TOTAL AND REGIONAL CEREBRAL BLOOD FLOW

A new quantitative non-invasive method for cerebrovascular disease

K.E. BRITTON, M. GRANOWSKA, C.C. NIMMON
Department of Nuclear Medicine
and Radioisotopes,
St. Bartholomew's Hospital,
London,
United Kingdom

Abstract

TOTAL AND REGIONAL CEREBRAL BLOOD FLOW: A NEW QUANTITATIVE NON-INVASIVE METHOD FOR CEREBROVASCULAR DISEASE.

This new method depends on a linear system approach, thus avoiding the problems of the lack of constancy of the partition coefficient and diffusion volume that occur with the xenon washout technique, particularly in cerebrovascular disease. Using first pass and equilibrium data after an intravenous bolus of $^{99}Tc^{m}$-labelled albumin or red cells, regional volume is measured as a fraction of total blood volume and regional mean transit time by deconvolution analysis of an input curve from an aortic probe with the activity/time curve from each region of interest. Reproducibility studies are reported together with results in patients before and after surgery for carotid occlusion, in subarachnoid haemorrhage and in a study of a hypotensive agent.

The reason for developing a new non-invasive method for total and regional cerebral flow is to aid the distinction between alternative managements in patients with cerebrovascular disease (Table I). The technique is summarized in Table II.

Any new technique requires validation [1]. For static imaging of the brain this is usually by comparison with the results of other imaging techniques such as X-ray transmission computer-assisted tomography or angiography, but for dynamic function studies this is much more difficult. Either the historical techniques measure different aspects of the problem, or else similar techniques have unacceptable sources of error leading to the development of the new technique to avoid such problems. This is certainly the case with total and regional cerebral blood flow studies in man. Validation of a new technique in such circumstances requires considerable thought, and one concludes that there is a hierarchy of validations, each of which has to be met. First is clinical acceptability, examples of which include a reduction in regional cerebral flow in a region supplied by a stenosed or occluded artery (Table III), and a global reduction in flow in patients with subarachnoid haemorrhage or demented because of diffuse brain damage (Table IV).

TABLE I. CEREBRAL BLOOD FLOW IN CLINICAL MANAGEMENT

1. Screening patients for cerebral angiography
   - Hypertensives
   - Transient cerebral episodes
   - Chronic brain damage for carotid occlusions
2. Assessment of the success of vascular surgery
   - Endarterectomy
   - Percranial microvascular bypass
3. Assessment of subarachnoid haemorrhage
   - Time for intervention
   - Prognosis
4. Assessment of drug therapy
   - Hypertensives
   - Psycho geriatrics

TABLE II. NON-INVASIVE MEASUREMENT OF TOTAL AND REGIONAL CEREBRAL FLOW

Patient supine
Computer-linked gamma camera over vertex
Probe over aorta checked by intravenous injection of 1 mCi $^{99}Tc^{m}$-pertechnetate
15 mCi $^{99}Tc^{m}$-labelled autologous red cells in 0.3 ml in 0.5 ml internal volume tube, injected with the arm abducted using a 20-ml saline flush
Record first pass activity/time curves
Record equilibrium activity between 2.5–3.5 min
Blood sample at 3 min, volume by weight, activity by camera

TABLE III. REGIONAL CEREBRAL FLOW MEASUREMENTS (ml/min)

A. Bilateral carotid angiography showing unilateral stenosis over 50%, contralateral side normal

	Middle cerebral region		Cerebral hemisphere	
	Mean	Range	Mean	Range
Stenosis	217	174–316	478	365–629
Normal side	295	229–346	665	458–785
Abnormal % total	42.4%	35.0–47.2	41.8%	38.1–44.3
p	<0.05		<0.05	

B. Mean regional flows in 18 patients with carotid occlusion before and after surgical percranial microvascular bypass

	Pre operative	Post operative	Difference	p value
Operated side				
Middle cerebral region	210	263	53	<0.05
Cerebral hemisphere	491	629	138	<0.02
Non-operated side				
Middle cerebral region	236	268	32	NS
Cerebral hemisphere	543	591	58	NS
Total cerebral flow mean	995	1184	189	<0.05

Validation requires that the technique is physiologically acceptable. The main problem here is the control of physiological variables: carbon dioxide level, blood pressue level and haematocrit; and the creation of a reproducible physiological state. Carbon dioxide as pCO_2 has an important influence on cerebral flow – retention of CO_2 causing vasodilation. Unfortunately the errors on estimating pCO_2 and the scatter of pCO_2 with CBF [2] are so great, particularly when arterialized venous blood is sampled, that to apply a correction for this to the estimated cerebral flow may be inadvisable. Furthermore, there is some doubt about the relationship between expired CO_2 estimation and the cerebrospinal fluid CO_2 which seems to be the important influence. In our hands, between study and between patient variability of pCO_2 was within the error of its measurement.

