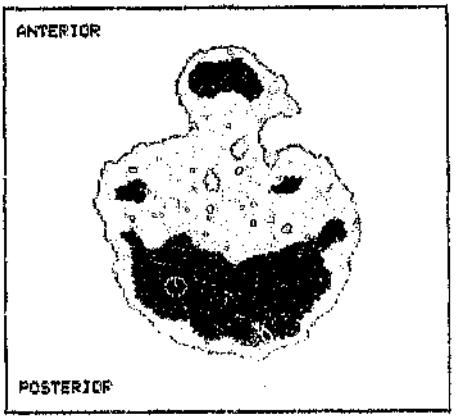
The count density in the affected area was expressed as a percentage of the count density of the cerebellum.

$$\frac{\text{Count density of the lesion ROI}}{\text{Count density of the cerebellar hemisphere}} \times 100\%$$

See fig 4.



a) Lesion region of interest



b) Cerebellar region of interest

Fig 4. Regions of interest selected for the lesion to Cerebellum ratio method of semi-quantification

This method has been previously used by Langen et al who expressed the opinion that the cerebellum represents a homogeneous reference and is a better reference region than the normal contralateral region (56).

Costa et al also used this method of semi-quantification when quantifying washout of Technetium-99m HMPAO (63).

The same ratio using rectangular regions of interest of the same size was utilized by Perani in 16 patients suffering from Alzheimers disease and in 16 healthy elderly subjects. Left to right count ratios were also assessed for each pair of symmetrical regions of interest (57).

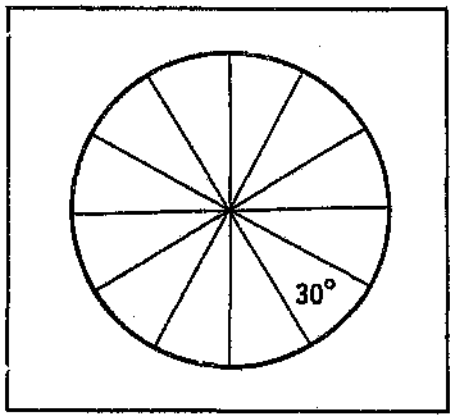
iv) Thirty degree segmental analysis

A suitable transverse slice was chosen in which the lesion was well represented. The same slice was taken for analysis from subsequent scans.

A circular region of interest was drawn around the image selected and was divided into thirty degree segments. Segmental analysis was performed, proceeding in a clockwise manner. The average count per pixel for each segment was calculated and expressed graphically for each segment using a Hewlett Packard personal computer. The highest count value was taken to be 100% and the rest of the image was scaled to this level.

The side to side difference was expressed in percentage points.

Side to side difference = Normal segment count - defect count density



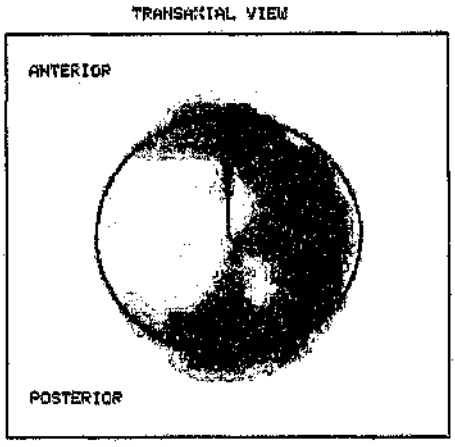


Fig 5. Circular region of interest selected for the thirty degree segmental analysis method

This difference reflected a negative value if the lesion count density was less than the normal side and a positive value when luxury perfusion occurred.

See fig. 5.

SPECT quantification of cerebral ischaemia using early and late I-123 iodoamphetamine scans was analysed by Maurer et al in 1990. The authors used quantitation of redistribution of isotope as an objective index of improved perfusion (8).

v) Area ratio method

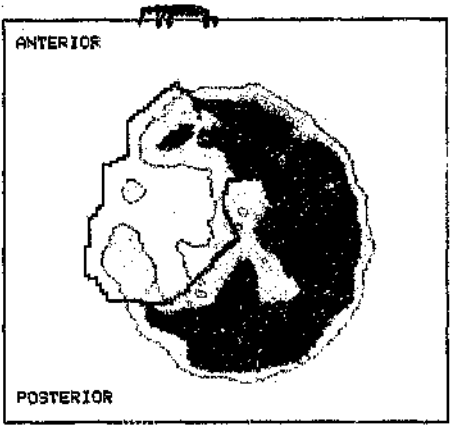
The transaxial image where the defect was largest was chosen. The same image was chosen on subsequent scans.

The area of decreased isotope uptake was delineated with an irregular ROI, and the area of the lesion determined.

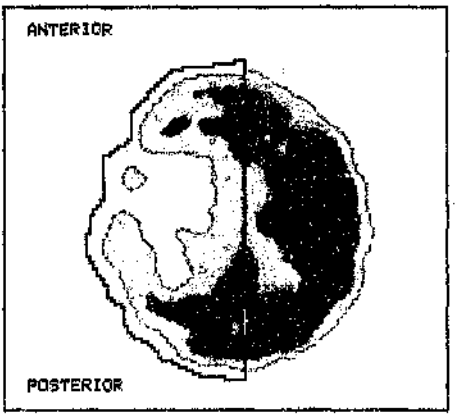
The area of the ipsilateral cerebral hemisphere was calculated. The defect area was expressed as a percentage of the ipsilateral cerebral hemispheric area.

$$\frac{\text{Area of the defect}}{\text{Area of the ipsilateral hemisphere}} \times 100\%$$

See fig. 6.



a) Lesion area region of interest



b) Ipsilateral cerebral hemisphere region of interest

Fig 6. Lesion area to ipsilateral cerebral hemisphere area ratio method of semi-quantification

G. CLINICAL SCORING

Patients were assessed clinically by means of the Canadian Stroke assessment system, introduced by Cote et al (64). The Canadian Neurological Scale was developed to assess conscious stroke patients who have neurologic deficit or aphasia (64).

The first part of the scale assesses mentation, with levels of consciousness, orientation and speech of importance, while the second section scores motor function.

See fig. 7.

All patients were evaluated clinically within 48 hours of the acute onset of neurological symptoms. Daily clinical assessment for a minimum of 10 days followed, with further examinations on days 20 and 30.

A clinical scoring system was chosen so as to be:-

- simple and non-ambiguous.
- have a minimum number of grades per modality tested.
- relevant for modalities most commonly affected in acute strokes.
- easy to use.
- easy to interpret.
- brief.
- practical.

