British Journal of Psychiatry (1989), **154**, 790–796

Cerebral Vascular Transit Time in Alzheimer's Disease and Korsakoff's Psychosis and its Relation to Cognitive Function

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The cerebral vascular transit time of 17 patients with pre-senile dementia of the Alzheimer type (ATD), nine abstinent patients with alcoholic Korsakoff's psychosis (KOR), and ten age-matched controls was determined by the bolus intravenous injection of pertechnetate. A gamma camera was used to estimate the median transit time (MTT) of the radioactive bolus in a planar (non-tomographic) projection normal to the vertex. The spread of the bolus arriving at the aortic arch was measured independently by a single external detector over the chest, and correction made for the transit time of this input function in calculating the net MTT for the head. Both ATD and KOR groups showed lengthened net MTTs, compatible with reduced cerebral blood flow, and which were correlated with reduced cognitive function. It is concluded that the method employed gives a simple, inexpensive estimate of function-related blood flow to the brain in pre-senile dementia.

Under most circumstances cerebral blood flow (CBF), perfusion, and metabolism, as evidenced by oxygen consumption and glucose intake, are closely linked (Roy & Sherrington, 1890; Frackowiack *et al*, 1981). Therefore, a measurement of cerebral perfusion may be used as an index of metabolism, which is itself related to functional activity, even to thinking (Roland *et al*, 1987). Earlier evidence of an association between cerebral metabolism, perfusion, and cognitive defects in dementia was presented by Gustafson & Risberg (1974), and was based on the estimated CBF by intracarotid injection of xenon-133. They concluded that there was an approximate relationship between the cognitive reduction and the decrease in hemispheric perfusion, especially in grey matter. Regional abnormalities of perfusion were associated with specific cognitive functions, in the same way as were focal brain lesions.

However, the intracarotid injection method was of limited clinical applicability, especially in routine diagnosis and follow-up of patients suffering from dementia. Intravenous (Lassen & Ingvar, 1972) or inhalational techniques (Mallett & Veall, 1963) for the administration of the inert gas were more acceptable, and have been used in dementia (Ingvar, 1982), but these approaches still require the head to be kept immobile for up to 15 minutes, which can present difficulties. Positron emission tomography has been shown to provide high-quality, regional, three-dimensional CBF measurements, but it is available in only a few centres. There remains a continuing need for simple and cheap methods for estimating cerebral perfusion in dementia and other brain diseases.

The aims of the present study were twofold: firstly, to assess the utility of a relatively simple and rapid method of measuring cerebral perfusion, using transit time of pertechnetate, in demented patients, and secondly to investigate the association between transit time and cognitive impairment. Transit time methods were originally developed by cardiologists to measure cardiac output (Thompson *et al*, 1964) but can, in principle, be applied to any determination of tracer dynamics (Davenport, 1983; Merrick, 1984).

Method

Patients and controls

None of the patients or controls had taken psychotropic medication for at least six months before the study. Informed consent was obtained in each case, and where there was doubt about a patient's understanding, the agreement of a close relative or independent nurse was sought before the patient was included. The study was approved by the Ethics of Medical Research Sub-Committee for Psychiatry and Psychology of the Royal Edinburgh Hospital and ARSAC. Groups were matched for age.

Alzheimer-type dementia (ATD)

Seventeen patients with pre-senile ATD were studied (three men, 14 women, aged 52–66 years, mean 59 years). All met criteria for probable Alzheimer's disease (McKhann *et al*, 1984). Briefly, these include:

(a) onset of symptoms before the age of 65, with dysmnesia as the initial feature
(b) steadily progressing dementia
(c) absence of a history suggestive of another type of dementia

(d) absence of focal neurological signs and hypertension
(e) computerised tomography scan normal or showing only cerebral atrophy and no additional pathology
(f) EEG showing no focal abnormalities
(g) normal haematological, biochemical, and clinical investigations of cerebrospinal fluid
(h) normal ECG.