TABLE IV. TOTAL CEREBRAL FLOW MEASUREMENTS (ml/min)

A. Subarachnoid haemorrhage, 37 patients

Clinical state	Total flow (ml/min)		
	Mean	SE of mean	p value
Normal conscious level Neck stiffness	1143	±313	<0.03
Normal conscious level + lateralizing signs	880	±187	<0.05
Altered consciousness ± lateralizing signs	702	±154	

B. Intellectual state, 15 patients

Clinical state	Total flow (ml/min)		
	Mean	Range	p value
Normal intellect	1053	982–1484	<0.05
Demented	713	614–893	

The autoregulation of CBF in relation to change in blood pressure is well documented, but again variation is great [2] and correction is not usually applied. The relationship between haematocrit and CBF shows considerable scatter [3], and in our hands the variation in haematocrit between studies in the same patient was too small to require correction to be applied. Anxiety causes a pronounced reduction in CBF, and we record an anxiety score when the patient is studied. This is the most important and most difficult factor to control and a relaxed patient in a relaxing environment is essential.

A technique for CBF should have a sound structural basis. This means that correction must be made for extracerebral activity. Variation in the volume of distribution of tracer in pathological sites and variation in its partition coefficient must all be taken into account. For these latter reasons, techniques based on radioactive gas washout are unsuitable [4, 5] and a stochastic linear model is

preferred to a compartmental one. Although techniques for correction of extracerebral activity have been described for gas washout studies [6, 7], they are rarely applied in practice, particularly by those using the 'two minute slope' method [8]. Our method enables correction for extracerebral activity to be made if the following assumption is taken into account. The cerebral tissue is a high flow, low volume system whereas the non-cerebral tissue is a low flow, high volume system. The activity injected as a bolus intravenously will flow rapidly via the internal carotid and vertebral vessels to the brain, and more slowly and in much lesser amount to extracerebral tissue, during a first pass study, whereas, considering the distribution of tracer at equilibrium, the large volume of extracerebral tissue will give a significant contribution to the activity recorded externally. If the extracerebral contribution may be neglected during the first pass study, then its contribution at equilibrium can be determined by dividing the equilibrium activity distribution image, Eq(t), obtained over a minute, by the first pass activity distribution image, N_T, to demonstrate the difference between the two. The equilibrium image therefore must be corrected by a factor, E(t), to give the true cerebral equilibrium image which may then be compared directly with the first pass image. This enables the total cerebral volume and regional volume, V_R, to be calculated with the help of a blood sample, S, taken at equilibrium for calibration purposes. The regional volume in millilitres is given by

$$V_R = \frac{N_R}{N_T} \times \frac{(Eq(t) - E(t))}{S}$$

where N_R is the first pass count content of a region of interest, N_T the first pass count content of the cerebral activity distribution image, and S is the activity per minute per millilitre of the blood sample counted in front of the gamma camera multiplied by a geometrical factor determined by phantom studies. This sample volume is measured by weight difference of the syringe empty and full. $\Sigma_1 Ri$, the remainder image following dividing the equilibrium activity image by the first pass activity image, is calculated as follows:

$$Eq(t) = FN_T + \Sigma_1 Ri$$

$$E(t) = \Sigma_1 Ri$$

where F is a proportionality factor relating N_T to Eq(t). E(t) is displayed to show the areas of extracerebral activity and is used to correct Eq(t) for such activity.

Lastly, physical stability and mathematical rigour are important requirements for validation. A good bolus is essential and 15 mCi of ^{99}Tc-labelled albumin

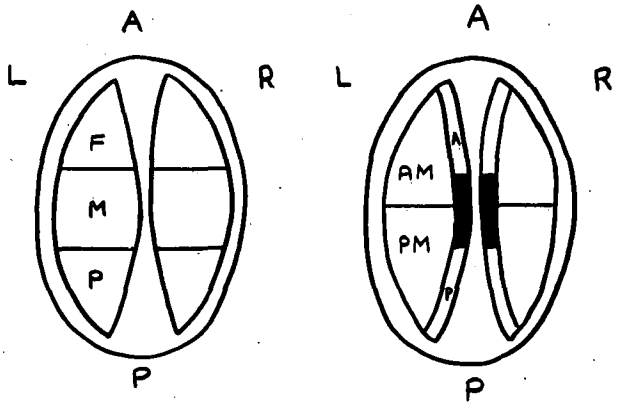

FIG. 1. Regions of interest for clinical cerebral flow studies. Left, the vertex is divided with thirds transversely. F, frontal; M, middle; P, posterior; L, left, R, right. Right, a composite diagram of regions of interest related to the hemispheres and branches of the middle cerebral artery (A and P, anterior and posterior branches; AM and PM, distribution of the middle cerebral artery). This technique, first developed with ^{99}Tc-labelled albumin and now with $^{99}Tc^{m}$-labelled red cells, is rigorous, and shown to be useful in clinical practice.

