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REGIONAL CEREBRAL BLOOD FLOW STUDIED BY XENON-133. INTRA-ARTERIAL INJECTION STUDIES AND INHALATION STUDIES USING EMISSION TOMOGRAPHY

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Summary

A survey of the Xenon-133 techniques for measurement of regional cerebral blood flow, rCBF, in man is presented. The intra-arterial Xe-133 injection method is very sensitive for detecting even small hyperemic areas, but cannot "see" smaller ischemic areas. The Xe-133 inhalation (or i.v. inj.) technique is insensitive both to hyperemia and ischemia yielding essentially only a mean flow value. A new rapidly moving single photon tomograph following D. Kuhl's principle is presented applicable to Xe-133. Preliminary clinical data show that this technique is able to detect ischemic areas both with Xe-133 intra-arterial injection and with Xe-133 inhalation. The practical and economic advantages of Xe-133 or Xe-127 tomography over positron tomography for rCBF are discussed.

Zusammenfassung

Die Xenon-133 Untersuchungsmethoden zur Messung der regionalen Hirndurchblutung beim Menschen werden dargestellt. Die intra-arterielle Xe-133-Injektionsmethode eignet sich, kleine hyperämische Areale zuverlässig zu erfassen; kleinere ischämische Bezirke werden nur ungenau registriert. Die Xe-133-Inhalationsmethode oder die intravenöse Applikationsmethode liefert nur mittlere regionale Perfusionswerte. Eine nach D. Kuhl gebaute, jedoch modifizierte bewegliche Einzelphotonen-Tomographiekamera eignet sich - wie erste klinische Studien zeigen - zur Erfassung der Xe-133-Aktivität in kleinen hyperämischen und ischämischen Bezirken, sowohl bei intraarterieller, als auch Inhalationsapplikation von Xe-133. Die praktischen und wirtschaftlichen Vorteile dieser Xe-133 (oder Xe-127) -Tomographie im Vergleich zur Positron-Emissionstomographie werden diskutiert.

Introduction

Inert gases as hydrogen or Xenon-133 and other freely diffusible tracers as iodoantipyrine can be used to measure blood flow to the brain or other organs. The principle was developed primarily by SEYMOUR S. KETY, who in collaboration with CARL F. SCHMIDT in 1945 devised the nitrous oxide method (5). This method has mainly been applied for measuring cerebral blood flow (CBF) in man, but is currently also used in small laboratory animals (1, 2). It is based on recording the saturation or desaturation of the brain by N_2O by following both the arterial and cerebral venous concentration curves.

The diffusible tracer is used to record the system's mean transit time, $\bar{t}$, for the indicator used. As inferred by previous investigators and formally shown in the classical paper by MEIER and ZIERLER, $\bar{t}$ equals the ratio of the volume of distribution over blood flow (10) and, because inert gases have a known and practically constant volume of distribution per gram of tissue (Kety's partition coefficient, λ), blood flow per gram of tissue can be calculated. In the human brain the mean transit time of N_2O is about 2 minutes and λ is about 1.0. Hence the flow f is $\lambda/\bar{t} = 1/2 = 0.5$ ml/g/min, and, as conventionally expressed per 100 grams of brain, CBF is in man normally about 50 ml/100 g/min.

The key to using inert freely diffusible tracers lies in the relative constancy of the partition coefficient, λ. This was recognized explicitly by Kety. This coefficient depends on the gross physico-chemical composition of tissue relative to that of blood: the percentage content of lipid (and the type of lipid), water, and protein. As long as this composition is about normal, then also λ is constant. This means that the functional state of the tissue is of no importance. Even when dead, the tissue does not alter its λ value.

Many different modes of tracer application and of tracer detection have been used. This brief review aims at discussing approaches mostly commonly used in man and in animals. Special attention will be given to Xenon-133, a radioactive indicator gas that in particular has been of practical value.

The Indicators; Comments on Xenon-133. The list of freely diffusible indicators is quite long. Among the non-radioactive ones hydrogen gas should be mentioned in particular.

Xenon-133 is a reactor-produced fission product of Uranium. It has a 5.5 days half life and amids two gamma energies, at 81 and at 35 KeV. This is a fairly weak energy that easily can be shielded by lead foil of about 1 mm thickness. In water and in soft tissue the half-thickness of absorption is about 5 cm. Hence, when used in combination with external counting in man, deeply situated Xenon-133 is less well recorded than isotope in the brain cortex just under the probe. Obviously, in laboratory animals having smaller brain size, this factor is of less importance than in man.