Alcoholic Korsakoff syndrome (KOR)

Nine patients with KOR were studied (six men, three women, aged 58–73 years, mean 62 years). All subjects except one were resident in a psychiatric hospital and met the following diagnostic criteria:

(a) definite history of prolonged alcohol abuse, usually in excess of 20 years
(b) severe anterograde memory deficit
(c) no history suggestive of progressive dementia
(d) definite history of past episodes of either acute confusion or Wernicke's encephalopathy (with or without peripheral neuropathy)
(e) EEG showing no focal activity
(f) normal haematological and biochemical tests
(g) no alcoholic beverage taken for at least six months.

Controls

Ten control subjects (one man, nine women, aged 50–76 years, mean 61 years) were recruited from local voluntary groups, and one was a patient's spouse. All volunteers were in good physical and psychiatric health.

CAMCOG

The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) was developed for diagnosis and measurement of dementia (Roth *et al*, 1986). The CAMDEX includes a section for assessment of cognitive function (CAMCOG), which consists of 14 of the 19 Mini Mental State Examination (MMSE) items (Folstein *et al*, 1975) plus 43 items covering additional aspects of cognitive function. The CAMCOG subscores used in this study were: orientation, language (which includes motor and verbal comprehension, expression, reading, and writing), total memory (comprising remote, recent, recognition, and recall), attention, and praxis. Total CAMCOG score (CAMTOTAL) was used as a global measure of cognitive function.

Measurement of cerebral blood flow

Almost a century ago, Stewart (1894) pointed out that the blood flow to any organ could be calculated if the volume of blood within it and the mean (more correctly median) transit time of a tracer through it could be measured. Formal proof of this relationship was provided by Zierler (1962).

The vascular median transit time (MTT) is the volume of blood in the organ under investigation divided by the rate of blood flow through it. The ratio blood flow:blood volume (1/MTT) is also known as the perfusion reserve (Gibbs *et al*, 1984), and is the most sensitive indicator of the extent to which cerebral perfusion is being maintained by reflex vasodilatation. It has been shown that transit times longer than 10 seconds indicate impending failure of the normal compensatory mechanisms (Powers *et al*, 1984).

The first passage of radioactivity (i.e. without recirculation) through a blood vessel can be described by a gamma-variate function of the form:

$$C(t) = k(t - T)^{\alpha}e^{-(t-T)/\beta}$$

where $C(t)$ is the tracer concentration (e.g. in counts/min) at time t after injection, T is appearance time (i.e. the time at which counts are first detected over the region of interest), and k, α, and β are constants. The MTT of the activity at any particular detection point can be estimated using $\text{MTT} = \beta(\alpha + 1)$ (Thompson *et al*, 1964; Davenport, 1983).

Measurements of MTT for cortical blood flow in resting conditions were undertaken in the Department of Nuclear Medicine, Western General Hospital, Edinburgh. The patient was asked to lie supine on a high couch; an 18-gauge Venflon cannula was inserted into the right antecubital vein and used for injection of the radionuclide tracer. The patient's head was placed in a standard position such that the face of the gamma camera was parallel to the plane between the outer canthus of the eye and the external auditory meatus. Data collection was initiated when 700 MBq activity of sodium pertechnetate (^{99m}Tc) was injected rapidly using the cannula, and the first pass of the activity through the brain was recorded.

To measure and correct for dispersion of the bolus reaching the head, a scintillation detector (20 mm diameter) was positioned over the angle of Louis, pointing towards the base of the heart, and the passage of activity measured below the probe. Data were collected using a BBC microcomputer, and displayed as count rate versus time. By fitting a gamma-variate function to the aortic activity curve, the MTT of what is defined as the input function (IF) was determined.

The MTT data for estimation of blood flow in the cortex was collected using a high-sensitivity collimator. In order to improve the count density and to produce a manageable number of frames for processing, the total first-pass curve is identified, and frames summed to produce a 20-frame condensed view of the first pass. This condensed view is then corrected for dead-time losses, smoothed, and analysed to find the MTT of the curve for each brain pixel. By subtracting the MTT of the IF from each brain-pixel MTT, we can derive net MTT (Davenport, 1983; Merrick, 1984), which can be used to construct a functional cortical image.