		Date
		Time
MENTATION	LEVEL CONSCIOUSNESS:	Alert(3)
		Drowsy(1.5)
	ORIENTATION:	Oriented(1)
		Disoriented or Non Applicable(0)
	SPEECH	Normal(1)
		Expressive Deficit(.5)
		Receptive Deficit(0)

MOTOR FUNCTIONS:

WEAKNESS:

SECTION A_1	NO COMPREHENSION DEFECT	FACE:	None(.5)
			Present(0)
		ARM:PROXIMAL	None(1.5)
			Mild(1)
			Significant(.5)
			Total(0)
		ARM:DISTAL	None(1.5)
			Mild(1)
			Significant(.5)
			Total(0)
		LEG:	None(1.5)
			Mild(1)
			Significant(.5)
			Total(0)
SECTION A_2	COMPREHENSION DEFECT	MOTOR RESPONSE:	
		FACE:	Symmetrical(.5)
			Asymmetrical(0)
		ARMS:	Equal(1.5)
			Unequal(0)
		LEGS:	Equal(1.5)
			Unequal(0)

GRAPH FOR TOTAL SCORE

10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

Fig 7. *Scoring Sheet.*

CHAPTER 4

RESULTS

A. CLINICAL RESULTS
B. CT SCAN RESULTS
C. VISUAL ANALYSIS OF SPECT SCANS
D. DEFECT VOLUME INDEX
E. SIDE TO SIDE COUNT DENSITY COMPARISON
F. LESION COUNT DENSITY TO CEREBELLAR COUNT DENSITY RATIO
G. SEGMENTAL ANALYSIS
H. AREA RATIO METHOD
I. LUXURY PERFUSION
J. CROSSED CEREBELLAR DIASCHISIS
K. STATISTICAL ANALYSIS

Biochemistry and full blood counts were also monitored on day 1 (baseline), day 10 and on day 30.

A. CLINICAL RESULTS

Two deaths occurred over the thirty day trial period. One patient died on day four due to cerebral infarct extension and the other patient improved initially to day twenty and then died from cardio-respiratory complications.

One further patient improved considerably until day twenty and then had another cerebral infarct on day twenty one in the opposite carotid territory.

In the first ten day period, eight of eighteen patients improved by a score of one point or more on the Canadian scale (44,4%).

Fourteen of sixteen patients (87,5%) remaining showed an improvement of more than a score of one over the whole thirty day trial period. The patient who restroked dropped by a score of two between days ten and thirty.

B. CT SCAN RESULTS

On day one 8 of 19 (42%) CT scans were positive as compared to 12 of 15 (80%) on day ten, and 11 of 13 (84,6%) performed on day thirty. These findings are in accordance with reported literature, where the CT scan is often negative in the first 24-48 hours after an acute cerebral infarction, when no structural brain changes may be identified (1, 30, 65).
See fig. 8

6 patients (40%) demonstrated luxury perfusion (post-contrast

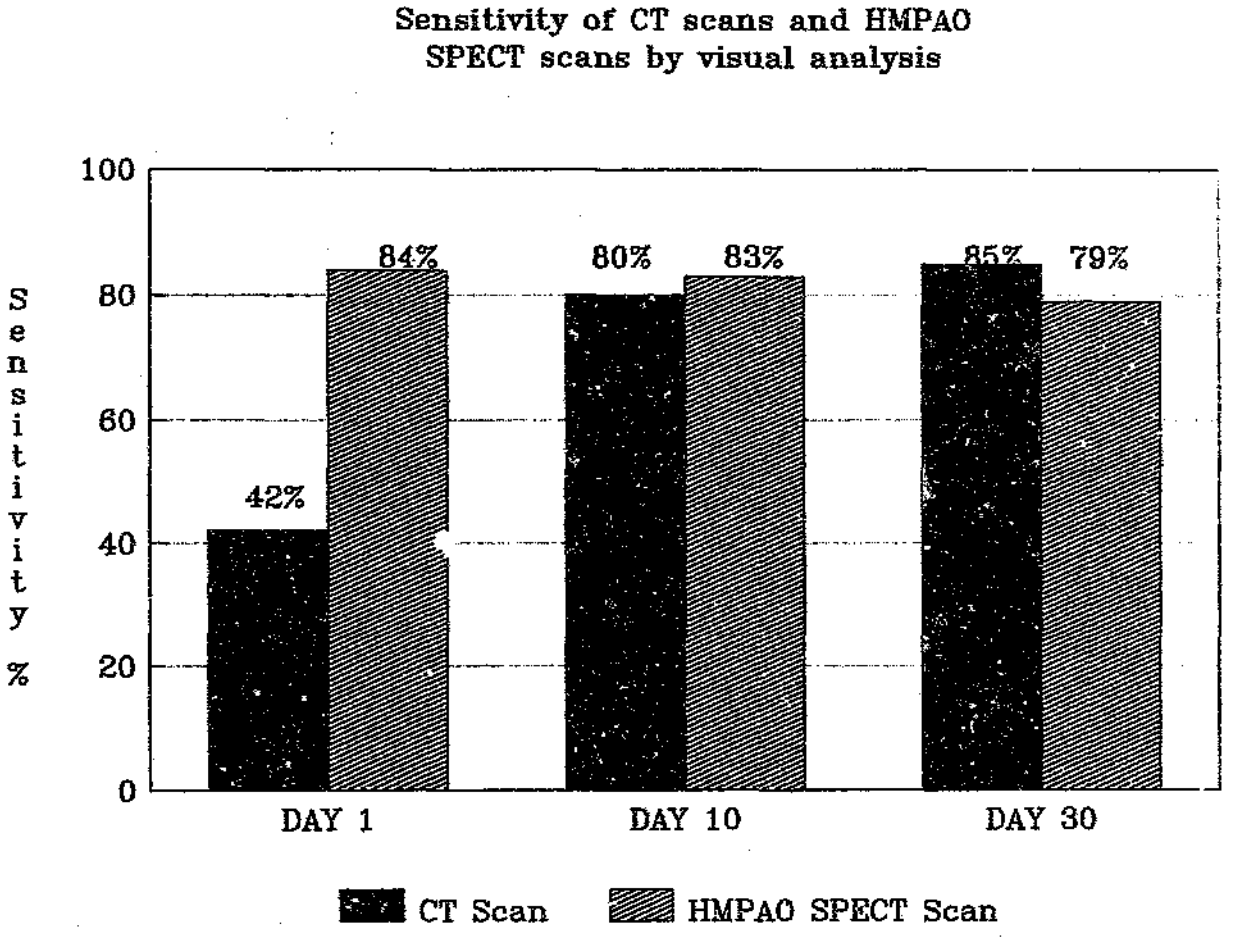

Sensitivity of CT scans and HMPAO SPECT scans by visual analysis
Sensitivity %
100
80
60
40
20
0
42%
84%
80%
83%
85%
79%
DAY 1
DAY 10
DAY 30
CT Scan
HMPAO SPECT Scan

Figure 8

enhancement) on day 10 and 2 patients (15,4%) demonstrated this phenomenon on day 30.

It is difficult to assess the change in lesion size over the thirty day trial period on CT scanning as many lesions were not seen on day one.

A decrease in visual lesion size was noted in 3 patients from day 10 to day 30.

C. VISUAL ANALYSIS SPECT SCANS

19 scans were performed on day 1, 18 on day 10 and 14 scans on day 30. The decreased number of scans performed on day 30 was due to non-compliance of the patients and the death of 2 of the patients.

16 scans (84%) were positive on day 1, with the site of the lesion correlating with clinical features. 6 were large lesions, 3 medium and 7 small lesions.

