Cerebral Circulation Studies Using Inhaled 133-Xenon and the Gamma Camera

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Abstract: Inhaled 133-xenon was utilized in conjunction with the Anger gamma scintillation camera to evaluate cerebral circulation in 20 asymptomatic control subjects and in 41 patients with clinical cerebrovascular disease. Sequential cerebral scintiphotos thus obtained revealed focal areas of decreased activity in 2 of 19 control subjects and in 15 of 38 patients. A computerized curve-fitting technique was used to calculate an index of cerebral blood flow ("K") by means of the 133-xenon clearance curves obtained from each half of the head. Shorter periods of 133-xenon inhalation resulted in more rapid rates of clearance. In patients with clinical cerebrovascular disease, cerebral clearance rates tended to be lower and to show more variation between the two sides of the head than in asymptomatic subjects.

ADDITIONAL KEY WORDS
- cerebrovascular disease
- cerebral blood flow
- scintiphotos

A number of radioisotopic methods for evaluating cerebral blood flow and circulation in human subjects are currently available (1–3). The development of simple, safe, and atraumatic methods for such studies has been the aim of numerous investigators. Unfortunately, quantitative accuracy combined with simplicity and safety has not as yet been attained with any of these methods.

Regional cerebral blood flow can be estimated with considerable accuracy from the clearance curves obtained by external monitoring of 133-xenon injected into the internal carotid artery (4–12). The need to perform internal carotid artery cannulation, however, has virtually limited its use to subjects in whom selective cerebral angiography is being done at the same time. In contrast, inhalation of 133-xenon provides a completely atraumatic method of administration suitable for repeated studies in the same individual and in a variety of clinical situations (13–24).

The gamma scintillation camera provides a large scintillation detector which, with adequate collimation, is capable of recording regional uptake and clearance of isotopes in various organs and tissues, including the brain. This study was undertaken to evaluate the use of the gamma camera in conjunction with the 133-xenon inhalation method for the assessment of the cerebral circulation in asymptomatic subjects and in patients with clinical cerebrovascular disease.

Methods

An Anger gamma scintillation camera with an 11-inch sodium iodide crystal and high resolution collimation was used. Vertical electronic division of the crystal permitted graphical recording of gamma activity on two chart recorders. Subjects were studied in the supine position. The face of the camera was placed directly against the patient's forehead perpendicular to a plane passing through the external auditory canals and supraor-
bital ridges. Lead shielding prevented recording of gamma activity from tissues below that plane. The head was carefully positioned so that the sagittal midline plane of the head corresponded to the location of the vertical electronic division of the crystal.

The isotope, 133-xenon in air, was administered by inhalation from a spirometer reservoir in a closed recirculating system. Approximately 20 mc of 133-xenon in 5 L of air were used in each study. The duration of inhalation was either eight or two minutes. At the end of the inhalation period, the subject inhaled room air while all exhaled air was exhausted to the outside.

Sequential polaroid scintiphotos of emitted gamma activity were obtained during both inhalation and clearance phases of each study. Approximately 30,000 counts were allowed to accumulate for each scintiphoto. A total of six to ten scintiphotos were obtained in each study.

Background activity was adjusted to zero on the chart recorders at the beginning of each study. Recording was continued for 40 minutes after the end of the inhalation period. The clearance or “washout” portions of the recorded curves from each half of the head were analyzed by means of a computerized curve-fitting technique. It was assumed that the curve form obtained represented an infinite or at least a very large number of exponential terms. This curve form can be represented by the equation:

\[ C(t) = \frac{C(0)}{(1 + At)^B} \]

where \( C \) = concentration, \( t \) = time, \( 0 \) = time zero, and \( A \) and \( B \) are positive constants for a given time series. The curve-fitting technique determined the \( A \) and \( B \) constants for each curve. The product \( (A \cdot B) \) was designated as “K”. The “K” value for each curve can thus be considered an index of the rate of clearance of 133-xenon from that half of the head. In turn, the rate of clearance of 133-xenon is assumed to be related closely to cerebral blood flow. Rapid clearance of cerebral 133-xenon would thus result in higher “K” values, while slower clearance would result in lower “K” values.

Inhalation studies were performed on 20 asymptomatic subjects aged 40 to 75 years and in 41 patients of similar age with clinical cerebrovascular disease. Six asymptomatic subjects were studied once using eight-minute and twice using two-minute inhalation periods. Thirty-two of the 41 patients were diagnosed as suffering from unilateral cerebral infarction of varying duration. The remaining nine patients were individuals who had experienced either bilateral cerebral infarction, brain stem infarction, or transient ischemic episodes.

