Regional Cerebral Blood Flow in Man Determined by the Initial Slope of the Clearance of Intra-arterially Injected $^{133}$Xe

THEORY OF THE METHOD, NORMAL VALUES, ERROR OF MEASUREMENT, CORRECTION FOR REMAINING RADIOACTIVITY, RELATION TO OTHER FLOW PARAMETERS AND RESPONSE TO $P_aCO_2$ CHANGES

BY JES OLESEN, M.D., OLAF B. PAULSON, M.D., AND NIELS A. LASSEN, M.D.

Abstract: Regional Cerebral Blood Flow in Man Determined by the Initial Slope of the Clearance of Intra-arterially Injected $^{133}$Xe

The regional cerebral blood flow can be calculated from the initial slope of the logarithmically displayed clearance curve following intra-arterial injection of $^{133}$Xe ($rCBF_{initial}$). The relationship between this parameter and the values resulting from stochastic (height over area) and compartmental analyses is extensively discussed. Experimental results demonstrate the theoretically expected close relationship between $rCBF_{initial}$ and flow of gray substance ($rCBF_{initial} 20\%$ to $30\%$ lower than $F_g$). It is shown how the cerebral clearance curve (normally biexponential) with low flow values becomes gradually monoexponential. Thus, only flow of gray substance changes, whereas flow of white substance is independent of $CBF_{ax}$. $CBF_{10}$ was shown to overestimate $CBF_{ax}$ with about $15\%$ independent of the flow level. Correlation between $CBF_{initial}$ and $CBF_{10}$ was linear ($r=0.98$) at $CBF_{10}$ values above $20\, \text{ml/100 gm/min}$.

The $CBF_{initial}$ normal value is found to be $64\pm 9\, \text{ml/100 gm/min}$, and the interchannel coefficient of variation is $8.2\%$. A correction for remaining radioactivity from previous measurements is described. Using this, no significant difference was found between repeated resting state measurements.

The $CBF_{initial}$-$P_aCO_2$ relationship was found to be best described as exponential. In a group of patients with various intracranial diseases, $1\, \text{mm Hg}$ change in $P_aCO_2$ resulted in $4\%$ change of $CBF_{initial}$ quite independent of the $CBF_{initial}$ level.

ADDITIONAL KEY WORDS: apoplexy, barbiturate poisoning, carbon dioxide tension, cerebral blood flow regulation, cerebral circulation, inert gas clearance, isotope clearance method.

The Kety-Schmidt method was the first technique which permitted accurate determination of the cerebral blood flow (CBF) in man.$^1,^2$ With the $^{133}$Xe intra-arterial injection method, measurement of blood flow in multiple small regions of a hemisphere ($rCBF$) became possible.$^3-^6$ Furthermore, the accuracy of the CBF determination was presumably improved, because the entire inert gas clearance curve is recorded in contrast to the multiple-point measurements of the Kety-Schmidt method.

Calculations of the blood flow from the $^{133}$Xe clearance curve are performed in three different ways, namely, by stochastic analysis.
according to the same principle as employed in the Kety-Schmidt method, \(^1\) \(^2\) \(^5\) \(^6\) \(^7\) by compartmental analysis, \(^8\) \(^9\) \(^10\) and by initial slope analysis. \(^6\) \(^7\) \(^8\) \(^9\) The first two analyses are made using the first 10 or 15 minutes of the clearance curve, whereas the initial slope analysis (\(r\text{CBF}_{\text{Initial}}\)) is based only on the first one to two minutes of the clearance curve. With this short period of recording a stable arterial blood pressure and arterial \(\text{PCO}_2\) (\(\text{PacO}_2\)) and constant drug action can be maintained more easily. Equipment is available which allows measurement of \(r\text{CBF}_{\text{Initial}}\) from 35 small individual areas of a hemisphere, and semiquantitative evaluation of such data can be performed immediately. \(^14\) Thus, the \(r\text{CBF}_{\text{Initial}}\) is well suited for the study of blood flow changes induced by altered blood pressure, altered \(\text{PacO}_2\), or drugs. For these reasons it has gained widespread use in human studies, \(^6\) \(^7\) \(^8\) \(^9\) \(^10\) \(^11\) \(^12\) \(^13\) \(^14\) \(^15\) \(^16\) \(^17\) but the theory underlying the \(r\text{CBF}_{\text{Initial}}\) method has been mentioned only briefly.

