Assessment of Regional Cerebral Blood Flow by Continuous Carotid Infusion of Krypton-81m

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In order to obtain functional images of brain perfusion, we exploited a new concept, which is to take advantage of the short half-life of a radioactive tracer. Under continuous intracarotid infusion of a solution of Kr-81m ($T_{1/2}$ = 13 sec; produced from its parent, 4.6-hr Rb-81), this tracer will never reach equilibrium within the brain because of the rapid radioactive decay. Its distribution will therefore reflect regional arrival of the nuclide, indicating regional cerebral blood flow rather than volume. During continuous infusion of Kr-81m, perfusion images can be obtained by simply collecting counts with a gamma camera and recording on Polaroid film. The procedure is readily repeatable in order to get images in multiple views or to follow minute-by-minute changes of cerebral perfusion.

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Regional cerebral blood flow is currently measured by intracarotid bolus injection of radioactive gases together with external recording over the head of the regional wash-out curves (*1*). This approach, like similar methods for assessment of regional blood flow in the heart using the wash-out principle (*2*), provides a measurement of flow in perfused tissue only, thereby failing to define the extent of unperfused or ischemic areas.

In order to investigate the extension of ischemic areas in cerebrovascular disease, we exploited a new concept, recently used for the assessment of regional lung ventilation (*3*). This led us to the development of a technique that provides functional images of brain perfusion, readily repeatable and in multiple views.

Continuous infusion of a solution of an inert diffusible gas into the arterial inflow of a vascular organ results in equilibration of the gas in the organ. If a radioactive gas is used, the count rate at equilibrium, as measured externally over the organ, will be theoretically proportional to:

$$\frac{\dot{Q}}{\frac{\dot{Q}}{Q \cdot \lambda} + \frac{\ln 2}{T_{1/2}}}, \qquad (1)$$

where $\dot{Q}$ is perfusion, $\dot{Q}/Q$ perfusion per unit volume, λ the partition coefficient for the gas between blood and tissue,* and $T_{1/2}$ the half-life of the tracer. By infusion of a gas with a relatively long half-life (for example, 5-day xenon-133), the second term in the denominator tends to zero, and the fraction is mainly dominated by the tissue volume, Q. The activity recorded externally over the organ during continuous arterial infusion of "conventional" radioactive gases such as Xe-133, Kr-85, or even of the cyclotron-produced 10-min N-13, will therefore be proportional to volume rather than perfusion.

Consider now the continuous intracarotid infusion of Kr-81m, which has a half-life of 13 sec. The rapid radioactive decay of this gas, relative to the perfusion turnover rate per unit volume, will result in a brain concentration at equilibrium much lower than that in the carotid inflow. Under these conditions, equilibrium of the nuclide in the brain depends on the balance between arrival of Kr-81m and radioactive decay, since the contribution of Kr-81m washout to

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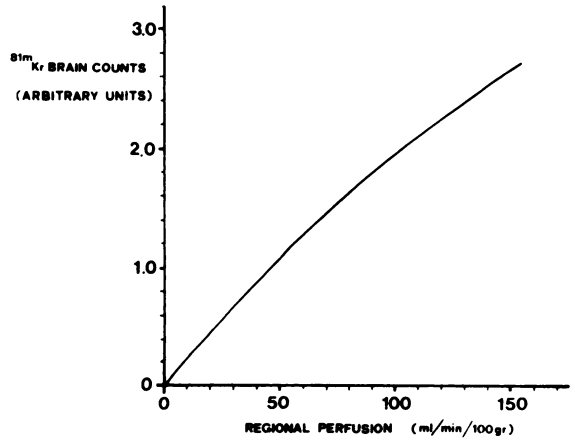

FIG. 1. Theoretical relationship between Kr-81m counts in brain and brain perfusion, calculated from equation (1).

this process is relatively small. Under continuous infusion of such a short-lived gas, it is seen from equation (1) that the denominator becomes dominated by the large value of the radioactive decay constant, $(\ln 2)/T_{1/2}$, which for Kr-81m is 3.2 when $T_{1/2}$ is in minutes. Hence the brain signal is more dependent on perfusion ($\dot{Q}$) than on washout ($\dot{Q}/Q \cdot \lambda$). Therefore, the equilibrium images recorded on a gamma camera during continuous intracarotid infusion of Kr-81m reflect the regional *arrival* of the gas—that is, regional cerebral flow ($_r$CBF).