When using Xenon-133 in combination with external counting over the head, Compton scattering is a problem of major concern. This scattering or deflection may, when it occurs in the tissue, even cause a heavily collimated detector to see radioactivity outside its field of vision. With the soft radiation in question the scattered radiation has almost the same energy as the primary radiation (12). Hence, in practice, Compton scatter by peak-height energy discrimination cannot be effectively eliminated. In order to do so one would have to count so precisely at the upper half of the 81 KeV peak, that the counting stability would suffer as well as the counting rate (and hence counting statistics). In particular, when administering Xenon-133 by inhalation or by intravenous injection this is a problem because, in either case, Xenon-133 in the air spaces of the head - nose, sinuses, mouth - will give rise to spurious scattered counts of up to 25 % or more of the total signal recorded.
Because of the problems outlined the 30 day-half-life Xenon-127, having maximal energy of 200 KeV, may prove advantageous. Current efforts at developing a single photon emission tomograph for measuring cerebral blood flow in three dimensions may make use of Xenon-127 for this very reason (4): Also its higher frequency of the gamma radiation per disintegration is favorable as it augments the ratio between counting rate and tissue radiation dose.
Currently much effort is put into dual-photon emission tomography, i.e. positron tomography. The only inert positron emitting gas so far used is the 100 minute-half-life Krypton-77 studied by the group in Montreal (14). But the low solubility of this gas means that when applied by inhalation only a very small fraction reaches the head. Ter-Pogossian has recently suggested the use of the more soluble nitrogen-13-N_2O. It would be interesting if this tracer really will become the tracer of choice for positron flow studies: To see Kety's original tracer gas reappears in a radioactive version!

Intra-arterial injection of Xenon-133

Injecting Xenon-133 or any other gamma emitting gas dissolved in saline in the artery going to the brain allows selective labelling of the brain region supplied by that artery. This method has been developed primarily by LASSEN and INGVAR (7, 8). It is so far the only reliable method permitting regional flow studies in man, the different regions seen being defined by the collimation used for the scintillation detector and by tissue absorption of radiation. Thus, with the usually employed cylindrical collimation a cone-shaped tissue block is counted from, a cone truncated in both ends at the respective surfaces (near and far) of the labelled tissue. To the sides the cone is seen with diminishing effectiveness as only part of the crystal sees the half-shadow. In depth the 5 cm-thickness of tissue half-absorption implies that the superficial cortex layer of brain tissue is seen with highest efficiency.

Often the distance to the detector is invoked to explain the weighting towards seeing the superficial tissue (cortex) best. But, as distance increases so does area seen. Hence, the inverse square law is invalidated because the brain is an "extensive" source, not a point source. The intra-arterial injection is made as a brief bolus lasting about 1 second. Care must be taken to keep the volume small as otherwise the bolus will fill the arterial tree retrogradely and hence tend to label non-cerebral tissues as well as cerebral ones.

With normal internal-carotid flow in man averaging about 4 ml/sec. a bolus with a volume of 1.0 to 1.5 ml can be used. Having the injection catheter threated up the internal carotid artery to reach the base of the skull, no retrograde overflow to the external carotid system is seen. Also, the method gives the same result as the arterio-venous method (9).

In laboratory animals great care must be taken to accomplish selective labelling of the brain. In adapting it to measurement of CBF in the rat, it was found necessary to tie off very small arterial side branches (3). In the baboon it has become routine to retract the soft tissues of the scalp as well as to use a narrow collimation to minimize non-cerebral effects. However, in view of the Compton scattering effects it is not possible completely to avoid counts from extracerebral tissues if they are injected with the isotope: selective injection to the brain is essential. Meticulous checking that this is in fact accomplished (e.g. by using microspheres) is recommended in any laboratory wanting to use the intra-arterial method in animals.