This communication discusses the theory of the \(r\text{CBF}_{\text{Initial}}\) method as related to stochastic and compartmental analyses and compares the theory to experimental determination of \(F_F\), \(F_w\), \(\text{CBF}_{\text{Initial}}\), \(\text{CBF}_{10}\) and \(\text{CBF}_{\text{Paco}}\) in a series of patients. Normal values and reproducibility of \(\text{CBF}_{\text{Initial}}\) are reported. For accurate determination of drug effects a precise correction for changes in \(\text{PacO}_2\) is necessary. The relationship between \(r\text{CBF}_{\text{Initial}}\) and \(\text{PacO}_2\) is reported for various groups of patients.
Methods

The $^{133}$Xe intra-arterial method has been described in detail previously. Following the introduction of a small polyethylene catheter in the internal carotid artery (Seldinger technique), a bolus of $^{133}$Xe dissolved in 1 to 3 ml sterile saline is injected and the washout of radioactivity is measured by multiple small scintillation detectors placed laterally over the ipsilateral side of the head (fig. 1). The equipment used for registration consists of 35 detectors directed a little centrally. Collimation is provided by cylindrical lead tubes 43 mm long and 12 mm in diameter, and the NaI (T1) crystals are 10 mm thick and 12 mm in diameter. Pulses from each detector are via a separate ratemeter and a multiplexer displayed logarithmically on an oscilloscope screen and photographed with a Polaroid camera during the first two minutes of clearance. On the photograph the 35 curves correspond to the localization of the probes over the hemisphere (figs. 2-4). The sum of the output from all 35 detectors is displayed continuously in the linear mode on a Beckman potentiometer writer for calculation of mean CBF with stochastic or compartmental analysis. The sum of the remaining radioactivity in all 35 regions from previous measurements can also be read off the potentiometer curve.

FIGURE 2

Original curves showing in the middle a set of clearance curves during normocapnia and to the right during hypercapnia in the same patient. Even though the curves are declining much faster, a well-defined straight curve is seen in the first minute. To the left is the localization of the probes over the cranium. Compare also with the anterior view in figure 1. Note how channels peripheral to carotid artery distribution are easily recognized by low height and bad counting statistics.
FOCAL LOSS OF AUTOREGULATION CORRESPONDING TO LOCALIZATION OF CEREBRAL METASTASIS

FIGURE 3

To the left the localization of the probes over the hemisphere is studied. Compare also with the anterior view in figure 1. Middle picture shows subnormal slope (flow) in all the hemisphere. To the right a focus with a steep, bending curve in the parietal region is revealed during increased blood pressure (Hypertensin®) (the curve in the upper row in the middle column [below the hemispheric mean curve above the others]). This focus with abolished autoregulation corresponds to the localization of a tumor. There was further a suspicious area in the posterior temporal region (lower curve in third column from left).

Theoretical Considerations Regarding Cerebral Blood Flow Measurements from the Initial Part of the $^{133}$Xe Clearance Curve

Measurements of cerebral blood flow with multichannel equipment yield a large amount of data, and calculations with conventional methods are very time consuming. Therefore, it was suggested that the slope of the logarithmically displayed first one to two minutes of the clearance curve could be used as measure of the cerebral blood flow ($\text{CBF}_{\text{initial}}$).6-12

INITIAL SLOPE ANALYSIS AS RELATED TO THE BIEXPONENTIAL MODEL OF THE CEREBRAL CIRCULATION

In normal man as well as in many patients with chronic brain disorders the $^{133}$Xe clearance curve can be dissolved in two exponential components representing the flow in gray and white matter respectively.5, 6, 8, 18, 19 The basic idea underlying the $\text{CBF}_{\text{initial}}$ measurement is that the gray substance dominates the initial part of the clearance curve. This dominance is so marked that the initial one to two minutes of the clearance curve can be regarded as monoexponential (figs. 1-5), for all practical purposes.