The relation between radioactivity and regional perfusion can be computed by solving equation (1) for different values of $\dot{Q}$ (Fig. 1). At very high flow rates a deviation from linearity is observed, since the signal gradually becomes proportional to volume rather than blood flow. The relation, however, is almost linear for flow rates ranging from zero to 100–150 ml/min per 100 g—that is, under virtually any condition of either reduced or increased cerebral blood flow in man.

METHODS

Krypton-81m, which emits 190-keV gamma photons, can be continuously produced in solution by passing water through a cation-exchange column to which its parent nuclide Rb-81, is bound (*5–7*). Rubidium-81 has a half-life of 4.6 hr and is produced weekly for us on the MRC Cyclotron at Hammersmith Hospital, London, and shipped to Pisa via ordinary commercial flights, being available all day after a morning production.

The aqueous Kr-81m solution continuously recovered from the generator is mixed by Y tube with constant flow, in equal volume, of 1.8% NaCl solution in order to obtain a continuous flow of Kr-81m dissolved in 0.9% NaCl. This solution is infused through a small polyethylene cannula into the internal carotid artery with the head of the patient positioned in front of a gamma camera until 300,000 counts are collected, which is usually achieved in 30 to 60 sec. A brain perfusion image is recorded in this way, either on photographic film with a Polaroid camera, on 35 mm film with a Nikon camera, or on life-sized photographic film with a suitable adaptor device.

Due to the rapid radioactive decay of Kr-81m, the procedure can be repeated within a few seconds from the completion of the image. This allows one to follow minute-to-minute changes of $_r$CBF, and in turn to obtain $_r$CBF images in multiple views.

Absorbed radiation dose to the brain is less than 5 millirads per view. Absorbed dose to heart and kidney resulting from Rb-81 breakthrough is less than 4 millirads.

RESULTS

Functional images of cerebral perfusion were obtained in two normal volunteers, in three patients without recent signs of central impairment, and in 11 additional patients with various brain disorders.

Under normal conditions the activity appears uniformly distributed in the territory of distribution of

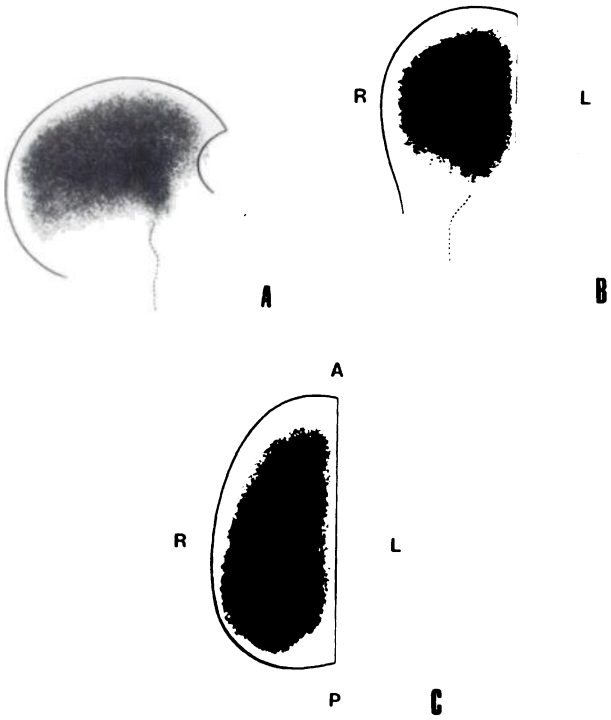

FIG. 2. Normal perfusion images (recorded on life-sized radiographic films) during right intracarotid infusion of Kr-81m. Distribution of activity is homogeneous in the right lateral (A), the frontal (B), and the vertex (C) views.

the internal carotid artery in the lateral, frontal, and vertex views (Fig. 2).

Patients with cerebrovascular disease and abnormal angiography showed sharply defined areas of reduced activity corresponding to the region supplied by the occluded vessel (Figs. 3A and 3B). The technique enables us to follow minute-by-minute changes of regional perfusion, which, in ischemic areas, can be shown to improve during hyperventilation (Fig. 3C) and subsequently to revert to the earlier distribution (Fig. 3D). Additional views can help to define diseased regions (Fig. 3E).

Areas of relatively increased blood flow due to brain tumors or arteriovenous malformations can also be visualized by the Kr-81m technique. A contrast angiogram and the perfusion scan of a patient with a highly malignant glioma are shown in Figs. 4A and 4B.