The data from this image can be examined as net MTT for right (RCx) and left (LCx) sides of the midline, or by subdividing each side of the image into four equal regions of interest, A, B, C and D (Fig. 1). We assumed that areas B and C will reflect activity in underlying central and parietal cortex, while A and D will reflect more frontal and occipital activity, respectively. However, a planar system of this sort does not allow precise identification of anatomical regions. In this study, regions of interest A, B and C are emphasised, as the posterior region (D) may be contaminated

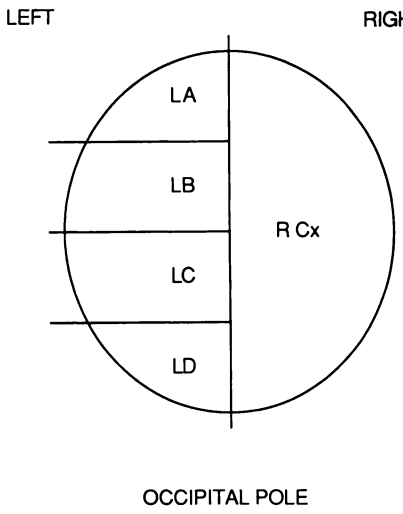

FIG. 1 Diagram showing the position of regions of interest in relation to the cortical image.

by neck blood flow. All data processing was performed by an investigator blind to diagnosis.

Statistical analysis

Kruskal–Wallis one-way analysis of variance was used to test the differences in blood flow and the differences in psychological parameters between the three groups, and *post hoc* Mann–Whitney *U*-tests were used to locate significant differences. The relationship between MTT parameters and cognitive scores was examined using Spearman's rank correlation coefficients, with a significance level of $P<0.01$ to take account of multiple comparisons.

Results

Net median transit times

The MTT of the input bolus (IF) of radioactivity, which is principally a function of cardiac output, was similar in all three groups (Table I). All the patients and controls had comparable cardiac function; thus a similar profile of radionuclide is presented to the cerebral circulation in each group, at the level of the aorta.

The distribution of net MTT over either hemisphere (LCx and RCx) between groups showed striking differences (Table I). Both ATD and KOR patients showed net MTTs that were prolonged by about 50%. Thus, flow through cortical areas appeared to be appreciably slowed in both patient groups (Fig. 2).

CAMCOG psychological scores

Orientation and memory score were impaired in both ATD and KOR patients compared with control subjects (Table II). Language function was also reduced in ATD patients compared with controls; KOR patients were less impaired. Scores for praxis were clearly reduced in ATD patients but not in KOR patients. Overall cognitive function, as measured by CAMTOTAL or MMSE, was lowest in the ATD group compared with controls, but also significantly reduced in KOR patients.

The correlation matrix of blood flow measures and cognitive function scores is shown in Table III. For the ATD

TABLE I

Net median transit time (in seconds) in cortical regions of interest (left and right Cx, A, B, C and D), and input function for control, Alzheimer and Korsakoff groups

	Control		*ATD*		*Korsakoff's*		*Kruskal–Wallis*
	Median	*Range*	*Median (% increase of control)*	*Range*	*Median (% increase of control)*	*Range*	*one-way ANOVA*
Left Cx	4.6	3.1–6.1	6.9(+50)***	5.7–14.2	7.1(+54)*	4.4–11.3	<0.0005
Right Cx	4.6	2.9–5.7	6.6(+43)***	5.3–14.0	6.9(+50)*	4.6–11.2	<0.0005
Left A	4.2	2.6–6.5	6.2(+48)**	3.7–14.9	6.0(+43)*	4.1–12.0	<0.005
Right A	4.2	2.2–6.0	6.5(+55)**	3.5–14.6	6.3(+50)*	3.6–10.7	<0.005
Left B	4.0	2.4–5.0	5.8(+45)**	3.9–13.3	6.0(+50)*	3.9–10.4	<0.001
Right B	4.1	2.3–5.1	5.5(+34)*	3.7–13.2	5.7(+40)*	3.5– 9.3	<0.005
Left C	4.4	2.8–5.9	6.8(+55)***	5.1–15.8	6.6(+50)*	4.6–10.9	<0.0005
Right C	4.5	2.7–5.5	6.9(+53)***	5.7–14.6	6.0(+33)*	4.6–10.7	<0.0005
Left D	5.4	3.3–7.8	8.7(+61)***	6.5–16.6	8.4(+56)*	4.9–12.1	<0.0005
Right D	5.4	3.8–7.1	8.7(+61)***	6.8–17.5	8.6(+59)*	5.8–14.3	<0.0005
IF	6.3	3.6–8.5	6.5(+3)	5.2– 9.1	7.7(+22)	5.7–11.4	NS