A monoexponential clearance curve of inert gas from a tissue can be described as (according to Kety10):

$$C(t) = C(0)e^{-t/\lambda} \cdot t$$ (1)

where $C(t)$ is the concentration of tracer at the time $t$; $C(0)$ the concentration at time zero.
FOCAL INCREASE OF REGIONAL CEREBRAL BLOOD FLOW
DURING WORK WITH CONTRALATERAL HAND

Two sets of curves are here superimposed for comparison. To the left the two resting state studies are seen. The upper curve in each of the 35 pairs is the first resting study. The lower curve in each pair is the second resting study. To the right the first resting state (lower curves) is compared to a measurement during work with the contralateral hand (upper curves). It is seen that two curves in the parietal region (ink mark) are much steeper and have an increased peak height compared to the resting state. This indicates a considerable but local blood flow increase which would not change the hemispheric mean flow significantly.

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<th>PaCO₂ (mm Hg)</th>
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FIGURE 4

(initial maximal height of the clearance curve); $f$ the blood flow in milliliter per gram tissue per minute; $\lambda$ the tissue to blood partition coefficient in milliliter/gram, and $t$ the time in minutes.

The equation can be rearranged and reduced to:

$$ f = -\lambda \cdot \ln(10) \cdot \frac{d(\ln C(t))}{dt} $$

or

$$ f = -\lambda \frac{d(\ln C(t))}{dt} = \lambda \alpha \text{ ml/g/min} \quad (2) $$

where $\alpha$ is the numerical value of the slope, $d(\ln C(t))/dt$ of the semilogarithmically recorded clearance curve. Using base 10 logarithm instead, equation 2 may be written:

$$ f = -\lambda \cdot \ln(10) \cdot D \text{ ml/g/min} $$

where $D$ is the numerical value of the slope in the base 10 logarithmic system and $\ln(10) \approx 2.30$ is the factor for converting base 10 to natural logarithm.

Since the first one to two minutes of the $^{133}$Xe clearance curve from the brain is practically monoexponential, let it be assumed that the dominance of the gray matter blood
flow was so great that one could disregard the slower component. A blood flow value can then be calculated from that part of the curve according to equation 3:

\[ f_{\text{initial}} = \lambda \cdot 2.30 \cdot D_{\text{initial}} \text{ ml/g/min} \] (4)

or with lambda of gray substance \( \lambda_g \) = 0.87 (because of dominance of gray substance in the initial part of the clearance curve) and calculating the flow per 100 gm of tissue:

\[ r\text{CBF}_{\text{initial}} = 200 \cdot D_{\text{initial}} \text{ ml/100 gm/min} \] (5)

where \( D_{\text{initial}} \) is the numerical value of the initial slope of the clearance curve in base 10 logarithmic system (in fraction of decade per minute).

As already mentioned, this calculation is, however, an approximation. In the following the biexponential curve which more adequately describes the isotope clearance from the brain shall be analyzed in order to estimate the error of the \( r\text{CBF}_{\text{initial}} \) approximation and to describe the relation of the \( r\text{CBF}_{\text{initial}} \) to flow in the gray and white substances. The biexponential expression is:

\[ C(t) = C(0)_0 \left( a e^{-t/\lambda_g} + b e^{-t/\lambda_w} \right) \] (6)

where \( f_g, \lambda_g, f_w \) and \( \lambda_w \) are flow and \( \lambda \) values in gray and white matter respectively, and \( a \) and \( b \) are the function of the ordinate value, \( C(0) \), belonging to each of the two compartments.

The initial distribution of \( ^{133}\text{Xe} \) to the gray and white matter is proportional to the flow within these substances multiplied by their weights (the bolus fractionation principle of Sapirstein).