15 of 18 scans (83%) on day 10 were positive. One patient had died on day 4. 11 scans were unchanged whilst the lesion size had visually decreased in 4 patients.

On day 30, 11 of the 14 scans (78,6%) were positive. Over the 30 day period of the trial, 5 lesions were unchanged in size, 5 decreased in size and 1 lesion increased in size. 3 lesions were not seen on SPECT scanning and 5 patients did not have day 30 scans due to various reasons.

It was noted that all those patients showing a visual decrease in lesion size were initially size three or large lesions.

D. DEFECT VOLUME INDEX

Using the defect volume index (DV index) method of semi-quantitation, 17 of 19 patients (89,5%) had a positive scan on day 1. Negative isotope scans were found in the patient with multiple small infarcts and in a patient with an anterior cerebral artery infarct with all the semi-quantitative methods investigated.

Of 18 patients scanned on day 10, the DV index remained at zero in 2 patients, improved by more than a score of 0,1 (out of 1) in 6, increased in 6 patients and remained the same (or a change of less than 0,1) in 4 patients.

By day 30, 2 patients still had a DV index of zero, 6 of 14 lesions improved by more than 0,1 (i.e. decreased in volume), and 3 had an increase in the DV index as compared to day 1 (i.e. lesion volume increased), and 3 lesions remained unchanged.

CHANGES IN DV INDEX

	DAY 1 TO DAY 10	DAY 1 TO DAY 30
LESION NOT SEEN	2	2
NO CHANGE	4	3
DECREASED INDEX	6	6
INCREASED INDEX	6	3

These changes were in agreement with patients showing clinical changes in 7 cases to day 10 (38,9%) and in only 4 patients over the 30 day trial period (28,6%).

E. SIDE TO SIDE COUNT DENSITY COMPARISON

17 of 19 scans were positive on day 1, although 4 of these scans showed a relative decrease of less than 10% in counts/pixel as compared to the normal side.

By day 10 a change of more than 1% was seen as an improvement in lesion count density in 11 patients, and as a worsening in count density in 4 patients. 1 patient showed no change and 2 patients consistently had negative scans. These changes were in agreement with clinical changes observed (i.e. improvement, deterioration or no change) from day 1 to day 10 in 27,8% of cases.

On day 30, an improvement was seen in 7 patients, deterioration in 4 and no change in relative count density in 1 case. These changes were in agreement with clinical changes in 27,8% of cases.

CHANGES IN SIDE TO SIDE COUNTS/VOXEL MEASUREMENT DIFFERENCES

	DAY 1 TO DAY 10	DAY 1 TO DAY 30
LESION NOT SEEN	2	2
NO CHANGE	1	1
IMPROVED COUNT DENSITY	11	7
DETERIORATING COUNT DENSITY	4	4

F. LESION COUNT DENSITY TO CEREBELLAR COUNT DENSITY RATIO

On day 1, a relative lesion count density of less than 95% of the cerebellar count density was seen in 17 of 19 patients scanned (89,5%).

An improvement in the relative count density of the lesion of more than 1% was seen in 7 patients to day 10. The relative count density got worse in 5 and remained the same in 4 cases. The lesion was not detected in 2 patients on day 10. These changes were in agreement with the trend in clinical change in 8 of 18 patients scanned to day 10 (44%).

By day 30 the relative count densities improved in 8 cases, 4 lesions decreased in relative count density (i.e. deterioration) and 2 lesions were not detected. The changes were in agreement with clinical changes in 7 of 14 cases (50%).

CHANGES IN LESION TO CEREBELLAR COUNT DENSITY RATIO

	DAY 1 TO DAY 10	DAY 1 TO DAY 30
LESION NOT SEEN	2	2
NO CHANGE	4	0
IMPROVED RATIO	7	8
DETERIORATING RATIO	5	4

G. THIRTY DEGREE SEGMENTAL ANALYSIS

On day one, 12 of 19 scans were positive with this semi-quantitative method, with side to side differences ranging from 4% to 44%.

Improvement was seen in 5 patients (i.e. a decreased difference), deterioration in 3 (i.e. an increased side to side difference) and no change in 4 lesions by day 10. 6 lesions were not detected. These changes were in agreement with clinical progress in 8 of 18 patients (44%).

By day 30, the lesion was not detected in 5 cases, improved semi-quantitatively in 5 deteriorated in 3 and remained unchanged in 1 case. This was in agreement with clinical changes in 5 of 14 cases (35,7%).

CHANGES IN SIDE TO SIDE DIFFERENCE ON SEGMENTAL ANALYSIS

	DAY 1 TO DAY 10	DAY 1 TO DAY 30
LESION NOT SEEN	6	5
NO CHANGE	4	1
DECREASED DIFFERENCE	5	5
INCREASED DIFFERENCE	3	3

H. AREA RATIO METHOD

With this semi-quantitative method 17 of 19 patients had a positive scan on day 1 (89,5%).

On day 10, 2 scans remained negative; the lesion area remained the same in 3 patients, decreased in size in 6 and got larger in 7 cases (when a change of more than 1% was used). These changes were in agreement with clinical score changes in 38,9%.

By day 30, 2 scans remained negative. The area of the lesion remained the same in 1 case, decreased in size by more than 1% in 6 and increased in size in 5 patients. The change in lesion area by day 30 only agreed with 28,6% of clinical changes seen.

CHANGES IN LESION AREA

	DAY 1 TO DAY 10	DAY 1 TO DAY 30
LESION NOT SEEN	2	2
NO CHANGE	3	1
DECREASE IN AREA	6	6
INCREASE IN AREA	7	5

I. LUXURY PERFUSION

So-called luxury perfusion as seen with contrast enhancement was seen in 5 patients on day 10, 1 patient on days 10 and 30, and in 1 patient on day 30 only, when using CAT scanning.

This luxury perfusion could also be detected on visual inspection of the SPECT scans in 5 patients on day 10 corresponding to that seen on the CAT scans.

An increase in count density above 100% (of the normal hemisphere) could be determined with 3 semi-quantitative methods, namely the side to side comparison of count density (4 patients), the lesion to cerebellar count density ratio method (3 patients), and on segmental analysis of the transverse image (2 patients).

J. CROSSED CEREBELLAR DIASCHISIS

Crossed cerebellar diaschisis was present when the count density of the contralateral cerebellar hemisphere was hypoperfused relative to the ipsilateral cerebellar hemisphere by a count density of more than 10 counts per pixel. This phenomenon was observed in 74% of patients in this trial.

K. STATISTICAL ANALYSIS

For statistical purposes results were divided into day 1, day 10 and day 30.

The correlation coefficients for each semi-quantitative method against clinical scoring were particularly low when all the patients were included for simple regression analysis i.e.

Range of correlation coefficients
Day 1 : range = 0,14 - 0,36
Day 10 : range = 0,13 - 0,33
Day 30 : range = 0,19 - 0,55

The data was then "cleaned" on a clinical basis with exclusion of two patients on days 1 and 10 (with multiple infarcts and with a posterior cerebral artery territory infarct), and with the exclusion of an additional patient on day 30 who had restroked on day 19. The correlation coefficients then changed on days 1, 10 and 30 i.e.