The site of infusion is not critical. Although better results are obtained with infusion into the internal carotid artery, perfusion images can also be recorded during infusion into the common carotid (compare Figs. 4B and 4C).

Two or more images for each view were obtained in all the subjects studied. Reproducibility was excellent in all instances (see Figs. 5A and 5B, and Figs. 3B and 3D).

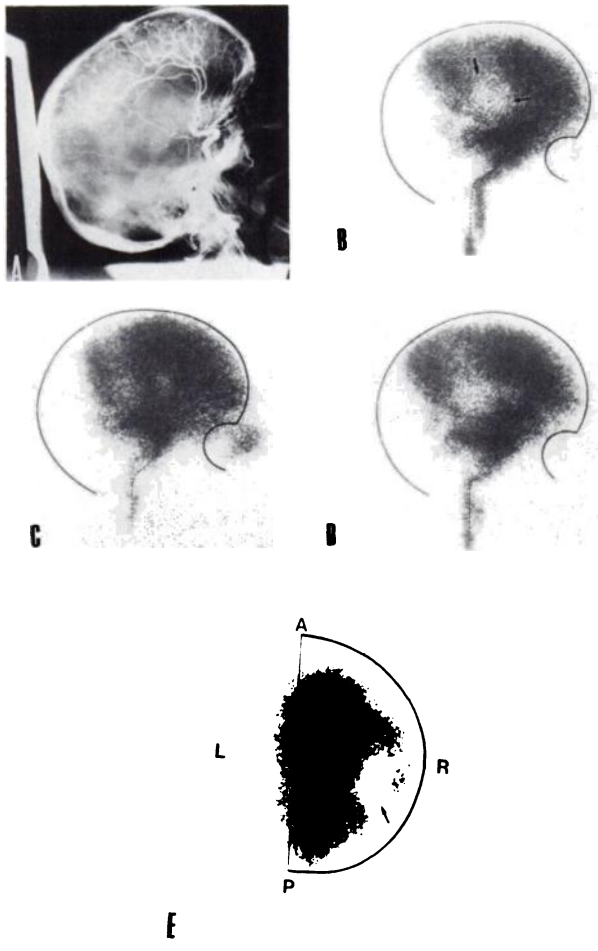

FIG. 3. Left-sided hemiplegia at 56 yr. Contrast angiography (A) shows occlusion of right middle cerebral artery. Right hemisphere Kr-81m perfusion scan in right lateral view (B) shows a sharply defined area of reduced activity (arrows) in territory of the middle cerebral artery. Arterial $PaCO_2$ was 31 mm Hg. Perfusion study repeated during hyperventilation (arterial $PaCO_2$ mm Hg) indicates a shift of perfusion toward the damaged area (C). Krypton-81m perfusion image repeated 10 min after cessation of hyperventilation, when arterial $PaCO_2$ was back to control values (32 mm Hg), is shown in D. The distribution of perfusion has returned to abnormal control pattern shown in B. Vertex view of the Kr-81m perfusion, obtained during normal breathing, is shown in E. A round, sharply defined area of reduced activity is seen in right hemisphere (arrows).

DISCUSSION

Regional cerebral blood flow is currently assessed from the regional washout curves recorded externally over the brain following intracarotid bolus injection or inhalation of inert, diffusible, radioactive gases [typically, xenon-133 and krypton-85 (*1,8*)]. These techniques provide quantitative numerical information, which can also be obtained in the form of computerized functional images (*9,10*) and has undoubtedly led to major achievements in the understanding of mechanisms regulating the cerebral circulation under both normal and pathologic conditions. As has already been pointed out (*11*), however, conflicting data have been reported on the impairment of $_rCBF$ in areas of infarction (including the influence on $_rCBF$ of acutely altered arterial $PaCO_2$) (*12–17*). This can be attributed in part to the lack of spatial resolution inherent in techniques that depend on a gamma emitter—namely, errors from the look-through phenomenon and Compton scatter (*11*). Indeed, the most important limitation (and source of error) essential to the washout principle is that of measuring flow in perfused tissue only, being theoretically unable to detect unperfused areas. This can eventually lead to large errors in the assessment of regional perfusion in cerebrovascular disease, since underperfusion can be intraregional and can exist simultaneously with a high flow rate in neighboring areas (*18*).

Inhalation methods, while noninvasive, may introduce additional errors mainly due to: a) the assumption that concentration in expired air is proportional to arterial concentration, which may be unwarranted, particularly in patients with lung disease; and b) the difficulty of measuring the concentration in the end-expired air (*19*).