Thus, if \( W_g \) and \( W_w \) represent the relative weight of gray and white matter respectively, \( a \) and \( b \) in equation 6 may be written:

\[ a = \frac{W_g f_g}{W_g f_g + W_w f_w} \quad \text{and} \quad b = \frac{W_w f_w}{W_g f_g + W_w f_w} \] (7)

\[ \text{FIGURE 5} \]

\( \text{Constructed clearance curves with their two monoexponential constituents representing flow in gray matter (} F_g \text{) and in white matter (} F_w \text{). Also the line representing the initial slope of the clearance curve is shown. In figure 5a} F_g = 80, F_w = 20, CBF_{\text{initial}} = 66 \text{ and} CBF_{\text{w}} = 50 \text{ ml/100 gm/min. Figure 5b is constructed assuming proportional changes in} F_g \text{ and} F_w, \text{i.e., the response on} PaCO_2 \text{ changes (see Discussion), whereas figure 5c assumes that only} F_g \text{ changes with decreasing flow as observed with functional changes (see Results).} \]
The slope of the clearance curve is obtained by differentiation of equation 6:

\[ \frac{dC(t)}{dt} = C(0) \left(-a \frac{f_g}{\lambda_g} e^{-\alpha_{init}} t - b \frac{f_w}{\lambda_w} e^{-\alpha_{w} t} \right) \]  

(8)

In a semilogarithmic system the slope of a curve is the slope of the linearly displayed curve divided with the height.

Thus from equation 8:

\[ \frac{d(\ln C(t))}{dt} = \frac{C(0)}{C(t)} \left(-a \frac{f_g}{\lambda_g} e^{-\alpha_{init}} t - b \frac{f_w}{\lambda_w} e^{-\alpha_{w} t} \right) \]  

(9)

The initial slope of the semilogarithmic clearance curve will therefore be:

\[ \lim_{t\to0} \frac{d(\ln C(t))}{dt} = -a \frac{f_g}{\lambda_g} - b \frac{f_w}{\lambda_w} \]  

(10)

From this equation, it is possible by inserting numerical values for \( f_g, f_w, \lambda_g, \lambda_w, W_g \) and \( W_w \) to calculate the slope of the initial part of the clearance curve and thus the CBF\(_{init}\) for comparison with the flow of the gray and white matter.

In normals \( f_g = 0.8 \text{ ml/gm/min}, f_w = 0.2 \text{ ml/gm/min}, \lambda_g = 0.87, \lambda_w = 1.63 \) and \( W_g = W_w = 50\% \). This yields according to equation 10 \( \alpha_{init} = 0.78 \). Thus CBF\(_{init}\) is according to equation 2 to 5 66 ml/100 gm/min, i.e., 17% below \( F_g \). This relationship is illustrated by experimental data in table 1 and in figure 6.

Figure 5 illustrates a theoretical bicompartamental clearance curve with two monoexponential constituents representing \( F_g \) and \( F_w \). Furthermore, the line with slope = \( D_{init} \) is drawn. In figure 5a \( F_g = 80 \) and \( F_w = 20 \) ml/100 gm/min. Figure 5b is constructed having \( F_g = 40 \) and \( F_w = 10 \) ml/100 gm/min, i.e., assuming that \( F_g \) and \( F_w \) undergo the same percentile change with decreasing cerebral blood flow. This means that the configuration of the curve has not changed, but only is transformed according to the difference in mean transit times (ideal curve transformation). Finally, figure 5c is constructed assuming, as exemplified later in this study, that only \( F_g \) changes with decreasing cerebral blood flow, whereas \( F_w \) stays constant. In both cases the \( W_g/W_w \) ratio is assumed to be 1.00. It is seen how the monoexponential part of the curve lasts for a shorter time at high flow than at low flow. The difference between the two low flows (5b and 5c) is in this respect very little. Both at high and low flow the curve is rectilinear until it has decreased about half a decade.

In the actual experiment determination of the initial slope at time zero is not possible, and one measures the slope of the first one to two minutes of the clearance curve. Therefore more influence of the slow component with slightly lower flow values will be obtained in practical measurements than when calculating the initial slope at time zero from equation 10.

