Analysis of Reproducibility and Sensitivity of Atraumatic Measurements of Regional Cerebral Blood Flow in Cerebrovascular Diseases

PH. MERIC, D. SC., A. LUFT, M.D., J. SEYLAZ, D. SC., AND H. MAMO, M.D.

SUMMARY We tested the reproducibility of consecutive measurements of regional cerebral blood flow (rCBF) made in 13 areas of each hemisphere in patients with cerebrovascular diseases by the atraumatic $^{133}$Xe intravenous injection method. The data were analysed by a two-compartment model similar to that used in the Obrist inhalation method. Four parameters derived from the model were tested: $\text{F}_g$ (flow of the fast-clearing compartment), $\text{FF}$ and $\text{W}$ (respectively fractional flow and relative tissue weight of the same compartment), $\text{ISI}$ (initial slope index as defined by Risberg et al.). No significant variation was found in these four parameters between two consecutive rest measurements for all the areas studied and whatever the time interval between the measurements. The variances of the differences of $\text{F}_g$ and $\text{ISI}$ between the two measurements were found to be similar to those found in normal healthy subjects. The variances of $\text{FF}$ and, consequently, $\text{W}$ were greater than the values determined in healthy volunteers. An attempt to improve the quality of the results, by correcting them for the effects of $\text{PaCO}_2$ changes between the measurements, resulted on the contrary in a general increase of the variances of the differences, showing the inadequacy of the correction coefficients used for healthy subjects at least for a proportion of the patients with cerebrovascular diseases. Sensitivity, tested by activation (hand work), shows a positive answer for $\text{F}_g$ but no significant change in $\text{ISI}$ in any area. These findings demonstrate that in cases of cerebrovascular diseases the raw data (uncorrected for the changes in $\text{PaCO}_2$) are the most reliable data but the meaning of the values found for $\text{FF}$ and $\text{W}$ must be regarded with caution since they may be affected by the "slippage" phenomenon. It is suggested that the $\text{ISI}$ should only be used when there is evidence of a failure of the compartmental model, but only as a rough estimation of the flow level because of its lack of sensitivity.

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THE MEASUREMENT OF REGIONAL CEREBRAL BLOOD FLOW (rCBF) by non-invasive techniques based on clearance of inhaled or intravenously injected $^{133}$Xe is now widely used in clinical investigations. These techniques enable simultaneous bilateral measurements of rCBF to be made and are mainly used for investigations in healthy volunteers subjected to neuropsychological tests and, obviously, for investigations in patients with cerebrovascular diseases. In these two fields, practically all the studies necessitate consecutive measurements in the same subject, for example, in order to compare resting rCBF to rCBF during the test in neuropsychological studies, to investigate the efficiency of a drug or to observe the characteristics of a specific cerebrovascular disease in patients. The interpretation of such consecutive measurements requires an intimate knowledge of the reproducibility of the measurements and its dependence on physiological variables influencing rCBF, such as, e.g., arterial $\text{PCO}_2$ or neuronal activity. A relatively wide range of information on these points is available for the measurements performed in healthy volunteers fully instructed and well accustomed to the conditions of the measurement, but there is little information on routine measurements performed on patients with cerebrovascular disease in whom the resting conditions can never be fully obtained (eyes closed, silence, no anxiety, stable breathing). In the present study we present an analysis of the reproducibility of measurements and its relationship to physiological variables in subjects randomly selected among patients with cerebrovascular disease, and who required a check of their rCBF.