We use the intra-arterial Xenon-133 method routinely as an adjunct to cerebral angiography. Analyzing the arrival of the bolus as seen by our 254 detectors camera ("Dynamic Gamma Camera") yields a quantitative angiogram (13). The initial slope of each curve as seen over about 40 seconds allows to calculate grey matter (cortical) blood flow (11). The method is very sensitive to record local cortical (superficial) hyperemia. The area counted from measures only about 1.0 cm (FWHM) in diameter and the cortex is only about 0.3 cm thick. We most likely would be able to detect a doubling of flow in one third of this tissue mass (or even in less than that). This means that hyperemia of that order of magnitude (which is typical of local tissue activation) may be detected if as little as 0.1 gram of brain tissue becomes active. While in practice we always rely on flow increases seen simultaneously in at least two detectors the estimate, nevertheless, gives an impression of the spatial resolution that can be achieved under optimal conditions. It is not surprising, either, that the regional flow increases accompanying activity of the cortex may not be detectable when using the a-v method of Kety and Schmidt, that estimates average hemispheric blood flow.

The intra-arterial Xenon-133 injection method is relatively insensitive for detecting ischemia and for seeing deeper structures. And, when applied to man, the trauma involved in catheterization and injection of the internal carotid (or the vertebral) artery is a very major limitation.

The risk inherent in the procedure is only acceptable if the clinical diagnostic workup of the patient indicates an angiogram. With the advent of CT-scanning angiography is less needed and hence also fewer Xenon-133 intra-arterial studies are made. Currently we mainly perform the procedure in 1) selected cases of apoplexy, where a much fuller understanding of the site and nature of the lesion is obtained, 2) some cases suspected of intracerebral tumor, as small tumors not seen on CT-scan sometimes can be detected, and 3) in cases of focal cortical epilepsy, where the active areas ("focus") often can be mapped.

Xenon-133 Inhalation and External Counting, Comments on Single Photon Emission Tomography of Xenon-133 or Xenon-127

For many years attempts have been made to analyze the head curve following inhalation or intravenous injection of Xenon-122. With this atraumatic approach a small number of grossly collimated scintillation detectors is usually employed (too narrow collimation would yield an unacceptably low counting rate). This method is insensitive to hyperemia and it overlooks ischemia. It allows only a fairly gross localization. In particular the cross-over of counts from the other hemisphere extracerebral labelling and the effect of Compton scatter from the nasal airspaces are of importance. Thus, in the view of the present author, the method should be considered semiquantitative.

Currently efforts are made in our laboratory to circumvent some of these difficulties by the use of a single photon tomograph of the type developed by KUHL (6). The detector head, having four banks of 16 detectors each, rotates rapidly so that time averaging is accomplished (4). This Dynamic Gamma Tomograph (Medimatic, Copenhagen) is designed to see three slices each of 1.5 cm width simultanously. In test runs the spatial resolution with Xenon-133 sources (suspended in water to cause a Compton scatter effect as in vivo) is in the order of 1.5 cm FWHM. Our clinical results are quite encouraging in that ischemic areas are readily seen (fig. 1). In this respect Xenon-133 tomographic blood flow studies are clearly superior to the use of the conventional stationary detectors.

The proposed calculation of CBF from a series of time averaged Xenon-133 scans (13) is currently being implemented with special regard to the Compton scatter effects already mentioned.

Dynamic emission tomography of Xenon-133 or Xenon-127 inhalation may constitute an interesting alternative to flow studies using positron tomography. Without going into details it should simply be recalled:

