Changes in cerebral tissue perfusion during the first 48 hours of ischaemic stroke: relation to clinical outcome

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Abstract

***Background*—One major therapeutic strategy to minimise the extent of infarction after ischaemic stroke is to improve early reperfusion using thrombolytic agents. However, reperfusion may be hazardous and the period during which reperfusion may have a beneficial effect on tissue and clinical outcome is not known.**

***Methods*—Fifty three patients were studied with serial cerebral perfusion (^{99m}Tc-HMPAO SPECT) during the first 48 hours of ischaemic stroke to determine if changes in tissue perfusion during this time were prognostically significant. Single and multiple linear regression non-parametric analyses were used to include other factors during the same period which may influence outcome.**

***Results*—In univariate analysis age, neurological score at admission, SPECT perfusion defect size in the first 24 hours, and percentage change in cerebral tissue perfusion at 24–48 hours (all $P < 0{\cdot}01$) correlated significantly with the Barthel score at three months. In multiple linear regression analysis only age ($P < 0{\cdot}01$) and percentage change in cerebral tissue perfusion at 24–48 hours ($P < 0{\cdot}01$) provided independent prognostic information at three months.**

***Conclusions*—changes in cerebral tissue perfusion during the first 48 hours of ischaemic stroke are significant outcome predictors and therapeutic efforts aimed at increasing perfusion during this period seem to be justified.**

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Keywords: reperfusion; computed tomography; ischaemic stroke; stroke outcome; prognosis

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The rationale for therapeutic intervention in acute ischaemic stroke with thrombolytic agents is to reopen occluded vessels and to reperfuse ischaemic tissue,[1] leading to salvage of the ischaemic penumbra. However, there is considerable controversy concerning the prognostic value of reperfusion in acute ischaemic stroke. Reperfusion may be complicated by haemorrhagic transformation, oedema, or reperfusion injury, and the duration of the time window in humans during which reperfusion may be accompanied by clinical recovery has yet to be determined.[2] In addition, salvage of the ischaemic penumbra may not appreciably reduce infarct size or improve outcome if the penumbra is confined to a narrow rim of tissue.

Reperfusion in the first 24 to 48 hours of cerebral ischaemia has been found in a limited number of SPECT and PET studies with conflicting findings. In some reperfusion was associated with a beneficial clinical outcome,[3–5] in one other the association was variable,[6] and in another there was no clinical benefit.[7] Reasons for the conflicting findings may include: (*a*) small patient numbers,[5–6] (*b*) different degrees of nutritional and non-nutritional reperfusion, (*c*) lack of semiquantitative analysis of data,[6] (*d*) inference that reperfusion had occurred in individual patients based on a single scan only,[3] (*e*) different time windows studied ranging from 18 hours[3] to 48 hours,[4–5 7] and (*f*) failure to take into account other factors which may influence outcome such as age and neurological deficit.[8–13]

To clarify this important issue, we have prospectively studied 53 patients with sequential SPECT within 48 hours of acute ischaemic stroke and then used multiple linear regression non-parametric analysis to account for other factors which may influence clinical outcome.[14]

Method

STUDY ESTABLISHMENT

The study was conducted prospectively from April 1991 through to October 1993. Patients admitted to the Austin Hospital stroke unit[15] with the sudden onset of a focal neurological event consistent with ischaemic stroke, who underwent serial ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime) SPECT studies during the first 48 hours of ischaemia (see below), who had abnormal perfusion images, and who did not have recurrent stroke during the follow up period, were included in the study. All patients had a non-contrast brain CT on admission and after seven days, or earlier if clinically indicated. Patients with reversible ischaemic neurological deficits (defined as lasting longer than 24 hours) were included if their perfusion study at admission was abnormal. Patients with prior stroke were included if they had made a full functional recovery and the current ischaemic locus was in a site remote from the current site. If the neurological

deficit was first noticed on awakening, the time of onset was back dated to the time the patient was last clinically normal. Some patients were participants in the pilot and randomised phases of the Australian streptokinase trial.[16]

CLINICAL ASSESSMENT

The validated modified Canadian neurological score (MCNS)[17] was used as the measure of neurological disability on admission. Outcome assessment was based on the Barthel index[18] at three months. This weighted disability scale has been extensively validated.[19] The maximum score of 100 indicates full functional independence. Deceased patients were given a score of zero. Other clinical variables recorded were age, sex, and history of hypertension or heart disease.[8] "Hypertension" was defined as a medical history of treated hypertension. Patients who were hypertensive at the time of presentation were not classified as "hypertensive" as patients may be hypertensive in the acute phase of ischaemic stroke.[8 20] "Heart disease" was defined as cardiac abnormalities based on information obtained from the medical history, clinical examination, and results of ECG and echocardiogram recordings. These included conditions such as atrial fibrillation, rheumatic valvar heart disease, ischaemic heart disease, and cardiomyopathy.

