The measurement of local blood flow in the cerebral cortex from the clearance of xenon¹³³

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Recently Lassen and Ingvar (1961) devised a technique for measuring local blood flow through the cerebral cortex. Their method, derived from the Fick principle, entailed the injection of the radioactive gas krypton⁸⁵ into the carotid artery and the subsequent measurement of the rate of clearance from the brain of the beta emissions of the isotope. As these have an average range in tissue of 0.7 mm., measurements of local blood flow can be made only on the exposed brain cortex. A more recent report describes the measurement of regional cerebral blood flow in man by monitoring the low incidence gamma emissions of krypton⁸⁵ with a scintillation detector placed over the scalp (Lassen, Høedt-Rasmussen, Sørensen, Skinhøj, Cronquist, Bodforss, and Ingvar, 1963). However, in that study uncollimated detectors were used in most patients, and the clearance of krypton⁸⁵ was recorded from almost one hemisphere of the brain.

Recently we reported the substitution of the gamma-emitting isotope xenon¹³³ for K⁸⁵ and the measurement of local blood flow in a fairly small area of the cerebral cortex by external counting through the intact skull using a depth-focusing collimator (Glass and Harper, 1963). This paper describes measurements made in several patients who were undergoing cerebral angiography.

METHOD

Xenon¹³³ was received in 100 mc. doses in a sealed glass ampoule, which was connected to a glass reservoir which had been previously evacuated with a vacuum pump. On breaking the seal the gas entered the reservoir and the remaining space was filled with normal saline. Aliquots of the solution, each of 20 ml., were withdrawn into syringes. Each syringe contained approximately 0.5-1 mc. of radioactivity.

Measurements of cortical blood flow were made on anaesthetized patients undergoing cerebral angiography for suspected intracranial lesions. Anaesthesia was induced with thiopentone and maintained with 75% N₂O and oxygen. D-tubocurarine (15-25 mg.) was ad-

ministered and additional doses of 10 mg. were given as required. The patients were ventilated with intermittent positive pressure on a Barnett ventilator. An open circuit was used and the expired gases led to the outside atmosphere through a thick-walled plastic tube.

The detector consisted of a focusing collimator, a 5-in. diameter sodium iodide crystal, and a photomultiplier. The last was connected to a ratemeter and direct writing recorder. The focusing collimator was mounted in front of the crystal and localized the area of cortex under view. The collimator was lowered by a special stand on to the patient's scalp, when the centre of the collimator lay above the posterior part of the frontal cortex.

A catheter was inserted into the internal carotid artery via the common carotid artery. The position of the catheter was confirmed by radiography.

About 10-15 ml. of the saline solution of xenon¹³³ was injected, rapidly at first, then more slowly into the cannula over two and a half minutes. On completion of the injection, a clearance curve was obtained on the recorder. This was transposed on to semilogarithmic paper and the flow calculated from the half-life of the initial slope of the clearance curve, using the formula, flow (ml./g./min.) = $\frac{\log_e 2 \times 60}{T_{\frac{1}{2}}}$ (Ingvar and Lassen, 1962), where $T_{\frac{1}{2}}$ = half-

life in seconds of the initial slope of the clearance curve and λ = brain-blood partition coefficient for xenon¹³³. The value used for the latter was 0.80 (Mallet and Veall, 1963). A sample of carotid artery blood was taken after each flow estimation for the measurement of the arterial carbon dioxide tension on the micro-Astrup apparatus (Siggaard Andersen, Engel, Jørgensen, and Astrup, 1960).

THEORY OF INERT GAS CLEARANCE METHOD

The rationale of inert gas clearance methods is illustrated in Figure 1. Following its injection into the carotid artery, xenon diffuses in a known ratio between the blood and brain tissue. After a sufficiently long injection period the brain tissue and venous blood will be in equilibrium. On cessation of the injection the carotid arterial blood, now containing virtually no radioactive xenon, will wash out the xenon in the brain tissue and the rate at which this

FIG. 1. Rationale of inert gas clearance method.