Range of correlation coefficients on "cleaned' data
Day 1 : range = 0,36 - 0,52
Day 10 : range = 0,26 - 0,46
Day 30 : range = 0,20 - 0,77

The semi-quantitative methods correlate well with each other on day 1 ($p = 0,81 - 0,93$) and on day 30 ($p = 0,34 - 0,92$). Poor correlation was seen on day 10 possibly due to the presence of luxury perfusion affecting three semi-quantitative methods and possibly due to clinical changes not adequately reflected on the SPECT scan at this time.

These observations led to the conclusion that the development of a multiple regression model or models would be the most appropriate way in which to relate the clinical score to the semi-quantitative method scores.

The day 1 data was examined first. It was found by forward stepwise regression that the only significant semi-quantitative variable was the thirty degree segmental analysis score, where :-

Day 1 Clinical Score = 6,8 + 0,078 x day 1 segmental analysis score
(adjusted R squared = 0,22, p = 0,033)

As can be seen this is far from satisfactory as only 22% of the clinical score is explained by this model. In addition the probability level is high.

The day 10 data did not yield a multiple regression model that was satisfactory.

The day 30 model gave the following equation :-

Day 30 Clinical Score = 8,6 - 4,18 x Day 30 DV index score
- 0,36 x Day 30 segmental analysis score
(adjusted R squared = 0,86, p = 0,0000)

An attempt was then made to determine whether day 1 SPECT scan findings could be used as a prognostic index for day 30 clinical scores. Limitations involved in this process were the strict initial selection of patients and the small sample size ; which was further compounded by clinical complications.

Various multiple regression models were developed differing in the patients excluded from statistical analysis on clinical grounds.

The most satisfactory prognostic model required exclusion of the multiple infarct patient only, and gave the following equation :-

Day 30 Clinical Score = 8,98 - 2,4 x Day 1 DV index + 0,08 x Day 1 area ratio score + 0,09 x Day 1 segmental analysis score

(adjusted R squared = 0,49, p = 0,008)

CHAPTER 5

DISCUSSION

A. TECHNETIUM-99m HEXAMETHYL PROPYLENE AMINE OXIME
   i) RADIOPHARMACOLOGY
   ii) NORMAL IMAGES
   iii) IMAGES SEEN IN ACUTE CEREBRAL INFARCTION
B. LUXURY PERFUSION
C. CROSSED CEREBELLAR DIASCHISIS
D. SEMI-QUANTITATIVE ANALYSIS
E. PROGNOSTIC VALUE OF SEMI-QUANTITATIVE SCORING

A. TECHNETIUM-99m HEXAMETHYL PROPYLENE AMINE OXIME

The major biological requirements for radiopharmaceuticals to perform as regional cerebral blood flow tracers are :-

1) The ability to cross the intact blood brain barrier.
2) To accumulate in the brain such that the regional distribution is proportional to blood flow (51).
3) To remain with a fixed distribution within the brain for a sufficiently long time to allow the acquisition of data for reconstruction of tomographic images (49).

i) Radiopharmacology

The d,l diasterioisomer of Hexamethyl propylene amine oxime was the tracer used in this study (HMPAO). It is lipophilic, neutral and of low molecular weight and can therefore cross the normal blood brain barrier. It complexes with Technetium-99m which has the ideal characteristics for the gamma camera (monoenergetic gamma ray emission of 141 KeV, physical half life of 6 hours) and which can be obtained from an on-site generator. Technetium-99m HMPAO has a long retention in the brain with very slow redistribution, making SPECT scanning possible. When complexed to Technetium-99m the compound is stable in vitro for 30 minutes (49, 50, 51, 66).
See fig. 9

The first pass extraction by the brain is proportional to cerebral blood flow. The unidirectional extraction into the brain is about 90% at normal blood flow but decreases to 70% in very high flow areas (30, 34, 65, 66, 67).

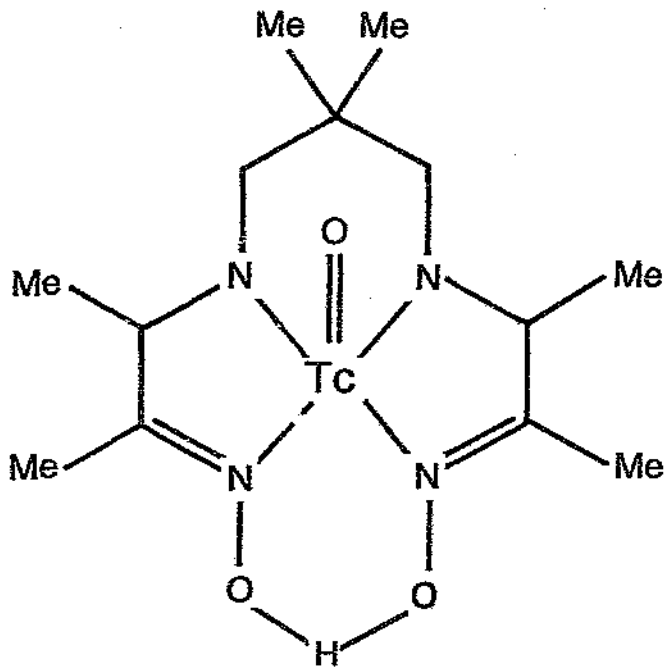


Fig 9. Structure of $^{99}Tc_m$-HM-PAO (ref 51)

Choksey et al speculate that although initial uptake of Tc-99m HMPAO is related to regional cerebral blood flow, the absolute levels retained in the brain are dependant on other parameters which require clarification, and that where abnormal uncoupling with metabolism occurs HMPAO uptake must be interpreted with care (68).

An average brain activity of 2,1 - 7% of the injected dose is seen at one minute after injection. There is initial rapid blood clearance with 15% of the injected dose remaining in the blood at 5 minutes (10% at 1 hour, 4% at 24 hours). 10 - 15% of the cerebral activity washes out by 2 minutes, and then remains constant from 15 minutes to 8 hours. Fixed regional distribution in the brain is required for 20 to 30 minutes for SPECT scanning. 86% of the initial activity is retained at 24 hours. (49, 65, 66, 69, 70, 71, 72, 73).

Once in the brain there is slow conversion of the primary lipophilic complex to a less lipophilic complex to permit retention in the brain. Conversion in the human brain is fast, having a conversion half-life of about 0,8 minutes. (67, 68, 74).

Costa et al found that HMPAO appears mainly in the organelles of the cell (>55%) with a higher uptake seen in neuronal nuclei than in glial nuclei in the rat brain (34, 63, 72).