Dynamic "brain blood flow" studies can be carried out by following the regional rate of appearance and disappearance of intravascular tracers. These methods will not be considered in detail here because

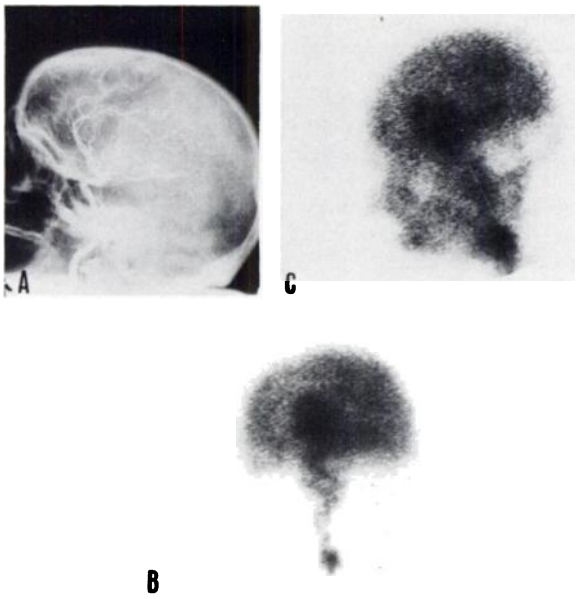

FIG. 4. Highly vascularized parietal glioma in a 66-year-old patient. (A) Contrast angiography. (B) Left lateral Kr-81m perfusion image, recorded on 35-mm film during infusion into left *internal* carotid artery; it shows increased blood flow corresponding to the tumor. (C) Perfusion scan (same view) obtained by infusing Kr-81m into left *common* carotid artery.

they provide information on mean transit time in large intracranial vessels rather than on regional brain perfusion.

Images of brain blood flow have been obtained following intracarotid injection of radioalbumin macroaggregates or microspheres (*20,21*), but the safety of this technique cannot yet be claimed with certainty (*21*).

Continuous intracarotid infusion of Kr-81m has been used to obtain functional images of brain perfusion in the dog (*22*) and in man (*23*). This method provides a simple and detailed assessment of the presence and the extension of ischemic areas in cerebrovascular disease as well as in other cerebral disorders. The technique is reproducible. Owing to the short time required, the procedure can be repeated in order to get brain-perfusion images in multiple views or to follow minute-by-minute changes of $_{r}$CBF.

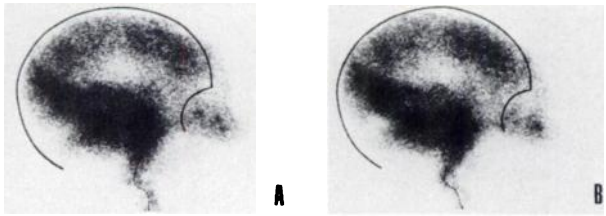

FIG. 5. Left-sided hemiplegia at 62 yr. Contrast angiography showed partial occlusion of right middle cerebral artery. (A) Kr-81m right hemisphere image, right lateral view, shows a large area of reduced activity. (B) Perfusion scan, repeated 45 min later. Comparison attests to reproducibility of the technique.

One practical disadvantage of the technique is the short half-life of the parent nuclide, Rb-81 (4.6 hr). This requires considerable planning and interest on the part of the user if a cyclotron is not available on site. The present study, however, confirms the feasibility of using Rb-81 generators at a considerable distance from the site of production—even in a different country (*24*). Indeed, availability of Rb-81 on a weekly basis has proved, in our hands, quite adequate for brain-perfusion studies.

Another disadvantage of the technique is its invasiveness. As pointed out before, however, present noninvasive techniques provide incomplete information on $_{r}$CBF. On the other hand, the relatively simple setup required (a portable gamma camera without the need of a computerized data acquisition and display system) allows the procedure to be performed easily during routine contrast angiography.

At the present stage, the technique is merely qualitative and does not provide quantitative information on $_{r}$CBF per unit mass. We feel, however, that in order to detect regional abnormalities and to follow minute-by-minute changes of regional brain perfusion, detailed functional images in multiple views may provide even more information than discrete numerical mapping. This has already proved true for other organs such as the lung, in which the qualitative lung scan with macroaggregates has completely replaced, for the assessment of pulmonary perfusion, quantitative methods involving the use of radioactive gases.

FOOTNOTE

* Blood-brain partition coefficient is 1.13 for xenon and 1.09 for krypton (*4*).

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