Methods

Two consecutive measurements were made in 30 patients. In 14 of them these measurements were made in resting conditions at an interval of 30 minutes, and in 8 others at an interval of several days; in the remaining 8, two measurements at an interval of 30 minutes were made, the first one in resting conditions, the second one during arm work, i.e., dynamic hand contractions with a frequency of about 1 Hz during the whole measurement. The patients were randomly selected among those whose cerebrovascular state necessitated an rCBF check. They presented various cerebrovascular disorders, such as transient ischemic attacks, chronic strokes, subarachnoid haemorrhage, polycythemia, etc. The 8 patients selected for the activation test were chosen from subjects presenting only a focal perturbation in one hemisphere and apparently no global perturbation of rCBF regulation.

rCBF was measured in 13 areas of each hemisphere (fig. 1) by a method similar to the Xenon-133 inhalation method described by Obrist et al., in which the isotope is introduced into the vascular bed by an intravenous injection instead of an inhalation of a Xenon-air mixture. The details of the measurement procedure and of the apparatus used are described elsewhere. The 26 probes, containing $\text{NaI (TI)}$ crystals (3/4" diameter × 3/4" long) and 3/4"T.D. × 1" lead collimators, recorded the clearance of $^{133}$Xe from the head and an identical probe recorded the end-tidal air activity, assumed to be a good estimation of the arterial blood.
The head clearance curves were registered through energy discriminators which accepted pulses between 75 and 100 KeV; this eliminated the majority of the Compton scattered radiation and thus improved the localization of the measurements, allowing however a count rate of 800–1000 cps at the peak of the clearance curve for the collimation and the injected dose of Xenon (15–20 mCi) used. The clearance curves were analysed by programs based upon the compartmental model described by Obrist et al. In this model the cerebral circulation is represented by two compartments in parallel, the faster-clearing one corresponding to the grey matter circulation and the slower clearing one to the circulation in the white matter and contaminated extracerebral tissue. This analysis makes use of the registered end-tidal air concentration curve to correct the head curves for the recirculation of the tracer, i.e., the arterial blood concentration curve. The part of the head curve used in the analysis is situated between the so-called start fit time and the end fit time. Previous studies have shown that in this method the start fit time must be delayed in patients with a low mean hemispheric blood flow compared with that determined for the healthy volunteers (fixed at 1.6 minutes) in order to obtain a good correlation of the results with those given by the intracarotid injection method. This is mainly due to the time lag between the registered head curves and the estimation of the curve of the arterial blood concentration by the end-tidal air concentration curves. The other cause of perturbation of the beginning of the clearance curves, scattered radiation from the contaminated airways, is substantially reduced by the energy window used. The time lag cannot be measured with sufficient precision to include it in the compartmental model to correct its perturbing effect on the rCBF calculation when the whole cerebral clearance curve is used in the analysis. The perturbations can only be made relatively negligible by removing, for the purposes of the calculation, the first part of the clearance curve, this part being relatively longer when flow levels are low, as has been shown elsewhere by computer simulations. These simulations indicated that the start fit time should be set at 2.5 minutes when flow levels are reduced by about 25% (± 10%) of the normal values and at 3 minutes when they are reduced by about 50% (± 15%). The overlapping of the two ranges of reduction indicates that for intermediate values the change of start fit time has negligible consequences. The end fit time is set at 11 minutes because this limitation minimizes the perturbations of the analysis caused by the slow clearance of the contaminated extracerebral tissues such as the skull and scalp. This end fit time however leaves a sufficient portion of the clearance curve to obtain satisfactory precision in the values of the parameters determined in the analysis, taking account of the counting statistics resulting from the quantity of isotope injected.

Several parameters are determined from the fit of this portion of the head curve by the equations derived from the compartmental model. In this study, only the most commonly used in the studies on cerebral circulation were retained: Fg, the grey matter flow computed from the clearance rate of the fast-clearing compartment and the blood tissue partition coefficient of grey matter, λg, which is hematocrit-dependent and is determined by the relation given by Purves; FF (%), the fractional flow in the grey matter compartment, expressed as a percentage of the total blood flow in the tissue under observation, as defined by Obrist et al; W (%), the relative weight of grey matter expressed as a percentage of the total weight of tissue in the field of the collimators; and ISI, Initial Slope Index, derived from the slope of the clearance curves between 2 and 3 minutes corrected for the recirculation of the tracer. The principals of the calculation ISI and the validity of this index have been extensively described by Risberg et al.