Retention in the brain is determined by clearance of the lipophilic portion by the blood and by conversion to the hydrophilic form. In the brain as a whole, about 50% of the lipophilic fraction is permanently retained in the brain substance. Lear et al have suggested that only half of the Tc-99m HMPAO is available for exchange per pass, possibly because of temporary localization in red cells or other blood

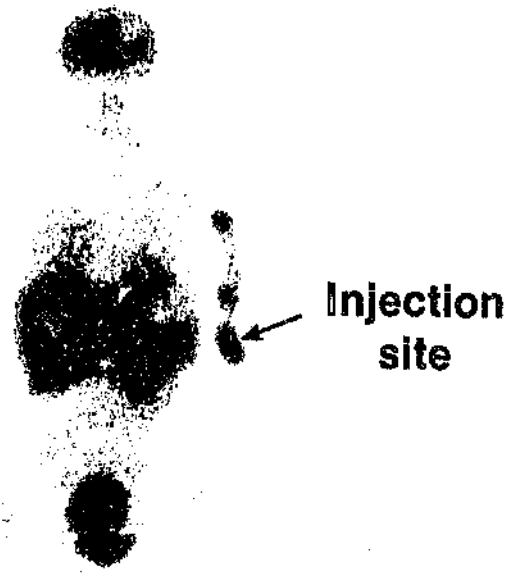
constituents, or due to possible conversion to a non-cerebrophilic compound (67, 75). Andersen suggests that only a fraction of the arterial radioactivity can be considered as brain input, as conversion to the hydrophilic form is rapid in the blood (67). Neirinckx et al suggested that the cellular uptake of HMPAO may be related to the tissue glutathione content and that uptake may, therefore, be related to the local metabolic rate (76). El-shirbiny in 1989 has found, however, that only the uptake of HMPAO in the liver is related to glutathione content in the cell (not brain uptake) (69).

The rest of the activity is widely distributed in skeletal muscle and soft tissue, especially subcutaneous fat. There may be slight uptake in the thyroid (<1%), lacrimal glands (<1%), nasal and oral mucosa, gastric mucosa, and the skin (possibly in the sebaceous glands) (49, 65, 66, 71).
See Fig. 10.

Lung uptake of 12-13% of the injected dose may be seen but appears to occur only in smokers. This uptake is seen in the first hour post-injection, then falls rapidly. The myocardium show 2% of the activity (65).

The urinary tract is the main route of excretion with 37-40% of the injected dose being excreted via the urine over 48 hours (66, 70, 71).

30% of the injected dose is found in the gastro-intestinal tract soon after injection, of which half is excreted over 48 hours (i.e. 15% of the injected dose). The liver extracts 13-15% which is excreted by the hepatobiliary tract. The tracer appears rapidly in the gallbladder and intestine (49, 66, 70).



c

Fig 10. Anterior view whole-body scan of Tc-99m HMPAO at 4 hours post-injection. Normal distribution (Ref 65)

Radiation doses are well below acceptable levels (49, 66).
See fig. 11.

ii) Normal Images

The images obtained are blood flow maps which supply information on the regional distribution of blood flow. They are comparable to images obtained with Iodine-123 iodoamphetamine and have the same distribution as Xenon-133 flow maps (21, 33, 66, 67, 71).

There is good differentiation between white and grey matter, there being greater uptake in grey matter. Uptake ratios for grey:white matter have variously been reported as 1,12 - 1,96. Grey matter is composed mainly of cellular structures, whilst white matter is mainly fibres and some oligodendroglial cells (33, 34, 65, 66, 71).

Uptake is seen along the convexities of the hemispheres and along the interhemispheric fissure, with greater uptake seen in the basal ganglia and cerebellum reflecting the greater blood flow in these areas (33, 50, 68). The periventricular space may appear larger than expected due to the relative lesser uptake seen in the white matter surrounding the ventricles (33, 50, 70). The caudate nucleus and thalamus are well demonstrated but smaller structures are not resolved (70).

iii) Images seen in Acute Cerebral Infarction

Tc-99m HMPAO SPECT scans are particularly useful in the first 48 hours after an acute infarction The SPECT scan shows physiological changes whereas CT scans demonstrate structural changes (which are in fact the

Fig. 11 RADIATION ABSORBED DOSES TO HUMANS

(Ref 49)

Target organ	Absorbed radiation dose (mGy per 500 MBq)
Lachrymal glands	34.7
Gall bladder wall	27.3
Kidney	18.5
Thyroid	15.0
Upper large intestine wall	13.7
Liver	8.9
Small intestine wall	7.8
Lower large intestine wall	5.9
Urinary bladder wall	5.4
Brain	3.8
Ovaries	3.2
Testes	0.6
Whole body	2.1

end result of a stroke) (14). This fact is demonstrated in this study as on day 1 only 42% of CT scans were positive as compared to 84% of SPECT scans. By day 10 the percentage positive scans was the same.

HMPAO shows a central area of infarction (demonstrated by CT scan) with a surrounding area of ischaemic but viable tissue (so-called ischaemic penumbra), which is not seen on CT scan (14, 23, 77, 78). Perfusion defects are initially larger than that seen on CT scanning. The discrepancy in the size of the lesion on CT and SPECT scans will become less obvious or disappear when surrounding temporary damage turns into permanent tissue changes (14, 78). The peri-infarct area is probably an area of deafferentated neurons with decreased metabolism. Histologically there is only a narrow transitional zone between ischaemic and viable tissue (24, 78). In 104 patients studied in a multicentre trial, those with chronic lesions showed the same defect as CT scans, whilst those with acute strokes showed areas of decreased perfusion greater than the low density areas seen on CT scan (66). In 5 of 9 patients, Garret et al found the area of hypoperfusion to be more extensive on HMPAO SPECT scans than on CT scans or on MRI with the remaining 4 patients showing corresponding results with CT and MRI (18).

Imaging of established cerebral infarction with Xenon-133 and PET studies show that the infarcted area is associated with low blood flow as well as low metabolism (68). The estimated lower limit of blood flow for cellular viability is 10-12 ml/100g/min and hypoperfusion must last for at least 15 minutes to produce infarction (23). A flow of 12-18 ml/100g/min can produce ischaemia with reversible failure of neuronal activity without infarction (79). Permanent neurological deficit may depend on the function of collateral circulation. Collaterally perfused areas are usually posterior and superior to the infarct, and are low flow areas with collateral circulation distal to the occlusion. These areas may modify the HMPAO scan picture. On Xenon-133 scans a

hyperaemic area may be seen anterior to the infarct, and it is queried whether this is normal brain tissue or not (23).

The ischaemic penumbra is viable but non-functional tissue located adjacent to an ischaemic infarct (23), and is not differentiated from infarcted tissue on HMPAO scans (14). Cerebral arterial occlusion may cause differing degrees of tissue damage depending on the amount of collateral blood supply to the ischaemic tissue.

The smallest cold spherical volume detectable on SPECT scanning is about 1 ml, and the smallest volume from which cerebral blood flow/cerebral blood volume ratios can be derived is 15 ml (30). Areas of increased and decreased flow may be demonstrated but uptake no longer correlates with flow above 150-200 ml/100g/min (30, 34). In lesions with regional hypoperfusion of 10-20% less than the non-affected area, reduced cerebral perfusion may not be clearly seen. Imaging of mild ischaemia may therefore be of limited value (80).