**Results**

By means of the “split-crystal” gamma camera detector system, it was found that inhalation periods of eight to ten minutes were necessary to attain approximate plateaus in recorded uptake curves (fig. 1, upper curve).
For this reason eight-minute inhalation periods were used in the initial studies. The "K" values obtained after eight minutes of 133-xenon inhalation in 17 asymptomatic control subjects and in 19 patients with clinical cerebrovascular disease are plotted in figure 2. Each point on this graph represents the "K" values from both sides of the head plotted against each other. Thus, if clearance rates were identical on both sides of the head, the plotted values would fall on the 45° axis of the graph.

In the 17 asymptomatic control subjects, "K" values ranged from 9 to 24 arbitrary units and tended to be approximately equal on both sides of the head for any given individual. In only two of these 17 control subjects was there a difference greater than 3 units in the "K" values from both sides of the head in the same subject.

Similar studies in 19 patients with clinical cerebrovascular disease, however, revealed a wider range of "K" values, as well as a tendency for a greater disparity between "K" values from the two sides of the head (fig. 2). The lowest "K" values obtained in these eight-minute inhalation studies were from patients with clinical cerebrovascular disease. The highest "K" values were obtained in two patients with clinical evidence of small brain infarcts.

A reduction in the duration of the inhalation period from eight to two minutes resulted in increased rates of clearance of inhaled 133-xenon (fig. 1, lower curve). In six asymptomatic control subjects studied with both eight- and two-minute inhalation periods, the "K" values were consistently higher following two-minute inhalation periods (fig. 3). Repeated two-minute inhalation studies in these same six subjects (data not shown) resulted in clearance curves with "K" values within this same range. However, the "K" values for any given individual tended to vary considerably within this range on repeated testing.

A total of nine asymptomatic control subjects and 22 patients with clinical cerebrovascular disease were then studied with two-minute inhalation periods (fig. 4). The "K" values in patients now tended to be lower than
in the control subjects. In addition, “K” values in patients tended to show more disparity between the two sides of the head than did the “K” values in asymptomatic subjects.

A total of 32 patients with clinical evidence of unilateral cerebral infarction were studied with either eight- or two-minute inhalation periods. In these patients “K” values were relatively lower on the side of the infarction in 18, higher in 4, and approximately equal in 10. In contrast, in only 3 of the 20 asymptomatic subjects studied with either eight- or two-minute inhalation periods did the “K” values differ by more than 3 arbitrary units between the two sides of the head (figs. 2 and 4).

Scintiphotos obtained in normal subjects during uptake and early clearance portions of both eight- and two-minute studies tended to show a uniform distribution of activity (fig. 5). In scintiphotos obtained near the end of the 40-minute “washout” period, however, much of the activity was evident in the periphery of the head, probably indicating residual activity in scalp and skull. Adequate series of scintiphotos were obtained in 19 of the 20 asymptomatic control subjects and in 38 of the 41 patients. The scintiphotos of 2 of the 19 asymptomatic subjects showed focal areas of apparent asymmetry of gamma activity. In contrast, apparently abnormal scintiphotos were observed in 15 of 38 patients with cerebrovascular disease (fig. 6). In 11 of these 15 patients the areas of decreased activity in the scintiphotos corresponded approximately to the site of cerebral infarction as diagnosed clinically. In two other patients the scintiphotos showed focal areas of decreased activity on the side of the head opposite to the side of the infarct. In addition, the scintiphotos obtained in two patients with brain stem infarction also revealed areas of decreased activity. Several patients who were considered to have suffered only small areas of unilateral cerebral infarction showed very large areas of decreased activity on the scintiphotos.

**Discussion**

Most methods currently being used for quantitative measurement of cerebral blood flow in humans require puncture or catheterization of the internal carotid artery and/or the jugular vein. The 133-xenon inhalation method, by virtue of its relative simplicity and atraumatic nature, thus offers an attractive alternative. This advantage is offset, however, by the problems raised by recirculation of isotope and contamination of the data by isotope in the scalp and skull. Absorption and subsequent slow release of xenon by other body tissues, especially the fat depots, or disturbances in pulmonary function may also result in prolonged elevation of tissue 133-xenon levels. Because of these problems the “two-compartmental” or bi-exponential model usually used in the carotid injection method is
not directly applicable to the inhalation method. Several complex mathematical approaches directed at the problems of recirculating isotope and contamination of the data by extracranial circulation have been proposed (19, 21).

The clearance curves obtained in this study (fig. 1) did not lend themselves to analysis with a three or even four exponential model. Instead, the curve form obtained appeared to be made up of a very large number of exponentials, which could be adequately represented by the equation:

$$C(t) = \frac{C(0)}{(1 + At)^B}$$

The "K" values (i.e., A · B) thus obtained could be considered as a numerical index of the rate of clearance of cerebral 133-xenon from a very large or infinite number of tissue compartments. No attempt has been made to translate this index into quantitative values of cerebral blood flow per unit weight of tissue.