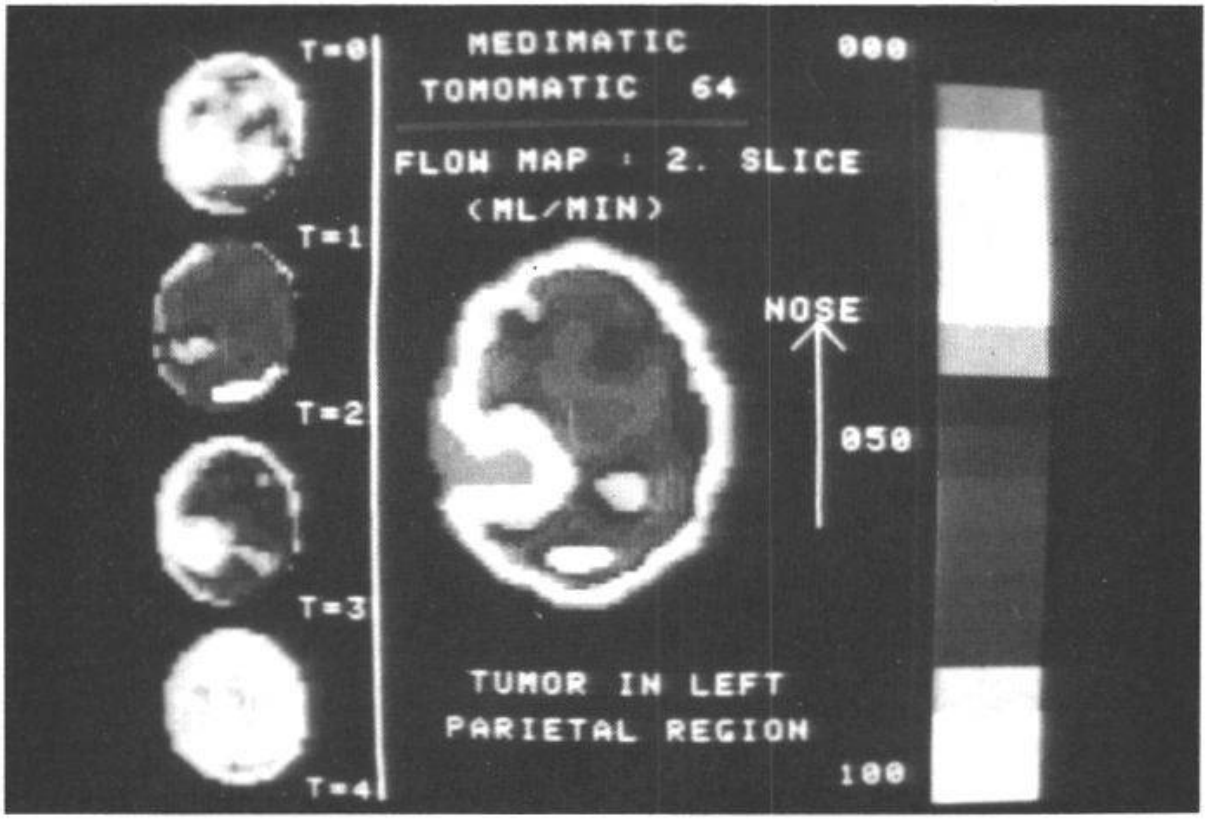

Fig. 1. Cystic tumor in left parietal region, dilatation of posterior horn. rCBF calculated for 4 minutes clearance.

1. That the cost of producing the short half-life positrons is prohibitive in most medical centers.

   Positron radiochemistry is also complex and costly. And, due to these difficulties it is, even when a cyclotron is available, virtually impossible to secure tracer availability on a 24 hour a day basis.
2. Positron cameras can achieve a good spatial resolution of about 1.0 cm only if many true coincidences are recorded, probably in the order of more than four million events. Hence the use of positron tomography for dynamic studies, that demand "exposure times" of 30 seconds or less (13), would seem to exclude high spatial resolution measurements. In practice the spatial resolution with positrons will consequently be expected to be about the same as with a high sensitivity single photon instrument, viz. about 1.5 cm.
3. The positron technology offers many very exciting possibilities other than those that can be studied by measurement of blood flow. Yet, to be able to measure flow in 3-dimensions would seem to be of considerable interest because of the clinical importance of cerebro-vascular disorders.

Even in the context of exploration of the localization of function in the brain the repeatability of the flow techniques is of some advantage. The 100 minutes half-time of Fluor-18-deoxyglucose precludes, to take an example, serial measurements in the same subject.

For the above reasons:

1. Around the clock availability of tracer at low cost,
2. presumed comparable spatial resolution, and
3. wide clinical applicability, single photon tomography of regional CBF in man may offer a more realistic solution to the development of a reliable and practical atraumatic rCBF method, than the positron technology?

Concluding Remark:

A major advantage of the inert gas methods for flow measurement has been that the same techniques can be applied both to experimental animals and to man. This has greatly facilitated the understanding of cerebral blood flow. It is tempting to postulate that this aspect is a key element in explaining the astounding increase in knowledge in the field. Many related techniques involving more traumatic experimental procedures were not mentioned. In particular Kety's local blood flow method, which is based on tissue sampling, the socalled autoradiographic method, might have deserved mention: it is the conceptual basis for Sokoloff's astrounding deoxyglucose method and even, in principle, for the tomographic techniques ("in vivo autoradiography of coarse resolution"). Truly the contribution of Kety and his many coworkers, foremost of Sokoloff, is opening up a new dimension of clinical and experimental neurophysiology that we present at this meeting are privilized to take part in.

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