Lacunar infarcts are very small infarctions in deep brain structures, and of low density on CT scan (which may be of normal appearance) (7, 53). Van Royen in 1987 after studying 100 stroke patients, found difficulty in localizing lacunar infarcts with Thallium-201 DDC and Iodine-123 iodoamphetamine (35). However, 1 patient in our trial with a lacunar infarct on CT scan (<1,5cm lesion with no cortical involvement) (81) was demonstrated with HMPAO both visually and semi-quantitatively.

B. LUXURY PERFUSION

Regional cerebral perfusion is regulated in part by the local metabolic needs of the brain. An inappropriate vascular dilatation occurs in

acute stroke due to loss of the normal autoregulatory mechanisms (82). Hyperperfusion has been defined as an overabundant cerebral blood flow as compared with metabolic needs (77). Late luxury perfusion, seen at 2 to 3 weeks post infarction has been attributed to focal vasodilatation, loss of autoregulation and new capillary formation. The pathophysiological basis for contrast enhancement on CT scanning is not clear. Possible explanations are luxury perfusion, destruction of the blood-brain barrier and new capillary growth (56, 77, 83).

So-called luxury perfusion (hyperaemic infarction) is well detected on Tc-99m HMPAO scans as an area of increased isotope uptake of greater intensity than the opposite normal side. In this study, 7 of 18 patients (38,9%) scanned to day 10 showed 'luxury' perfusion or contrast enhancement on CT scanning, and 5 patients (27,8%) demonstrated this phenomenon on SPECT scanning.

Holmes et al reported luxury perfusion demonstration with Tc-99m HMPAO in 7 patients (84), while Van Royen et al demonstrated 'hot spots' in some patients in the second week post-infarct using Thallium-201 DDC, but observed that this area seemed to correspond to the area of damaged blood-brain barrier (35). Raynaud et al found 5 of 27 patients to demonstrate luxury perfusion on Iodine-123 IMP scanning (77).

C. CROSSED CEREBELLAR DIASCHISIS

Crossed cerebellar diaschisis or hypometabolism has been reported in approximately 50% of stroke patients. It is most prominent in large lesions involving two or three cerebral lobes or after small lesions destroying the internal capsule at basal ganglia level. Some metabolic depression may also be seen in the ipsilateral cerebellar hemisphere, although less severe (26, 28).

Holmes et al found post-infarction contralateral cerebellar hypoperfusion to be commonly seen in the recent stroke patient, especially if the infarct was extensive and involved multiple branches of the middle cerebral artery. They did not, however, report this to be a common finding in chronic infarcts (84).

Graveline et al found 26 of 27 patients with motor lesions to have crossed cerebellar diaschisis when studied with Tc-99m HMPAO from 5 days to 2 weeks after the acute stroke event. 15 of 15 patients with non-motor lesions did not show significant cerebellar asymmetry (85).

In our study 72% of patients showed crossed cerebellar diaschisis (i.e. a count density difference of more than 10 counts/pixel in a small cerebellar region of interest as compared to the ipsilateral cerebellar count density). Costa et al have reported a normal right to left cerebellum ratio as being 0,95 - 1,05 (63).

D. SEMI-QUANTITATION

Initial Tc-99m HMPAO uptake generally reflects local cerebral blood flow, although in conditions of high flow above 150-200 ml/g/min, retention of HMPAO is non-linear (30, 34). Absolute blood flow quantitation is complicated by :-

1. Probable rapid conversion to a non-lipophilic compound.
2. Blood cell binding of the radiopharmaceutical.
3. Non-instantaneous cerebral trapping (86).
4. Initial back diffusion of the diffusible tracer from brain to blood (87).

Isotope retention is the result of initial uptake and subsequent retention. Initial uptake is related to :-

1. The amount of free tracer in the blood.
2. Blood flow.
3. Transit time through the cerebral capillary bed (68).

Retention depends on :-

1. The rate of intracellular conversion to a non-diffusible form.
2. Outward diffusion of the unconverted form (68).

Due to the difficulty in absolute flow quantitation with Tc-99m HMPAO (68), several methods of semi-quantification of regional cerebral blood flow have been attempted. The methods used in this thesis are five different kinds of semi-quantitation To validate these methods, comparison to a "gold standard" such as PET scanning is indicated but is both costly and difficult. For practical usage, a comparison to clinical scoring of neurological deficit is required.

As expected, the site of the perfusion defect on SPECT scan images agreed with clinical signs and symptoms in our study. There was no correlation between clinical and semi-quantitative score changes over the 30 day trial period (range of correlation coefficients = 0,08 - 0,19). Statistically it was found that actual individual semi-quantitative methods did not always correlate with the clinical score at that time. This seemed to indicate the necessity of a multiple regression model. The best correlation was seen on day 30 using the multiple regression model described in Chapter 4, where 86% of the clinical score was explained by the model, and where both the defect volume index and the thirty degree segmental analysis score (the least observer dependant method) were of importance.

Some technical and physiological drawbacks to semi-quantification have become apparent, which may result in non-correlation of semi-quantitative values with clinical scores.

1. In all the methods except the thirty degree segmental analysis, a degree of observer experience was required to locate the exact site and outline of the lesion and region of interest used for day 1 and subsequent sans. Region of interest count densities may vary slightly depending on the exact location of the ROI. This problem could be alleviated somewhat by having an automatic edge detection of the hypoperfused area with a threshold measurement. Mountz et al in 1989 defined lesion margins where uptake values (counts/pixel) increased to within 10% of those in the contralateral region of the uninvolved hemisphere, as determined by moving a horizontal profile through the portion of brain containing the lesion (88). This lesion region of interest was mirrored on the contralateral hemisphere.

2. All the semi-quantitative methods used, except the defect volume index and area ratio method, require comparison of the lesion to an assumed normal area.

   Intraindividual variation of mean hemispheric blood flow was reported as 0,3% ± 15% by Podreka (60). This implies that the assumed normal cerebral hemisphere blood flow may not remain a constant during a trial period for serial scan comparison.

   The assumed normal hemispheric blood flow may be depressed by variable amounts in acute stroke patients, which may be due to transcallosal diaschisis (26). The contralateral cerebral blood flow has been reported as being significantly decreased in 56% of patients (89). Should this depression of contralateral blood flow not remain constant throughout the trial period,

semi-quantitative measurement comparisons would be inaccurate.

3. Langen et al have suggested that a lesion to cerebellum ratio is a superior method of semi-quantitation as the contralateral assumed normal hemisphere contains variable amounts of grey and white matter and count densities in a region of interest may vary from area to area (56). The cerebellum represents a homogenous reference region.

   The cerebellar hemisphere with the highest counts should be used if crossed cerebellar diaschisis is present, with the same cerebellar hemisphere being used in subsequent scans, for the lesion to cerebellar count density ratio method.

   However, a normal right to left cerebellar ratio can range from 0,95 - 1,05 which is a variation of 10% (63). A difference of more than 10% is required before crossed cerebellar diaschisis can be determined. This variation in uptake could also affect serial measurements when mild strokes are imaged.