Flow values Fg and ISI can be expressed in absolute values or in relative values compared to the mean hemispheric flow. These relative values, in contrast to absolute values, allow comparison of the regional flow distribution in the hemispheres between several subjects at different levels of hemispheric mean flow. It must be emphasized that Fg and FF are quantitative values assigned to the grey matter whereas W, which can only be computed with the help of a complementary hypothesis (roughly speaking, the second compartment is assumed to consist only of white matter) must be regarded rather as an index than as a strictly quantitative value.

The ISI apparently provides no particular information in addition to those given by Fg, FF and W. In fact this parameter is useful mainly in highly pathological states where the computer fails to distinguish between lowered grey matter flows and the white matter flows, or when the partition coefficient of the grey matter may be suspected to be modified. The conditions of resting measurement performed in this study are not as rigorous as those used in measurements on healthy volunteers, but they are closer to those used in “routine” measurements. Patients were first briefly informed of the procedure of the measurement and requested, as far as their level of conscious-
ness allowed, to be relaxed but not asleep and to breathe regularly. Next, patients were allowed about 10 minutes before the start of the injection to relax and become accustomed to the apparatus. The measurement was started when the level of arterial carbon dioxide tension (Paco$_2$) appeared stable as estimated by the end-tidal CO$_2$ measured with a capnograph (Siemens 323). The level of end-tidal carbon dioxide tension was also monitored during the measurement and subjects with more than 2 mm Hg of variation during the measurement were rejected from the sample.

Results
This study was carried out on a nonhomogeneous group of pathological subjects, so that no inter-individual comparison of the flow levels or other parameters nor any comparison of different areas in a given subject can validly be made, since the extent of the perturbations of the brain circulation of the subjects is highly variable as well as their localization (unilateral or bilateral, symmetrical or asymmetrical). Furthermore, we cannot distinguish between physiological variations (due to age for example) and pathological variations. This is also true for the third group of subjects with a healthy hemisphere because it has been shown that a focal perturbation in one hemisphere may affect in some cases flow levels in the contralateral hemisphere. Moreover, this group, selected for a specific type of cerebral vascular disease, can be regarded as nonhomogeneous in other ways, such as age and side of the focal perturbation.

This explains why in this study only variations of the parameters between the two measurements performed in the same patient are analysed. For the same reason, i.e., gross inter-individual and inter-hemispheric variations, the changes of the parameters are expressed in absolute values and not as a coefficient of variation (C.V. = standard deviation expressed as a percentage of the mean).

The analysis of the results includes three steps: i) a study of the reproducibility of the uncorrected raw data, ii) owing to the large range of PaCO$_2$ of the various subjects, a study of the reproducibility of the data corrected for the influence of the PaCO$_2$, iii) a parallel test of sensitivity of the measurements to brain activation by hand work to assure that the results of the two preceding steps are not due to a lack of sensitivity of the method.

Reproducibility of the CBF Measurements
As mentioned above, two groups of subjects had pairs of measurements made in resting conditions: one group (I) with an interval of 30 minutes, the other one (II) with an interval of several days.

Table 1 shows for the two groups the mean and the standard deviation of the mean hemispheric flows, i.e., the arithmetic mean of the regional grey matter flows over each hemisphere for the first and second measurements. Although the data are different for the two groups due to the heterogeneity of the subjects, the differences between the two injections (tested by Student's t test) are not significant. In order to test the reproducibility of the measurements of the four parameters ISI, Fg, FF and W, for each one of them the differences between the results of the two measurements were tested by a paired t test for each of the detectors and for the hemispheric mean, first, on the original values, and second, on the values of the ratio of the local value to the mean hemispheric value, constituting a hemispheric pattern of distribution (HPD%). No significant changes were found between the measurements for all four parameters both for absolute and for H.P.D. values. An analysis of variance (Anova) performed on these data show that the results are homogeneous for all the detectors. These results are summarized in table 2 where the mean differences and their standard deviations are computed for all detectors in all patients.

The study of the variances of the data show that ISI is at least twice as stable as Fg as already indicated by Blauenstein et al. By and large, the reproducibility of these parameters is similar to that encountered in healthy subjects for the mean hemispheric values. For regional values of Fg the reproducibility is slightly lower than in healthy subjects in which repetitive measurements show variations of Fg of about ± 10 ml/100g/min.

