Xenon-133 Inhalation Method for Regional Cerebral Blood Flow Measurements: Normal Values and Test-Retest Results

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SUMMARY  The purpose of this investigation is to determine the normal values for regional cerebral blood flow (rCBF) as determined by the xenon inhalation method of Obrist. Normal values for all rCBF parameters were measured in 15 healthy individuals. Our data are compared with the normal data obtained by other investigators. In addition, test-retest rCBF measurements were performed to determine the reproducibility of the method. Our results show that the method is highly reproducible when carried out in serial studies over a short period of time.

ONE METHOD for determining the pathophysiological alterations in cerebral vascular disease is by regional cerebral blood flow (rCBF) measurements. These can be done in a serial manner to follow the natural history of the regional blood flow disturbance or to determine the effect of therapy in patients with transient ischemic attacks and acute strokes. A great deal of work has been performed using the invasive carotid injection method to measure regional cerebral blood flow. At the present time there is available a non-invasive method to measure regional cerebral blood flow. This was originally described by Mallett and Veall1-2 and was subsequently modified by Obrist and his colleagues.3-4 Data on normal values using this method have been reported by Obrist et al.,6 Corbett and Eidelman,6 and by Meyer et al.7 Normal values as well as test-retest results were described by Blauenstein and his associates.8 The background of the xenon-inhalation method has been discussed by Merory et al.9 and Meyer et al.10 The purpose of this paper is to report the results of regional cerebral blood flow measurements by the xenon inhalation method in normal individuals and to test the reproducibility of the method by serial measurements.

Methods

The equipment and methods used consisted of a 16-channel Harshaw TASC-5 system with the PDP-11-05 computer along with the computer program described by Obrist. Seven regions were measured over each side of the head. The studies were performed by having the subject breathe 8 millicuries of xenon-133 per liter for a period of 1 minute from a 10 liter Radx Ventl-Con Spirometer. The xenon in air was administered via a Bennett Benefit mask No. 5253 containing a port for withdrawal of continuous samples for radioisotopic analysis of the air curve and for an estimation of carbon dioxide levels. End-tidal air sampling was taken directly from the mouthpiece over a 2 inch scintillation probe in the shielded Ventl-Con to obtain the air curve for xenon. End-tidal air was pulled over the air probe at a rate of 1.5 liters per second and took less than 2 seconds to reach the air probe from the mouthpiece. The probe was a Harshaw type M12 SHA1/3/4-x consisting of a 0.5 X 0.5 inch NaI (T1) crystal fitted with a 1 inch lead and stainless steel collimator with an 0.5 inch internal diameter.

Probes were placed in fixed positions mounted on a modified motorcycle helmet as suggested by Meyer et al.
A stable reference to the orbitomeatal line was maintained when placing the helmet on patients. Probe positions were established for a plastic embedded skull. There were 7 probes per side. Tests were performed in the sitting position. Blood pressure was monitored with a sphygmomanometer cuff.

Recording windows were set to include both x-ray and gamma peaks. Unedited data were processed by a TASC-5 Dynamic CBF Analysers (Harshaw) linked to a PDP-11/05 computer. The program was obtained from Tenncomp Systems and consisted of the Scanner TP-5200-11-004D version of the Obrist calculations. The computer fits the clearance curves by a least squares method, and the curve fitting begins at approximately the peak of the head curve, which corresponds to the 20 percent point on the air curve.

The following CBF measurements are printed out by the computer using formulae in the computer program developed by Obrist, et al.\(^4\) Flow gray (FF\(_G\)) is derived from the clearance rate, K\(_G\), of the first compartment. Flow white (FW) or “slow flow” is derived from the clearance rate, K\(_W\), of the second compartment.

\[
egin{align*}
\text{Mean flow (MF)} & = \frac{100 \times \text{mean clearance rate}}{	ext{in black and white corrected for the hemoglobin value. Flow white (FW) or “slow flow” is derived from the clearance rate, K\(_W\), of the second compartment.} \\
\text{Mean flow (MF)} & = \frac{100 \times \text{mean clearance rate}}{	ext{in black and white corrected for the hemoglobin value. Flow white (FW) or “slow flow” is derived from the clearance rate, K\(_W\), of the second compartment.}}
\end{align*}
\]

The mean fractional flow gray (FF\(_G\)) and fractional flow white (FF\(_W\)) are derived from F\(_F_1\) = P\(_1\)/P\(_2\) and F\(_F_2\) = (1 - F\(_F_1\)), both expressed as percentages. Weight gray (WG) and weight white (WW) are computed from WG = P\(_2\)/F\(_F_1\) and WW = 1 - WG. These are the relative weights of gray and white matter (or “slow clearing tissue”) expressed as percentages. CBF\(_\text{total}\) is the sum of the products of the fractional flows (FF\(_G\) and FF\(_W\)) times the clearance rates (K\(_G\) and K\(_W\)) for each of the two compartments, i.e., 100 \times (FF\(_G\) \times K\(_D\) + FF\(_W\) \times K\(_D\)). The ISI\(_2\) is a modification of the initial slope index of Risberg et al.\(^{11}\)

At the end of 1 minute xenon inhalation the subject was switched to room air. Clearance of the xenon was then monitored for 10 minutes during the actual regional cerebral blood flow measurement. During this time counts were accumulated from the air and head probes and stored in the computer. At the end of the cerebral blood flow study, the raw and interpolated head and air curve data were displayed on a Tektronix 4010-1 terminal along with a digital display of peak counts. Our peak counts for the head curve were usually around 3,000 counts 0.1 minute. After the study was completed and the curves visualized, the study data were then analyzed by the Obrist computer program on the PDP-11/05 computer. Answers were obtained by using an iterative technique furnished by Tenncomp based on the Obrist equations. Results of the cerebral blood flow were then printed on teletype.