TABLE V. REPRODUCIBILITY STUDY IN TEN PATIENTS

Cerebral flows in ml/min for regions of interest shown in Fig. 1 (left)

	Right			Left			Total
	Front	Middle	Posterior	Front	Middle	Posterior	
1st study means	126	214	160	106	209	150	965
2nd study means	123	227	163	112	213	150	986
Mean of differences	3	13	3	6	4	0	21
SE of mean	±7	±12	±13	±8	±10	±11	±30
% SE of mean	5	6	8	8	5	8	3

TABLE VI. COMPARISON OF XENON WASHOUT, TECHNETIUM-99m RED CELL FLOW AND POSITRON EMISSION TOMOGRAPHY

	Xenon	Technetium red cells	'Positrons'
1. Non-invasive	Partly	Yes	Yes
2. Standard nuclear equipment	No	Yes	No
3. Standard radio-pharmaceutical	Yes	Yes	No
4. Separate measurement of volume and time	No	Yes	Yes
5. Avoidance of estimation of partition coefficient	No	Yes	No
6. Incorporates direct correction for extracerebral activity	No	Yes	Yes
7. Adaptable to cerebral metabolism	No	Yes	Yes

or autologous red cells are injected in a volume of 0.3 ml with the arm abducted using a flush technique [4].[1]

The number and size of the Regions of Interest are determined mainly by the counting statistics, but their position is determined by convenience, e.g. dividing the vertex view of the brain into thirds transversely, but first excluding the scalp edge and the sagital sinus, or else into regions related to the superficial distribution of the branches of the middle cerebral artery (Fig.1). Phantom studies are necessary to determine the factors relating the blood sample to activity as determined by the gamma camera to the activity in the brain [9].

Reproducibility is an essential aspect of validation and has two separate aspects. Firstly the reproducibility of the analysis must be checked. This includes not only the sequence of program steps performed by different operators including their judgements of where to place regions of interest and how to manipulate activity/time curves, but also the mathematical operations, especially where iteration

[1] 1 Ci = 3.70×10^{10} Bq.

or deconvolution techniques are used [10, 11]. The analytical reproducibility is about 7%, on a flow measurement in ml/min. The reproducibility between patients depends on their relaxed physiological state as noted above, and results are shown in Table V. These were taken from ten patients either studied twice before or twice after surgery who had low anxiety scores. Separation of months between studies gave better reproducibility than repetition of studies within 30 min.

In conclusion, this new non-invasive technique has a number of advantages over the ^{133}Xe washout technique and the forthcoming positron emission tomography (Table VI).

REFERENCES

[1] BRITTON, K.E., et al., "Regional cerebral flow in cerebro vascular disease: validation of a non invasive quantitative radionuclide technique", Information Processing in Medical Imaging, Inserm, Paris (1979) 469.
[2] MARSHALL, J., The Management of Cerebrovascular Disease, 3rd Edn, Blackwell, Oxford (1976).
[3] THOMAS, D.J., et al., Cerebral blood flow in polycythaemia, Lancet ii (1977) 161.
[4] BRITTON, K.E., et al., "Cerebrovascular disorder, assessment with radionuclides", Advanced Medicine **13** (BESSER, M., Ed.), Pitman Medical, London (1977) 444.
[5] BRITTON, K.E., GRANOWSKA, M., Images of brain function, Lancet ii (1979) 1080.
[6] CRAWLEY, J.C.W., Progress in Stroke Research **1** (GREENHALGH, R.M., ROSE, F.C., Eds), Pitman, London (1979) 319.
[7] OBRIST, W.D., et al., Regional cerebral blood flow estimated by $^{133}Xenon$ inhalation, Stroke **6** (1975) 245.
[8] LASSEN, N.A., INGVAR, D.H., Radioisotopic assessment of regional cerebral blood flow, Prog. Nucl. Med. **1** (1972) 376.
[9] GRANOWSKA, M., et al., Total and regional cerebral flow: non invasive quantitation in patients with subarachnoid haemorrhage, J. Neurosurg. (in press).
[10] NIMMON, C.C., LEE, T.Y., BRITTON, K.E., GRANOWSKA, M., GRUENEWALD, S., "Practical application of deconvolution to dynamic studies", these Proceedings, IAEA-SM-247/26.
[11] LEE, T.Y., Cerebral Blood Flow by a Radioisotope Technique, Experimental and Clinical Aspects, PhD Thesis, University of London, 1980.

DISCUSSION

J.P. OLIVA GONZÁLEZ: Do you think that the use of three or four detectors for the study of cerebral blood flow is no longer applicable?

K.E. BRITTON: Multidetector systems for the brain are not standard equipment but acceptable for $^{99}Tc^{m}$ red cell studies. Xenon-133 studies in cerebral pathology are not recommended since volumes and partition coefficients cannot be assumed to be constant.