In contrast, the standard deviations of FF and W are increased by at least twofold in pathological conditions compared with those in healthy subjects. These relatively large variances can be attributed to a possible limitation of the two compartment model for at least some of the subjects. In these subjects the fast clearing compartment would correspond to the fraction of brain tissue which have clearance rates distinctly faster than white matter and extracerebral tissues, the remaining fractions being lumped altogether in the second slow-clearing compartment ("slippage phenomenon").

This hypothesis is supported by the larger variances of group I with lower flow levels compared with the variances of group II with higher flow levels, more easily detected by the computer. This is, however, the only difference which can be found between the two groups, the variances of ISI and Fg being similar in both of them. The time delay between the injections seems then to bear no relation to the reproducibility of the results of the measurements for the latter parameters.

The H.P.D. values show larger variances due to the
generally decreased mean hemispheric values combined with particularly low levels in some areas; a slight change in absolute values inducing significant variation in the H.P.D. values. This mode of presentation of the results thus seems unsatisfactory for pathological cases with large inter-individual and inter-regional variations.

Effects of Corrections Based on \( \text{PaCO}_2 \) Variations

The \( \text{PaCO}_2 \) estimated by the end-tidal \( \text{CO}_2 \) show large random variations from one rCBF measurement to another in several patients in both group I and group II (for group I: mean \( \text{PaCO}_2 \) difference = 1.5 mm Hg, S.D. = 3.8 mm Hg; for group II: mean \( \text{PaCO}_2 \) difference = 2.5 mm Hg, S.D. = 2.8 mm Hg).

Several groups\(^{2,3,18,19}\) have suggested correction factors for \( \text{PaCO}_2 \) variations which were obtained from the differences of flow observed in healthy volunteers whose \( \text{PaCO}_2 \) was varied experimentally by inhalation of a mixture of air plus \( \text{CO}_2 \), or by hyperventilation. These correction factors were tested on the data presented in Table 1 as far as possible, although often correction factors were given only for grey matter flow or sometimes for the mean of the regional grey and white matter flows.\(^{3}\) In order to eliminate possible bias, only variations higher than 2 mm Hg of \( \text{PaCO}_2 \) were taken into account, and the corrections were not made to a standard \( \text{PaCO}_2 \) of 40 mm Hg, but only to correct the flows corresponding to the lower \( \text{PaCO}_2 \) of the patient by computing their theoretical values for the higher \( \text{PaCO}_2 \) value of the paired measurements.

The mean and the standard deviation of the differences in the parameters using the corrected values were computed as for the uncorrected data. All the proposed correction factors result in a significant increase in the standard deviations compared with those obtained from the raw data. As an example, table 3 presents the results obtained with the lowest correction factors proposed by Maximilian et al.\(^{18}\) for two parameters, ISI and Fg (2.3 ml/mm Hg and 0.75 units of index/mm Hg, respectively for Fg and ISI). No significant change in the mean differences can be noted, compared to the results presented for the raw data in Table 2. On the other hand, there is an increase in the standard deviation for the results computed from the absolute values for the original values as well as for the hemispheric mean values. The H.P.D. values show no significant change, confirming the results of Maximilian et al.\(^{18}\) in which no significant variation of the distribution pattern of regional flow was found when the \( \text{PaCO}_2 \) was varied in healthy volunteers. This increase of the variances of the difference between two measurements is amplified when larger correction factors are used.\(^{3,3}\) The lack of accuracy of the correction is in good agreement with the poor correlation of the differences of mean hemispheric flow and the differences of \( \text{PaCO}_2 \) (right hemisphere, \( r = -0.363 \); left hemisphere, \( r = -0.356 \)), in contrast to the observations in healthy subjects.\(^{18}\) These results can have two explanations: in the first place, dysregulation of the CBF in a large proportion of the atheromatous subjects impaired the validity of the correction factors or secondly, a lack of sensitivity of the method due either to physiological variations of CBF resulting from the conditions of the measurement (general activation, anxiety, variation of ventilation) or to technical limitations.