In this report, 15 normal volunteers between the ages of 20 and 36 years (mean 28 ± 4 years) were studied by the method described above. All subjects were normotensive and the PCO\(_2\) ranged from 38 to 42 mm Hg. Since the PCO\(_2\) values fall within the physiologic range, no CBF correction for PCO\(_2\) was necessary. The test-retest results were obtained from 10 neurological patients. All subjects and patients were examined in the sitting position in a well-lighted room. The procedure was explained to all volunteers and patients and they became acclimatized to the facemask before the study was carried out. All of our subjects were familiar with our method and hence were fully relaxed during the procedure.

**Results**

The mean values for the superior frontal region, the mid-frontal region, the precentral region, the anterior temporal region, the inferior parietal region, the superior parietal region, the posterior temporal region, and for the hemispheric mean values for both the right and left sides in the 15 normal subjects are shown in table 1. The average of the right and left side

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<th>SD</th>
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<th>SD</th>
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<th>SD</th>
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for CBFINITIAL was 78.0 ± 12.1; the ISI4 was 59.5 ± 8.4; the flow gray, 77.6 ± 10.4 ml per 100 grams of brain per minute; the flow white, 18.2 ± 2.7 ml per 100 grams of brain per minute; the mean flow, 49.0 ± 8.9 ml per 100 grams of brain per minute; the flow white, 18.2 ± 2.7 grams of brain per minute; the mean flow, 49.0 ± 8.9 ml per 100 grams of brain per minute; the FF,, 79.0 ± 3.4; and the weight gray, 48.0 ± 6.0.

In the test-retest study (table 2), initial rCBF measurements were performed and 20 minutes later a repeat rCBF study was carried out. The Pco2 was monitored on a Goddart capnograph and was consistent from study to study. Results were obtained from 140 individual probe measurements in these 10 patients. The means and standard deviations for all rCBF parameters are shown in table 2, along with test-retest correlation coefficients (all significant at P < 0.001).

Discriminate function analysis was employed to test for differences in the 7 rCBF variables in the volunteer and patient populations. This procedure establishes which of the variables best separate or discriminate between the populations (measured by Mahalanobis' D2) and also classifies each patient into 1 of the populations (table 3). Of the 7 variables, WG proved to have the greatest discriminatory power, and only FG failed to have significant discriminative value. Three of the variables (WG, MF, and FW) classified 100% of the patients with the correct population.

Discussion

As can be seen from table 4, the normal values we have obtained by the xenon inhalation rCBF method are similar to those of other investigators. In our study, there was essentially no difference between the right and left hemispheres. In comparison to others, however, we were unable to demonstrate the hyperfrontality. This is possibly due to habituation as described by Risberg et al.12 since all of our subjects were familiar with our rCBF method and the procedure.

Using the invasive technique, Perez et al.13 reported similar results in the discriminate value of WG and FG separating dementia patients from controls. While WG proved to be the most powerful statistical measure for separating groups of patients, it is our impression that FG may be the best clinical measure for demonstrating regional dysfunctions. It is our opinion that these regional differences in FG in the patient population did not affect the mean FG sufficiently for the variable to have significant discriminative value.

The xenon inhalation rCBF method has been compared with the xenon injection rCBF method by Reivich et al.14 In 11 patients they found a correlation coefficient of 0.96 (P < 0.001) between inhalation and injection measurements. Their interregional coefficient of variation in 9 normal individuals was 5.5% ± 1.5%. Wyper et al.15 also carried out studies in 11 subjects comparing the xenon injection and xenon inhalation method using the 2 minute flow index method. They found that more than 84% of the results fall within the 95% confidence limits for the reproducibility of the inhalation technique.

The reproducibility of the method has also been tested by Blauenstein et al.4 Their study and ours show that this method is highly reproducible. Since we now

<table>
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<th>Author</th>
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<th>SD</th>
<th>ISI4 Mean</th>
<th>SD</th>
<th>FG Mean</th>
<th>SD</th>
<th>FW Mean</th>
<th>SD</th>
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<th>SD</th>
<th>WG Mean</th>
<th>SD</th>
<th>FF1 Mean</th>
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<td>Corbett and Eidelman (1975)*</td>
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<td>Meyer, et al. (1978)</td>
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<td>79.0 ± 3.0</td>
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* = Sig. at P < .01. ** = Sig. at P < .001.
have an atraumatic method to study regional cerebral circulation we will now be able to study the pathophysiological alterations in hemodynamics that are occurring in patients with transient ischemic attacks and stroke. The effects of treatment can be determined as well as new information acquired concerning the natural history of cerebral vascular insufficiency.

Acknowledgment

We wish to thank Dr. Walter Obrist for his assistance during the development of our laboratory.

References

Xenon-133 inhalation method for regional cerebral blood flow measurements: normal values and test-retest results.

L C McHenry, Jr, J Merory, E Bass, D A Stump, R Williams, R Witcofski, G Howard and J F Toole

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