All *post-hoc* comparisons were made between patient groups and controls using Mann–Whitney *U*-tests: *$P<0.005$; **$P<0.001$; ***$P<0.0001$.

https://doi.org/10.1192/bjp.154.6.790 Published online by Cambridge University Press

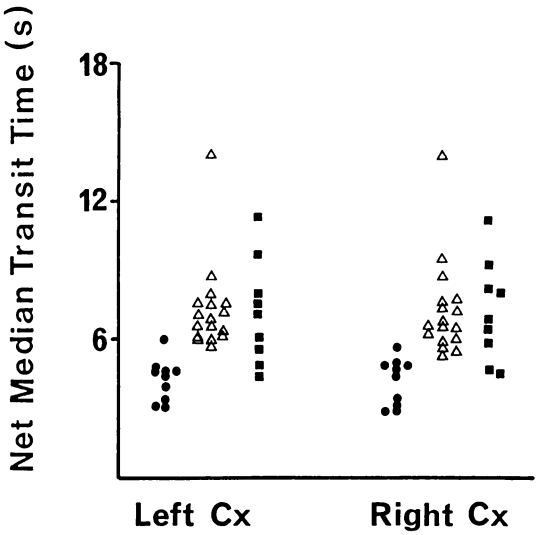

FIG. 2 Net MTT for right and left sides of cortical image for control subjects (●), Alzheimer (△), and Korsakoff (■) patients.

group, negative association at the $P<0.01$ level was detected only between orientation scores and right frontal cortex, although there is clearly a strong overall trend for low cognitive scores to be associated with prolonged net MTT. This relationship is most apparent between hemispheric net MTT (LCx and RCx) and CAMTOTAL, orientation, language, and, to a lesser extent, memory function. However, all areas tend to show some level of association between impaired function and prolonged net MTT. It is striking that no association is seen between cognitive function scores and the IF.

The association between net MTT and psychological measures in KOR patients is also shown in Table III. It is evident from Table III that language and praxis scores show an appreciable 'ceiling' effect when compared with ATD patients, and no association with net MTT for these variables emerges in Table III. Memory and orientation scores tend, as for ATD patients, to show a negative association with net MTT. The only contradictory finding was of a strong positive association between attention and net MTT in KOR patients.

Discussion

The prolongation of net MTTs in ATD and KOR patients compared with control subjects is likely

TABLE II
CAMCOG subscores, MMSE and total CAMCOG score for control, ATD and KOR subjects

	Controls (n = 10)	*ATD (n = 17)*	*KOR (n = 9)*	*Kruskal–Wallis one-way ANOVA*
Orientation	10 (10)	4 (0–9)**	5 (1–9)**	<0.0005
Language	29 (28–30)	20 (0–27)**	26 (23–29)*	<0.0005
Memory	24 (23–26)	7 (0–15)**	12 (4–24)**	<0.0005
Attention	7 (5–7)	1 (0–3)**	5 (3–7)	<0.0005
Praxis	12 (12)	7 (0–11)**	11 (7–12)	<0.0005
CAMTOTAL	102 (100–105)	51 (0–82)**	75 (56–99)*	<0.0005
MMSE	30 (29–30)	12 (0–24)**	20 (11–29)*	<0.0005

Results expressed as median and range. All *post-hoc* comparisons were made between patient groups and control subjects using Mann–Whitney *U*-tests; *$P<0.005$; **$P<0.001$.