In order to check this second point an activation test was performed on the 8 patients described above.

Sensitivity of the Method to Focal Activation by Hand Exercise

A focal activation test (on the healthy hemisphere of the subjects) was made by exercise of the contralateral hand (opening and closing the hand at a frequency of about one movement per second) during the whole...
duration of the measurement (11 minutes). This test was chosen because it had already been studied using the intracarotid method and showed a focal increase in flow in an area of the same order of magnitude as the diameter of our detectors. Table 4 shows the mean differences with their standard deviations between test measurements and previous measurements for the same parameters as in table 2. Arterial pressure and \( \text{PaCO}_2 \) were monitored and did not show any difference between the resting and test measurements. The statistical significance of the variations of the regional and mean hemispheric values of the parameters was analysed by paired \( \text{t} \) tests as in the reproducibility test. Activation does not significantly affect the mean hemispheric values of any of the parameters. The differences in the non-activated hemisphere were not considered because this hemisphere was affected by lesions of varying size and location. The absolute regional values of the parameters do not show significant variations in the activated hemisphere (A), except \( F_g \) in probe No. 4 which is mainly located in the sensory-motor cortical area corresponding to hand and arm. For the H.P.D. values, the results are less clear because, apart from the significant increase of \( F_g \) in the No. 4 probe (\( p < 0.01 \)), another significant increase appears in probe No. 5 (\( p < 0.01 \)). Surprisingly, the parameter \( \text{ISI} \), usually regarded as more stable than \( F_g \) in pathological subjects, does not show significant focal variations either for absolute values or for relative values. Such results hint to some lack of sensitivity of this parameter, as already emphasized in the case of a hyperemic situation in healthy volunteers. Reducing the level of the statistical confidence limit to 95% (\( p < 0.05 \)) reveals further differences for \( F_g \) and \( \text{Wg} \), mainly in the non-activated hemisphere, which are most probably due to phenomena extraneous to the activation test itself. This indicates that a high degree of statistical significance is needed to draw conclusions when more complex phenomena of activation are studied involving a greater scattering of flow variations than in the simple test studied here. However, this test has shown that this method is suitable to detect phenomena as slight as a very moderate muscular exercise.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mean Values and Standard Deviations of the Differences for Four CBF Parameters and Their Hemispheric Means, Between 2 Consecutive Measurements (the First One in Resting Conditions, the Second One During Hand Work) in 13 Cerebral Areas in 8 Subjects. Units and Definition of the H.P.D. Values are the Same as in Table 2.</th>
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**H.P.D.**

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A. refers to the cerebral areas of the activated hemisphere (contralateral to the working hand), N.A. refers to the cerebral areas of the non-activated hemisphere.
The amplitude of regional flow flow changes obtained in this study on a sample of subjects of various ages is in good agreement with the results obtained by the inhalation method in young healthy volunteers. The smaller changes observed in these atraumatic methods compared to the results obtained by intracarotid injection may be explained by two factors: first, the exercises were less severe than in the study of Olesen, and second, the number of detectors and the collimation were different in the study of Roland et al., which, combined with the better counting statistics obtained by the intracarotid injection, gave better spatial resolution.

Conclusions

The atraumatic method of rCBF measurement by intravenous injection of 133Xe can be used routinely in subjects with cerebrovascular disease with a reproducibility for absolute values of ISI and Fg similar to that in young healthy volunteers. This reproducibility is similar for various time delays between the measurements, so that valid rCBF comparisons can be made over long time periods. The relatively large variances of FF and W can be explained by the limitations of the model in very low ranges of grey matter flow. Several limitations, however, appear: 1) The lack of sensitivity of ISI, which should therefore be used mainly as an estimate of the level of flow, and 2) The poor efficiency of the corrections suggested for PaCO2 variations, due probably to dysregulation of cerebral circulation in a large number of the subjects. This means that raw data rather than corrected data should be used in unselected pathological subjects.

If these limitations are taken into consideration, the method appears to be usable even for complex neurological tests as shown by the test of sensitivity.

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