FIG. 2. Diagram of simple collimator.

takes place will depend on the quantity of blood perfusing the brain. As the air:blood partition coefficient for xenon is 10:1, the gas is almost completely cleared in the lungs and the effect of the small amount of arterial recirculation on the initial slope of the clearance curve can be calculated. It must be emphasized that the entry of xenon into the brain tissue and its subsequent clearance is a purely physical process, and depends only on diffusion and solubility.

As the cerebral cortex is not a completely homogeneous tissue and has a multi-exponential clearance curve, the injection time must be long enough to ensure equal concentrations of the inert gas in all the cortical tissue components. We have found that an initially rapid, then slow, injection of approximately two and a half minutes will achieve this.

DETECTION OF RADIOACTIVITY

The level of radioactivity in an area of the cerebral cortex is detected by means of a depth-focusing

collimator placed in front of a scintillation crystal. A cross-section of a very simple collimator is shown diagrammatically in Figure 2. It consists of a lead disc $\frac{1}{2}$ in. thick in which a circular tapered channel has been cut. Radioactive emissions can reach the crystal only through this channel. The maximum efficiency of counting comes from the area of cortex completely enclosed by the dotted lines. Outside the radiating lines some radioactivity will be recorded on a more limited area of the crystal but its effect will be reduced by distance, by absorption in tissue, and by the fact that white matter, with its much slower blood flow, contains less radioactivity.

With the more complex twin-channel multisegmented collimators which we now use for our measurements in man (Glass, 1963), the initial slope of the clearance curve is due to clearance of xenon from a volume of brain tissue approximately 4 cm. in diameter by up to 2 cm. in depth, the latter being controlled by adjusting the position of the collimator relative to the skin.

RADIATION HAZARD

Xenon¹³³ has a biological half-life of only a few minutes and is cleared very rapidly from the lungs. The radiation dose to the lungs for a two-minute re-breathing of a concentration of xenon of 1 mc./litre of inspired air is 70 millirads (Dollery, Hugh-Jones, and Matthews, 1962; Matthews, Fowler, and Turner, 1962) and the dose following an intravascular injection of 0.5 mc. is much smaller (Dollery, Fowler, Hugh-Jones, Matthews, and West, 1963). Patients undergoing cerebral angiography would have about 20 skull radiographs taken, with a radiation dose to the skull of approximately 1.5 rads for each radiograph. This is many times more than the radiation received for each injection of Xe¹³³. As the expired gas is led to the outside atmosphere, the radiation hazard to persons in the theatre is negligible.

RESULTS

Measurements of blood flow through the postero-frontal cortex were made in seven patients undergoing cerebral angiograms. Four of the patients had normal angiograms, one had an aneurysm of the basilar artery, one a small subdural haematoma, and one a right parietal tumour. In five of the patients duplicate determinations were made, before and after passive hyperventilation. The results are shown in Table I. There appears to be a wide scatter of values but these relate extremely well to changes in arterial pCO₂. In Table II the flow measurements have been divided into two groups, those measured at arterial pCO₂ values greater than 35 mm. Hg and those less than 30 mm. Hg. (The second result from one patient has been excluded, as no pCO₂ value was obtained.) The mean value for flow measurements at a mean pCO₂ of 43 was 0.77 ml./g./min. At a mean pCO₂ of 25 mm. Hg, the mean flow value is 0.45 ml./g./min.

TABLE I

RESULTS OF BLOOD FLOW THROUGH BRAIN CORTEX AND ARTERIAL CARBON DIOXIDE TENSION IN SUBJECTS STUDIED

Patient	Arterial pCO ₂ (mm. Hg)	Blood Flow (ml./g./min.)	Angiogram
G.G.	35	0.65	Aneurysm basilar artery
F.B.	42	0.76	Normal
	20	0.44	
W.I.	27.5	0.44	Normal
A.S.	29.5	0.52	Subdural haematoma
	19.5	0.38	
A.B.	27.5	0.53	Right parietal tumour (glioblastoma)
	—	0.28	
B.G.	56	0.92	Normal
	30	0.38	
F.R.	40	0.75	Normal
	20	0.44	