FUNCTIONAL IMAGING

^{99m}Tc-HMPAO SPECT (15–25 mCi, Ceretec-Amersham, Australasia) was performed with a rotating General Electric 400 AC Starcam camera (Milwaukee USA) during the working hours of the nuclear medicine department. Sixty four images were acquired over 360° on a 128 × 128 matrix with a pixel size of 3·1 mm and acquisition time of 15–30 s/ frame. After scatter correction and attenuation correction using an attenuation coefficient of 0·15,[21] slices one pixel thick were reconstructed on a 64 × 64 matrix. Image resolution measured in a resolution phantom was 12 mm at full width half maximum.

Repeat ^{99m}Tc-HMPAO and scanning were performed about 24 hours after the initial ^{99m}Tc-HMPAO study to measure the extent of perfusion change. The dose, time of injection, time of scanning, head position during scanning, and count rate were matched as closely as possible for each scan. No correction was made for residual activity that may have still been present at the time of the second study.

Semiquantitative volumetric analysis of size and severity of the perfusion defect was performed using a previously described semiautomated and validated analysis.[4] The number of transaxial slices over which the perfusion defect extended was defined initially. The slice with the largest perfusion defect was selected and an elliptical region of interest was placed over the hypoperfused region; as the analysis was automated, the same region of interest was subsequently used to analyse the remaining transaxial slices to avoid manual region of interest placement. On each transaxial slice the region of interest was mirrored from the hypoperfused hemisphere on to the contralateral hemisphere and the pixels in the affected hemisphere which had a count rate of < 12% of the mirror pixel on the normal side[22] were identified. A lower cut off value (about 50% maximum count in the study) was set to eliminate asymmetries arising from the white matter and ventricles. A volumetric perfusion defect index was then calculated in which each voxel was weighted in proportion to the severity of hypoperfusion.

The formula (volume day 1-volume day 2 /volume day 1) × 100 was used to calculate percentage change in cerebral tissue perfusion. Regions of hyperperfusion were defined as (maximum) 100% reperfusion in view of the report of HMPAO hyperfixation relative to cerebral blood flow.[23] If the perfusion defect increased in the second study, a negative reperfusion value was applied.

STATISTICAL ANALYSIS

As the Barthel score provided qualitative ranked data and was not normally distributed at three months, single and multiple linear regression analyses for non-parametric variables[24] (χ^2) were used. The relation between the Barthel score at three months and the following covariates were analysed: age, sex, history of treated hypertension, heart disease, neurological score at admission, size of the perfusion defect on the SPECT study in the first 24 hours, and percentage reperfusion at 24 to 48 hours. Results were considered statistically significant at $P < 0·05$.

Table 1 Demographic details of the 53 patients in the study

Variable	
Age (y)	69·3 (1·6)
Sex (M/F)	23/30
Admission neurological score*	4·3 (0·4)
Hypertension (n)	33
Heart disease (n)	35
Perfusion defect size in first 24 hours (cm^3)	64·3 (7·2)
Percentage perfusion change at 24–48 hours (%)	30·6 (7·0)

Results are mean (SEM) or numbers of patients.
*Modified Canadian neurological score.

Results

ALL PATIENTS

During the study period 53 patients fulfilled the inclusion criteria (table 1). Twenty three additional patients were excluded because they had normal perfusion studies (21 patients) or had recurrent stroke during the follow up period (two patients). The mean time of the first ^{99m}Tc-HMPAO injection was 8·2 (SD 0·8) hours after the onset of symptoms, and the mean time of the second injection was 32·5 (SD 1·1) hours. Eight patients were treated with intravenous streptokinase during the pilot phase of the Australian streptokinase trial.[1] Thirteen patients were participants in the blind phase of the trial (treated with either placebo or intravenous streptokinase) and seven patients were treated with intra-arterial streptokinase.[16] At three months 13 patients had died and 14 patients had full functional recovery (Barthel score of 100).

UNIVARIATE ANALYSIS

In univariate analysis, the following variables correlated significantly with the Barthel score at three months: age, neurological score at admission, perfusion defect size on the SPECT study in the first 24 hours, and percentage change in cerebral tissue perfusion at 24 to 48 hours (all $P < 0.01$, table 2). The correlation of heart disease with functional outcome at three months approached significance ($P = 0.07$).

MULTIPLE LINEAR REGRESSION ANALYSIS

In multiple linear regression analysis age ($P < 0.01$) and percentage change in cerebral tissue perfusion at 24 to 48 hours ($P < 0.01$; table 3) provided independent prognostic information at three months. The admission neurological score ($P = 0.07$) approached significance as an independent outcome predictor at three months. The size of the perfusion defect on the SPECT study in the first 24 hours was not an independent outcome predictor, even after the analysis was performed with percentage change in cerebral perfusion excluded. The time of the first ^{99m}Tc-HMPAO injection was not a significant outcome predictor when it was included in the univariate and multivariate analyses.