4. The reference region cerebral blood flow may be altered by distant functional depression of regional cerebral blood flow (transcallosal diaschisis), occult structural disease or systemic determinants of regional cerebral blood flow. If contralateral values used as normal reference points were already low, the decrease in the infarcted hemisphere would be less marked (89).

5. Patients with severe bilateral flow decrease may still be identified as normal (89) as was the case in the multiple infarct patient in this study.

6. For correlation with clinical scoring, the clinical score must accurately reflect the type of infarction present. For example, the semi-quantitative values did not agree with the clinical score for the patient with the posterior cerebral artery territory infarct. Posterior cerebral artery territory infarcts are not fully represented on the Canadian neurologic rating scale. It has been suggested that two types of scores could be used to determine stroke severity, and may be different at entry to the trial from outcome of the trial (11). For example, initial severity scored with regard to prognostic factors at entry, and outcome scores depending on functional performance as well as neurologic examination.

   A small infarct located in the internal capsule may produce striking clinical deficit (15) but be represented only as a mild semi-quantitative score in our observation.

7. Nishizawa found that in lesions with regional hypoperfusion of only 10 - 20% less than the non-affected area, decreased cerebral perfusion may not be clearly seen (80). Differences of less than 20% were seen in our study, in 11 of 19 patients with the lesion to normal count density method, and in 14 of 19 patients using the thirty degree segmental analysis method, both of which are side to side comparisons.

   Contrast between high and low flow areas seen with HMPAO is less than expected due to preferential washout from high flow areas (67). This may affect semi-quantitative serial measurements if washout differences do not remain constant.

8. Clinical changes such as the presence of luxury perfusion, the appearance and resolution of cerebral oedema and the development

of collateral flow (63) will all influence the correlation between clinical scores and semi-quantitative methods. Better correlation may be seen when the clinical picture has completely settled down, as indicated in our study by the improved correlation at thirty days.

A varying degree of involvement of clinically silent regions of the brain (16) may also cause problems when relating semi-quantitative scores to clinical scores.

9. Technical problems may include errors in head position, errors in attenuation correction (89), lesion margin detection and region of interest positioning.

10. Hayashida et al have reported the problem of masking reduced cerebral blood flow by an increase in regional cerebral blood volume in early HMPAO images in regions of mild cerebral ischaemia. Leakage of HMPAO is seen in the late image at 5 hours in these regions and the filling out phenomenon was attributed to a significant reduction of blood activity of the radiopharmaceutical. This phenomenon was observed in 7 of 21 cases studied with cerebrovascular disease (90). The blood pool image may interfere with the detection of true regional cerebral perfusion deficits on early images.

A decrease in cerebral blood flow (CBF) can initially be prevented physiologically by increased cerebral blood volume (CBV) (91). This cerebral vascular reserve may affect initial semi-quantitative measurements. Flow-volume-cerebral vascular reserve imaging using HMPAO and Technetium pertechnetate with pyrophosphate was found to increase sensitivity in cerebrovascular disease by 48% as compared to mere cerebral flow imaging (59, 91). A decrease in cerebral perfusion pressure may

be compensated for by an initial increase in cerebral blood volume. The smallest volume from which accurate CBF/CBV ratios can be derived is about 15 ml. Knapp et al found that the CBF of affected territories was 85 ± 19% when related to the nonsymptomatic contralateral side (100%), using I-123 iodoamphetamine. CBF/CBV ratios were 60 ± 32% showing a more sensitive approach to cerebrovascular disease (61).

The above problems are highlighted by the fact that on statistical analysis of our data, a correlation between semi-quantitative analysis scores and clinical scores was only of significance once the data had been 'cleaned", that is, when multiple infarcts, posterior infarcts and restrokes were excluded. Correlation was still poor on day 10 which may be due to the presence of luxury perfusion or possibly due to a state of clinical flux as described above.

Misleading results can occur if intra-individual standardization is used in patients with cerebrovascular disease. Inter-subject comparison of semi-quantitative regional cerebral blood flow values may, however, be difficult due to physiologic variability of regional cerebral blood flow, as has been seen with PET scanning quantification (89).

Changes from day 1 to day 30 on semi-quantitative analysis of SPECT scans reflected clinical improvement or deterioration poorly in this study (ranging from 27,8% of cases in the thirty degree segmental analysis method to 50% in the lesion to cerebellar count density ratio method). Changes in scan appearance and clinical improvement may correlate better when follow up at one year is performed or where a larger study sample is possible.

Smith et al found some correlation between the size and site of perfusion deficits on HMPAO scans and clinical signs in the first 3 days after a stroke (no correlation factor given). However, in this study, scans appear to have been visually assessed in a wide range of infarction sites. When 12 patients were again assessed at day 14, the clinical progress was not accurately reflected by changes on the scan (92).

Yeh found that complete or partial clinical remission does not always accompany resolution of a perfusion defect on HMPAO scans when scanned on days 1, 14 and 21. The authors concluded, however, that serial scans provided an objective visual assessment of perfusion changes (93).

E. PROGNOSTIC VALUE OF SCORES

Simple correlations between day 1 SPECT semi-quantitative scores and day 30 clinical scores were not satisfactory. However, a multiple regression model utilizing the day 1 Defect Volume index, day 1 area ratio method score and the day 1 thirty degree segmental analysis score was correlated with day 30 clinical scores (adjusted R squared = 0,48, p = 0,008). It may be that with a larger sample size or longer follow up of patients this predictive equation could be found to correlate with greater accuracy. Individual method correlations may also improve.

Clinically, poor prognostic features that can be detected soon after stroke onset are :-

- Impaired consciousness.
- Dense hemiplegia.
- Failure of conjugate ocular gaze towards the side of limb weakness.
- Overt unconsciousness

- Bilateral plantar response.
- High haematocrit at hospital admission.
- Underlying medical complications, especially the co-existence of cardiac disease and renal insufficiency.

These signs usually indicate infarction of the whole of a middle cerebral artery territory, and these patients are prone to develop severe cerebral oedema. (16, 24, 52, 94, 95)

The outcome of a major cerebrovascular event is difficult to establish and depends on the type, extent and localization of the lesion (63) as well as the clinical state of the patient (degree of neurological deficit) (52).

Several authors have found that outcome can be predicted from clinical scoring. The Canadian neurological score used in this study is related more to actual neurological deficit than to daily living activities or rehabilitative factors. However, there was a good correlation between day 1 and day 30 clinical scores ($r = 0,94$, $p = 0,00$). The Scandinavian Stroke study group found that neurologic scores at entry to the multicentre haemodilution trial strongly predicted mortality and neurologic performance at 3 months using a 0 - 48 point scale (including activities of daily living) (94).

Using a prognostic clinical score of 100 points in 200 unselected patients with a first episode of acute cerebrovascular disease, Britton correctly predicted mortality and functional outcome in 60%. It is suggested that the clinical state of the patient is more important for the immediate prognosis than the nature of cerebral damage, and that a subjective evaluation of the overall clinical state as well as neurologic scoring is required (52).