TABLE III
Relationship between net transit times for different cortical regions and CAMCOG scores in ATD and KOR patients

	LCx	*RCx*	*LA*	*RA*	*LB*	*RB*	*LC*	*RC*	*LD*	*RD*	*IF*
ATD patients											
CAMTOTAL	−0.33	−0.60	−0.33	−0.57	−0.11	−0.46	−0.32	−0.42	−0.47	−0.46	−0.01
Orientation	−0.38	−0.68*	−0.48	−0.68*	−0.14	−0.57	−0.33	−0.58	−0.51	−0.56	−0.04
Language	−0.53	−0.66	−0.63	−0.54	−0.43	−0.57	−0.45	−0.25	−0.35	−0.38	+0.08
Memory	−0.38	−0.58	−0.35	−0.41	−0.18	−0.35	−0.21	−0.23	−0.35	−0.48	+0.16
Attention	+0.04	−0.18	−0.27	−0.26	−0.08	−0.18	−0.02	−0.16	−0.19	−0.10	+0.09
Praxis	−0.15	−0.36	−0.34	−0.38	−0.06	−0.28	−0.12	−0.22	−0.34	−0.30	−0.007
KOR patients											
CAMTOTAL	+0.07	+0.07	+0.07	+0.17	+0.07	+0.07	+0.06	+0.02	+0.02	+0.07	−0.07
Orientation	−0.44	−0.44	−0.44	−0.39	−0.44	−0.44	−0.47	−0.38	−0.50	−0.44	−0.90*
Language	+0.10	−0.09	−0.10	−0.22	+0.09	−0.10	−0.08	+0.02	−0.01	+0.10	+0.02
Memory	−0.31	−0.31	−0.31	−0.15	−0.31	−0.31	−0.32	−0.32	−0.33	−0.31	+0.02
Attention	+0.82*	+0.82*	+0.82*	+0.67	+0.82*	+0.82*	+0.84*	+0.78	+0.75	+0.82	+0.49
Praxis	+0.05	+0.05	+0.05	+0.17	+0.05	+0.05	−0.04	+0.05	+0.09	+0.05	+0.05

Spearman's rank correlation coefficients: *$P<0.01$.

https://doi.org/10.1192/bjp.154.6.790 Published online by Cambridge University Press

to reflect reduced cortical blood flow, as measured by other techniques. Lengthening of MTT may reflect reduced flow through a constant cerebral blood volume or normal flow through an increased cerebral blood volume, or some intermediate situation. There are no independent estimates of cerebral blood volume in dementia that suggest it is increased, and hence a reduced CBF is the most likely cause of lengthened net MTT. In Alzheimer's disease, CBF appears to be a reliable indicator of brain metabolism (Frackowiak *et al*, 1981), and measurement of net MTT may thus provide a simple method of estimating brain metabolism in dementia.

Positron emission tomography (PET) permits direct investigation of brain metabolism *in vivo*. Relative decreases in cortical glucose metabolism (de Leon *et al*, 1983; Kuhl *et al*, 1985), cerebral oxygen utilisation, and CBF (Frackowiack *et al*, 1981) have been demonstrated in ATD. Such impairment of cerebral metabolism was seen in all areas, but most clearly in temporoparietal and frontal regions, with a decrease in CBF of 25–40% in severely demented patients (Frackowiack *et al*, 1981). These findings are consistent with the results of this study, where net MTT was prolonged symmetrically in both hemispheres in patients with moderate to severe ATD. The differentiation from control subjects was very clear. In part this will have been because the mean age of the ATD group was 59, and there is evidence that neuropathological and neurochemical abnormalities are more marked and widespread throughout the cortex in younger ATD patients compared with older subjects (Roth, 1986).

In KOR patients, MTTs were prolonged compared with controls, and similar to those of ATD patients, suggesting that KOR patients who are abstinent from alcohol have reduced CBF and also perhaps metabolism in the centroparietal cortex. There are many studies that have described reduced CBF in chronic alcoholism, but they have usually emphasised recovery of CBF on treatment with thiamine and following abstinence (e.g. Hata *et al*, 1987). Thus, the finding of reduced cerebral perfusion in stable abstinent subjects is somewhat unexpected, as KOR patients have a relatively localised macroscopic neuropathological lesion in the diencephalon or hippocampal formation, and a discrete impairment of memory without necessarily more global impairment of cognitive function (Victor *et al*, 1971; Blackburn & Tyrer, 1985). Correspondingly, our neuropsychological data clearly separated the KOR patients from the more globally impaired ATD group, especially with respect to language, attention, praxis, and total score.