Discussion

The finding that cerebral perfusion changes on ^{99m}Tc-HMPAO SPECT in the first 24 to 48 hours are powerful independent predictors of outcome, strongly supports the notion that an early reperfusion window exists in humans. This has important implications for therapeutic trials for acute stroke. It is most likely that when an improvement in perfusion occurred on the second study, there had been embolic clearing or recruitment of the collateral circulation. However, it is acknowledged that many factors may affect ^{99m}Tc-HMPAO distribution including rheological factors, blood pressure, tracer redistribution depending on the time that scanning was performed after radiopharmaceutical administration, drugs, or altered glutathione concentrations.

The exact time window during which purely nutritional reperfusion occurs has yet to be determined and is likely to be shorter than 24 to 48 hours and to be dependent on the combination of the duration and severity of ischaemia.[25] In this study it was not possible to determine the exact time window during which purely nutritional reperfusion occurred; the time of the first ^{99m}Tc-HMPAO injection was not an independent predictor when it was included in the analysis. Based on experimental evidence in animals, severely ischaemic tissue, in which ionic disruption has occurred, may be viable for less than one to two hours.[26] Mildly to moderately ischaemic tissue, in which electrical function is disturbed without loss of ionic homeostasis—"the ischaemic penumbra"[27]—may be viable for up to three hours in rat models of middle cerebral artery occlusion[28] and six to eight hours in baboons and squirrel monkeys.[2 25 29] Evidence from studies of stroke patients, using PET, suggests that in some patients ischaemic tissue may be viable for up to 48 hours or longer, based on the finding of the "misery perfusion" pattern of blood flow and metabolism.[30–31]

Improved outcome and restriction of infarct size has been reported in patients in whom middle cerebral artery recanalisation, measured by transcranial doppler ultrasonography, occurred within eight hours in the presence of a good collateral circulation.[32] In patients with middle cerebral artery reopening within the first 24 hours, reduced frequency of haemorrhagic transformation and oedema have been described.[33] However, these studies did not use multiple linear regression analyses to account for other variables which may affect outcome and it is uncertain as to whether there is always a direct relation between arterial recanalisation and tissue reperfusion.

A study of shorter time windows using SPECT and other functional imaging techniques such as PET and echoplanar perfusion gadolinium enhanced imaging[34] may allow a more precise quantification of the extent of the reperfusion time window. In such studies, measurements of the severity of blood flow reduction, together with measurements of tissue salvage, by coregistering structural and functional studies, may provide valuable additional information.

An important feature of this study was the use of multiple linear regression analyses to compare the prognostic value of SPECT measurements with established clinical measures.[8–13] A major difficulty with such analyses is that the outcome variable, the Barthel score at three months, is a qualitative ranked variable and is not normally distributed, as at three months many patients have died (score 0) or are functionally independent (score 100). For this study a non-parametric multiple linear regression analysis was used,[23] which may be applied to future outcome studies.

The clinical variables of age, sex, admission neurological score, hypertension, and heart disease were included in the analysis as they

Table 2 Univariate analysis (non-parametric): correlation between variables and the Barthel score at three months

Variable	*χ^2 Statistic*	*P value*
Age	10·37	< 0·01
Sex	1·34	0·25
Admission neurological score*	12·95	< 0·01
Hypertension	0·01	0·93
Heart disease	3·39	0·07
Perfusion defect size in first 24 hours	7·94	< 0·01
Percentage perfusion change at 24–48 hours	17·44	< 0·01

*Modified Canadian neurological score.

Table 3 Multiple linear regression analysis (non-parametric): correlation between the variables and the Barthel score at three months

Variable	*χ^2 Statistic*	*P value*
Age	7·70	< 0·01
Sex	0·19	0·66
Admission neurological score*	3·40	0·07
Hypertension	0·03	0·86
Heart disease	0·01	0·92
Perfusion defect size in first 24 hours	1·24	0·27
Percentage perfusion change at 24–48 hours	16·13	<0·01

*Modified Canadian neurological score.

have been shown to provide prognostic information[8 9] for acute and late outcome.

Perfusion defect size by SPECT was also included as some studies have shown a strong correlation with outcome in the past[35] although not universally.[36 37] A number of explanations may exist for this, including different methods for assessing defect size, different radiopharmaceuticals, and different times of study after stroke onset.

In this study, a correlation was found between the SPECT defect size in the first 24 hours in univariate analysis but this was not sustained in multiple linear regression analysis, even after reperfusion was removed as one of the covariates. This is probably because of a close relation between neurological score at admission and the size of the perfusion defect in the first 24 hours.

Because serial changes in cerebral perfusion within the first 24 to 48 hours are of independent prognostic value and because perfusion defect size in the first 24 hours is not, we hypothesise that haemodynamic changes occurring during this time may significantly affect outcome and possibly account for the disparate results between the studies described earlier.

In the setting of acute stroke therapies, functional imaging techniques may allow the reperfusion and therapeutic windows to be determined in humans. Given the strong predictive value of serial cerebral perfusion measurements within the first 48 hours after ischaemic stroke, therapeutic efforts aimed at further improving perfusion more during this time seem to be justified.

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