Prescott et al, using a multiple regression formula, could clinically predict independence or functional outcome, which is the optimal end-point in stroke trials, in 75% of cases in week 4 post-infarction, in patients entered in a rehabilitation program. This may be of value in determining those with little chance of responding to rehabilitation (6).

Frithz et al, in 344 patients, found that the level of consciousness and a calculated score based on neurological symptoms on admission had the highest predictive value. Using this score it was possible to predict the outcome in about 85% (95).

The above reports indicate that there are many factors of possible importance for stroke outcome and that the situation calls for a multivariate analysis of prognostic features. The same was found in our study for semi-quantitative analysis of prognostic features.

It is important to emphasize that the clinical scoring in the quoted papers, as occurred in our pilot study, was performed by specialised units with experienced observers. This might not be the case in a routine clinical setting.

Signs on CT scan carrying a bad prognosis in connection with major stroke symptoms are :-

- Mass effect.
- Involvement of the internal capsule.
- Right parietal lesions (rather than left sided lesions).
- Dense middle cerebral artery sign in the first 24 hours (an early warning of a large infarction, brain oedema and poor prognosis).

- Large volume of infarction on CT scan.
  (16, 96, 97)

Valdimarsson et al found that a positive correlation existed between the state of patients on admission and the lesion volume on CT scanning (in 69 patients), but that the lesion volume was of low prognostic significance when initial disability was slight [16].

In our study, it was found that a multi-factorial equation is required to predict Day 30 clinical scores from Day 1 SPECT semi-quantitative scores using HMPAO.

Lee et al studied 16 patients with acute cerebral infarction of middle cerebral artery distribution with I-131 iodoamphetamine and PET scanning to assess the predictive value of the perfusion defect size and lesion count density, with respect to clinical outcome. Scans were performed in the first week with a mean follow up of 19,4 months (much longer than in our study). Lesion size and decreased count density correlated well with presenting clinical severity but not with outcome It is suggested that lack of a prognostic index may be because areas of ischaemia are also being imaged which do not necessarily result in cell death (62). This may also be a factor with HMPAO.

Launes et al using HMPAO to define a defect volume index (as used in this study) found a significant correlation between the clinical outcome and the Defect Volume index. This was best seen in middle cerebral artery infarcts, with no prognostic correlation seen in posterior cerebral artery infarcts. 64 patients were included in the study, but were initially scanned between 1 to 46 days after stroke onset with clinical follow up varying from 6 - 412 days (24). Although the DV index in our study was found to be an important factor in the multiple

regression model defined for prediction of day 30 clinical scores, simple correlation of the day 1 index with the day 30 clinical picture was not satisfactory. This may be due to the smaller sample size, shorter follow up and more rigid timing of scans in our study.

Costa reported a method of quantifying washout of Tc-99m HMPAO using a ratio of abnormal brain to cerebellar activity on 15 minute and 5 hour scans. The washout activity was much higher in the abnormal area as compared to other regions of the brain. This washed out activity was probably from the capillary bed, as HMPAO in the brain cells is retained. This washout could, therefore, agree with an area of increased 'vascular reserve' with high blood volume. Incomplete washout would indicate the presence of viable brain tissue. It is suggested that a prognostic index may be devised if this method is used (63).

Semi-quantitative methods evaluating the ischaemic penumbra (viable but non-functional tissue adjacent to the ischaemic infarct (23)) may have more prognostic and therapeutic value than simple determinations of the perfusion defect on HMPAO imaging. Restoration of blood flow to such areas may restore normal function and facilitate recovery. Wise et al using PET scanning to determine oxygen extraction following acute strokes found that the period after the onset of the stroke when tissue damage remains potentially reversible is between 24 - 48 hours (22).

With this aim in mind, Mountz et al found that with regression analysis, complete or near complete recovery at one year was seen in patients who at initial evaluation had a HMPAO SPECT lesion that was 3,9 $\pm$ 0,9 times greater than the CT scan lesion indicating a large area of ischaemic penumbra. Patients with some or no recovery had a lesion which was 1,4 $\pm$ 0,3 times larger on CT scan than on SPECT scan (i.e. almost the same size defect). Comparative analysis of CT and HMPAO SPECT scans are useful in prognosis (88, 98). A high ratio between the functional

defect seen on SPECT scan and the anatomical defect seen on CT scan indicates viable but dysfunctional tissue with a capacity for restoration and therefore better clinical recovery. The larger the log (SPECT divided by CT) result the greater the likelihood of good clinical outcome.

Raynaud et al using I-123 IMP found two differing areas of infarction; a central area of persistent decrease of IMP uptake and hypodensity on CT scan, and a peripheral area with a filling in of IMP at 5 hours and no CAT hypodensity. Neurological status correlated only with peripheral area volume (not central area volume) (78).

Moretti found that the size of redistribution of I-123 IMP between early (1 hour) and delayed (4 hour) scans significantly correlated with the three month clinical outcome, whereas the value of hypoactivity on early SPECT only, did not. The higher the redistribution amplitude, the better the clinical outcome (99).

Current literature and our observations appears that the long-term prognosis of stroke patients depends mainly on the degree of ischaemic damage done to the brain tissue (100). Partial ischaemia may result in the loss of normal neuronal function without inducing the changes that result in irreversible damage for some hours (22).

CHAPTER 6

CONCLUSION

CONCLUSION

In this study the following trends could be identified:-

1. SPECT cerebral perfusion studies using Technetium-99m HMPAO are of value on day 1, for the early localization of acute ischaemic cerebral infarction. Reversibly damaged brain tissue may be identified in conjunction with CT scanning, by defining the ischaemic penumbra.

   SPECT scan images represent functional changes in blood supply and their use may help the physician to better understand the pathophysiologic basis of brain infarction.

2a. The semi-quantitative SPECT scores correlated well with each other on days 1 and 30. Poor correlation is seen on day ten.

b. Semi-quantitative score changes from day 1 to day 30 did not agree with clinical score changes. This may not be true for long term follow-up scans.

c. No correlation between semiquantitative method scores and clinical scores was seen on day 1. On day 30, only the area ratio method showed significant correlation with day 30 clinical scoring.

d. Multiple regression models are required for comparison of semi-quantitative and clinical scores. In our study, multiple regression analysis was only satisfactory on day 30.

3. A multiple regression model can be devised to predict outcome at day 30, using the day 1 Defect Volume index, day 1 area ratio score and day 1 segmental analysis score.

This suggests that a better prognostic correlation may be achieved with a larger sample size and longer follow up period.

A trend is shown that SPECT scans at day 1 are valuable in the prediction of the day 30 clinical score.

APPENDIX

PERCENTAGE POSITIVE SCANS SEEN WITH EACH SEMI-QUANTITATIVE METHOD AND WITH VISUAL ANALYSIS

METHOD	DAY 1	DAY 10	DAY 30
Defect Volume Index	89,5%	88,9%	78,6%
Side to side count density comparison	89,5%	88,9%	78,6%
Percentage of cerebellar count density	89,5%	83,3%	78,6%
Segmental analysis	63%	66,7%	64,3%
Area ratio method	89,5%	88,9%	78,6%
Visual analysis	84%	83,3%	78,6%

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