However, there is evidence that the dysfunction in Korsakoff's psychosis is more extensive than neuropathological and clinical findings might suggest; magnetic resonance imaging studies have demonstrated that a significant proportion of KOR patients who do not appear to have a generalised alcoholic dementia have high proton spin-lattice relaxation times (T_1 values) for both frontal and parietal white matter (Christie *et al*, 1988). This finding suggests increased tissue water and/or cellular water binding. Furthermore, Hata *et al* (1987) have shown that KOR patients have a widespread reduction in regional CBF throughout cortical and subcortical structures. Using xenon-133 contrast CT, they have demonstrated reduced regional CBF in hippocampus, nucleus basalis of Meynert, and frontal white matter, as well as throughout cortical grey matter. Other techniques have shown similar abnormalities in KOR patients, including reduced mean hemispheric grey matter CBF using xenon-133 inhalation (Rogers *et al*, 1983), and reduced whole-brain CBF, and reduced cerebral metabolic rates for oxygen and glucose (Kruger *et al*, 1980) using the Kety–Schmidt technique.

Lishman (1986) has suggested a unifying hypothesis to account for the symptoms common to ATD and KOR patients. He suggests that in Korsakoff's psychosis, alcohol exerts toxic effects on the basal forebrain nuclei, causing damage to cholinergic projections to cortex, with resultant cognitive impairment. Such a pathological process might result in a diffuse and variable reduction in cortical metabolism and blood flow, as found in the present study and that of Hata *et al* (1987). However, we could not rule out the possibility that cerebral perfusion is maintained in the patients by persistent vasodilatation, so that they are functioning permanently close to the limits of their reserve capacity.

Neuropathological studies of patients with moderate to severe pre-senile ATD show that the temporal, frontal, and parietal lobes are all directly affected by neurofibrillary tangles, plaques, and neuronal degeneration (Pearson *et al*, 1985). This predicts both global intellectual impairment and widespread effects on cerebral metabolism. In ATD patients there was a marked and consistent trend for cognitive scores to be inversely associated with net MTT, as would be expected if net MTT gives a valid reflection of cerebral function. This association might have been even more convincing but for prominent 'floor' effects in the neuropsychological tests that were used (see Table II). On the other hand, the reduced level of association between MTT and cognitive function in KOR patients in part reflects their greater preservation of language and praxis, and corresponding 'ceiling' effects. The paradoxical finding of an increased level of attention in association with

impaired flow in KOR patients will require replication before speculation is justified. Overall, the persistent pattern of negative correlation between test scores and net MTT in both patient groups supports the proposition that net MTT gives a meaningful estimate of functional cortical activity in dementia.

Non-tomographic methods of CBF measurement, such as the nitrous oxide method for measuring hemispheric blood flow (Kety & Schmidt, 1945), estimate flow as a function of an ill-defined volume of distribution said to be a function of brain volume, although there is ample evidence that this is an oversimplification. By contrast, any tomographic method, such as PET, because of inherent limitations of spacial resolution, measures blood flow or other metabolic parameters per unit volume of intracranial contents, including metabolically inactive CSF spaces. Thus, artefacts in tomographic measurements of CBF may be lower in dementia owing to brain atrophy. Such effects may be appreciable, and could represent a significant fraction of the apparent reduction in flow that is measured (Chawluk *et al*, 1987). There are advantages, accordingly, of a simple, direct approach to blood flow measurement, such as the net MTT method. Not only is the method rapid, non-invasive, and inexpensive, but in our experience is well tolerated by demented patients of varying degrees of severity, and could be employed widely using existing gamma-camera systems available in most departments of nuclear medicine.

Acknowledgements

We thank the patients and staff of the Royal Edinburgh Hospital, the Edinburgh branch of the Women's Royal Voluntary Service, and the radiography and medical physics staff of the Department of Nuclear Medicine, Western General Hospital. We are also grateful to Norma Brearley for the careful preparation of the manuscript, and Professor George Fink for advice and encouragement.

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