TABLE II

BLOOD FLOW RESULTS AT CARBON DIOXIDE TENSIONS GREATER THAN 35 MM. HG AND LESS THAN 30 MM. HG

Group 1 (pCO ₂ > 35)		Group 2 (pCO ₂ < 30)	
Flow	pCO ₂	Flow	pCO ₂
0.65	35	0.44	20
0.76	42	0.44	27.5
0.92	56	0.52	29.5
0.75	40	0.38	19.5
		0.53	27.5
		0.38	30
		0.44	20
Mean	0.77	0.45	25
S.D.	0.11	0.035	5
Coefficient of variation (%)	14.5	7.8	20

DISCUSSION

The theory of the inert gas clearance method has been extensively discussed elsewhere (Ingvar and Lassen, 1962). However, one point must be raised. The radioactive gas krypton⁸⁵ used by Lassen and Ingvar has an air:blood partition coefficient of about 20 (Kety, 1951), and is therefore almost completely cleared by the lungs, the effective arterial recirculation to the brain being only a few per cent. However, as xenon¹³³ has an air:blood partition coefficient of only 10, the lung clearance is less efficient and with a two-minute injection period, we have found in preliminary animal experiments that the effect on the initial slope due to recirculation is approximately 5%. Our calculated flow values may, therefore, err slightly on the low side. We would emphasize the importance of using this technique only in patients with normal cardio-pulmonary function. Any lung pathology may interfere with the exchange of xenon in the lungs, with the result of an unacceptably high arterial recirculation.

In these measurements, care was taken to ensure that the injections were made into the internal carotid artery, thus preventing any distortion of the clearance curve by radiation from extracerebral tissues.

The contribution of the white matter to the clearance curve is considered to be small for the following reasons. The collimator is so designed that the maximum efficiency of counting comes from cortical tissue. As white matter has a blood flow very much less than that of grey matter (Landau, Freygang, Roland, Sokoloff, and Kety, 1955), the initial concentration of radioactivity in white matter will be much less than in grey matter and the contribution to the clearance curve correspondingly small.

The blood-flow estimations at a mean arterial pCO₂ of 43 mm. Hg gave a value of 0.77 ml./g. brain cortex/minute. The only other figure available for blood flow through the cerebral cortex in man is

0.51 ml./g./min. (Ingvar and Lassen, 1961). However, this measurement was made on the exposed brain cortex of a patient with a large intracerebral tumour which may have influenced the result. Kety and Schmidt (1948), using the nitrous oxide technique, found values of 0.54 ml./g./min. for total cerebral blood flow in conscious man. As the brain is composed of approximately three-fifths grey matter and two-fifths white matter (Rose, 1935), the former having a blood flow approximately three times as great as the latter under light anaesthesia (Kety, 1963), results indicate a total cerebral flow of about 0.56 ml./g./min. if one assumes a fairly uniform blood flow through grey matter under general anaesthesia. There is some evidence that this is true as far as cortical tissue is concerned (Landau *et al.*, 1955; Harper, Glass, and Glover, 1961) but not necessarily so for grey matter in mid-brain structures.

The reduction in cortical blood flow on hyperventilation was 42%. This is slightly greater than the 35% reduction in total cerebral blood flow reported by Kety and Schmidt (1946) in conscious human volunteers.

There was no significant difference in the blood-flow results between patients with abnormal and normal angiograms. However, these patients were carefully selected beforehand on the grounds that they were fully conscious, rational, and had minimal clinical symptoms. In addition, measurements of blood flow were made at some distance from the lesion.

In conclusion, we consider that this adaptation of Lassen and Ingvar's method offers many advantages over other methods for the indirect measurement of cerebral blood flow in man. First, it can be performed very rapidly; there is no tedious analysis of blood samples required by the standard method of Kety and Schmidt (1948). The clearance curves can be analysed and an answer obtained in a few minutes. Secondly, the method gives the average local cortical blood flow over the first 30 seconds of the clearance curve and not the average intracranial blood flow over 15 minutes, as with Kety's method. Thirdly, local changes in cortical blood flow can be detected which might be missed in measurements of total cerebral blood flow. The main disadvantage is that it necessitates cannulation of the carotid artery, for which reason the procedure will normally be combined with cerebral angiography.