It is apparent that the duration of the period of inhalation also affects the externally recorded clearance curves (fig. 1) and thus affects the "K" values obtained (fig. 3). The relatively slower clearance rates and lower "K" values following longer inhalation periods are probably related to increased absorption and retention of 133-xenon by various tissues, including those of the skull and scalp. A similar relationship between the duration of the inhalation period and clearance rates has been previously demonstrated (17).

On the basis of the "K" values obtained from both sides of the head, it would appear that some individuals with cerebrovascular disease may be differentiated from asymptomatic subjects of similar age (figs. 2 and 4). The differences in "K" values between asymptomatic subjects and patients were somewhat more apparent when two-minute inhalation periods were used. Some patients with clinically unilateral cerebral infarction studied with either two- or eight-minute inhalation periods demonstrated unusually low "K" values (i.e., slow clearance rates) on both sides of the head. This bilateral effect may be related to the presence of bilateral cerebrovascular disease or...
to some neural influence of a unilateral cerebral infarct on the circulation in the opposite hemisphere (25, 26).

Differences in “K” values of more than 3 units between the two sides of the head were present more often in patients with clinical cerebrovascular disease than in asymptomatic subjects. Thus, in 18 of 32 patients with unilateral cerebral infarction, “K” values were lower on the side of the lesion. However, in four patients “K” values were relatively higher on the side of the infarct.

The highest “K” values obtained in the eight-minute inhalation studies (fig. 2) were from two patients with small brain stem infarcts, one recent and the other old. Since the completion of these studies, two additional patients with brain stem infarcts have been studied, using two-minute inhalation periods (but with a somewhat different recording technique), and have also shown unusually rapid clearance rates. The possibility of alterations in cerebral blood flow in patients with brain stem lesions will be investigated further.

A major reason for using the gamma camera in this study was to evaluate the capability of rapid sequence scintiphotos as an indicator of regional tissue blood flow. To our knowledge only one other report describing cerebral scintiphotos produced by inhaled or injected 133-xenon is available (27). The present series thus represents the only comparative study of such 133-xenon “brain scans” in asymptomatic subjects and in patients with cerebral infarction. In 17 of 19 asymptomatic subjects, the scintiphotos thus obtained showed a uniform and bilaterally symmetrical distribution of gamma activity. However, in 15 of 38 patients with clinical cerebrovascular disease, localized areas of decreased gamma activity were evident in the scintiphotos. These areas of decreased gamma activity usually, but not always, corresponded approximately to the site and side of the cerebral infarction. In all patients in whom an apparent scintiphoto abnormality was found, the area of decreased gamma activity was present during both inhalation and clearance phases of the study. In no case did the scintiphotos reveal focal areas of increased gamma activity or regions of delayed clearance of 133-xenon activity.

It would therefore appear that anterior cerebral scintiphotos obtained during and after 133-xenon inhalation are more often abnormal in patients with clinical cerebrovascular disease than in asymptomatic subjects. The use of rapid sequence xenon scintiphotos does, however, have rather obvious limitations when applied to the study of the cerebral circulation. Because of the anterior position of the camera, much information from other portions of the head is lost or at least obscured. It is possible that further technical modifications, such as increasing the amounts of 133-xenon inhaled, decreasing the exposure periods, and using additional lateral views, might increase the accuracy of such a test for the detection of regional tissue perfusion abnormalities.

Despite the rather obvious limitations of the 133-xenon inhalation method, as shown in this study, it is our feeling that this approach is worthy of further investigation. Recent technical developments, particularly the addition of a 1600-channel memory system for the gamma camera, are currently being evaluated in an attempt to define better the regional changes in tissue perfusion. The major problems of recirculation of isotope, the effect of extracranial circulation, and the effect of abnormalities in pulmonary function will require further solutions before valid quantitative results may be obtained with this method.

**Conclusion**

Inhaled 133-xenon and the gamma scintillation camera have been utilized to evaluate the cerebral circulation in asymptomatic subjects and in patients with clinical cerebrovascular disease. The rate of clearance of inhaled 133-xenon is to some extent dependent on the duration of inhalation. Clearance rates in patients with cerebrovascular disease tend to be lower and to show more variation between the two sides of the head as compared with clearance rates in asymptomatic subjects. Similarly, sequential cerebral scintiphotos obtained during each study more often show focal abnormalities in patients with cerebrovascular disease than in asymptomatic subjects. This atraumatic method is capable of detecting some abnormalities of cerebral circulation related to cerebrovascular disease. Further studies with this system appear to be warranted.
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