SUMMARY

Quantitative measurements of local blood flow in the cerebral cortex through the intact skull have been made in anaesthetized patients undergoing carotid angiography. Blood flow was calculated from the rate of clearance from the cortex of xenon¹³³ following its injection into the internal carotid artery. The values

obtained in normocapnic and hypocapnic patients are reported.

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REFERENCES

- Dollery, C. T., Fowler, J. F., Hugh-Jones, P., Matthews, C. M. E., and West, J. B. (1963). The preparation and use of radioactive oxygen, carbon monoxide, and carbon dioxide for investigation of regional lung function, and their comparison with Xenon-133. In *Radioactive Isotopes in Klinik und Forschung*, Vol. 5. Vorträge am Gasteiner internationaler Symposium 1962, edited by K. Fellinger and R. Höfer, pp. 88-103. Urban and Schwarzenberg, Munich. [Suppl. to *Strahlentherapie* 53.]
- , Hugh-Jones, P., and Matthews, C. M. E. (1962). Use of radioactive Xenon for studies of regional lung function. *Brit. med. J.*, 2, 1006-1016.
- Glass, H. I. (1963). A depth focusing collimator for the measurement of local cerebral blood flow. To be published.
- , and Harper, A. M. (1963). Measurement of regional blood flow in cerebral cortex of man through intact skull. *Brit. med. J.*, 1, 593.
- Harper, A. M., Glass, H. I., and Glover, M. M. (1961). Measurement of blood flow in the cerebral cortex of dogs, by the clearance of Krypton⁸⁵. *Scot. med. J.*, 6, 12-17.
- Ingvar, D. H., and Lassen, N. A. (1961). Quantitative determination of regional cerebral blood flow in man. *Lancet*, 2, 806-807.
- , — (1962). Regional blood flow of the cerebral cortex determined by Krypton 85. *Acta physiol. scand.*, 54, 325-338.
- Kety, S. S. (1951). The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.*, 3, 1-41.
- (1963). Regional circulation of the brain under physiological conditions—possible relationship to selective vulnerability. In *Selective Vulnerability of the Brain in Hypoxaemia*, edited by J. P. Schädé and W. H. McMenemey, p. 21. Blackwell, Oxford.
- , and Schmidt, C. F. (1946). The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. *J. clin. Invest.*, 25, 107-119.
- (1948). The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J. clin. Invest.*, 27, 476-483.
- Landau, W. M., Freygang, W. H., Roland, L. P., Sokoloff, L., and Kety, S. S. (1955). The local circulation of the living brain; values in the unanesthetized and anesthetized cat. *Trans. Amer. neurol. Ass.*, 80, 125-129.
- Lassen, N. A., and Ingvar, D. H. (1961). The blood flow of the cerebral cortex determined by radioactive Krypton 85. *Experientia (Basel)*, 17, 42.
- , Høedt-Rasmussen, K., Sørensen, S. C., Skinhøj, E., Cronquist, S., Bodforss, B., and Ingvar, D. H. (1963). Regional cerebral blood flow in man determined by a radioactive inert gas (Krypton⁸⁵). *Neurology (Minneapolis)*, 13, 719.
- Mallett, B. L., and Veall, N. (1963). Investigation of cerebral blood flow in hypertension using radioactive-Xenon inhalation and extracranial recording. *Lancet*, 1, 1081.
- Matthews, C. M. E., Fowler, J. F., and Turner, P. C. R. (1962). *Med. Res. Coun. Cyclotron Unit, Tech. Mem. No. 84*.
- Rose, M. (1935). *Anatomie des Gehirns*, Berlin. Quoted by Ingvar, D. H., and Lassen, N. A. (1962). *Acta physiol. scand.*, 54, 325-338.
- Siggaard Andersen, O., Engel, K., Jørgensen, K., and Astrup, P. (1960). A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. *Scand. J. clin. Lab. Invest.*, 12, 172-176.