INITIAL SLOPE AS RELATED TO THE STOCHASTIC ANALYSIS OF THE CEREBRAL BLOOD FLOW

According to Zierler\(^2\) the cerebral blood flow can be calculated from the externally recorded clearance curve as:

\[ \text{CBF}_{\infty} = \frac{H_0}{A_{\infty}} \cdot \bar{\lambda} \cdot 100 \text{ ml/100 g/min} \]  

(11)

where \( H_0 \) is the initial height of the curve, \( A_{\infty} \) the total area under the curve (total number of \(^{188}\text{Xe} \) counts) and \( \bar{\lambda} \) the average brain to blood partition coefficient.* What is actually measured experimentally is the mean transit time \( t \) which equals the \( A_{\infty}/H_0 \) ratio. However, it is not possible to follow a clearance curve to infinity, and a practical way for estimating the total area is to assume that the tail part of the curve is monoexponential, thus allowing estimation of the area by monoexponential extrapolation.\(^2\)

For practical reasons, it has become a convention to measure the clearance curve only for the first ten minutes and to omit

\[ \text{CBF}_{\infty} = \frac{H_0}{A_{\infty}} \cdot \bar{\lambda} \cdot 100 \text{ ml/100 g/min} \]

*If CBF\(_{\infty}\) is calculated from the weighted average of \( F_g \) and \( F_w \), then a slightly higher value is obtained. This is due to two discrepancies. The \( \bar{\lambda} \) used in the stochastic analysis is based on a \( W_g/W_w \) ratio of 60/40; but this ratio is usually determined lower in the compartmental analysis and hence the corresponding \( \bar{\lambda} \) is higher. Second, the area under the upstroke (and peak) of the curve is used in the stochastic analyses but not in the compartmental analyses.

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525
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extrapolation by calculating the blood flow value \( CBF_{10} \) as in Kety's nitrous oxide method: 

\[
CBF_{10} = \frac{H_0 - H_{10}}{A_{o-10}} \cdot \lambda \cdot 100 \text{ ml}/100\text{gm/min} \quad (12)
\]

where \( H_0 \) is the initial height of the clearance curve (peak height), \( H_{10} \) is the height of the curve at time 10, \( A_{o-10} \) is the area under the curve in the first 10 minutes of clearance.

The equation is an approximation, and overestimates flow because it partly disregards the tail of the curve representing the slow flow components (fig. 7). In a normal brain with \( CBF_x = 50 \) this equation would give a \( CBF_{10} \) value of 58 \text{ ml}/100\text{gm/min}. Thus, in the stochastic analysis the most accurate flow value is the \( CBF_x \). But its determination is beset with defects: the precise lambda is unknown because the \( W/\lambda \) ratio is not measured individually and the necessary monoexponential extrapolation is influenced by recirculating tracer. In the compartmental analysis the theoretically correct flow values are \( F_g \) and \( F_w \) and the weighted average of the two (\( F_{\text{mean}} \)). Here again, the monoexponential fit to the tail part of the curve is necessary, and the values of course depend on the strict applicability of the concept, that flows in gray and white substance really are described by the two exponential components observed in the \( ^{133}\text{Xe} \) clearance curve from the brain.

Because of the experimental difficulties involved in the determination of the theoretically correct flow parameters, and in view of the unclarified assumptions underlying them, it has become common to measure the approximate values: \( CBF_{10} \) corresponding to \( CBF_x \) and \( CBF_{\text{initial}} \) corresponding to \( F_g \). Both expressions result in an error, respectively in the direction of overestimation (\( CBF_{10} > CBF_x \)) and in the direction of underestimation (\( CBF_{\text{initial}} < F_g \)). But the approximations have the advantage of being easily and accurately determined.

**WHICH \( \lambda \) VALUE SHOULD BE USED**

As described above, the clearance curve is initially dominated by the gray substance, and consequently the \( \lambda_g \) is the best choice for the \( CBF_{\text{initial}} \) calculation. Usually a fixed value of 0.87 has been used.\(^1\), \(^2\)

Since \( CBF_{\text{initial}} \) to some extent is influenced by the white substance, a somewhat higher value than \( \lambda_g \) could be justified. This would make the \( CBF_{\text{initial}} \) more similar to the \( F_g \) which is desirable because changes of \( CBF_{\text{initial}} \) represent changes in flow of the gray substance. The use of the low \( \lambda \) (\( \lambda_g \)) has

---

**FIGURE 6**

Comparison between different flow parameters. As indicated in the discussion the bicompartamental analysis is not valid at low flow values. Therefore, the number of observations in the graphs are not identical (see also table 1). 6a and 6b show the absolute and relative (percentile) relationship between \( CBF_{\text{initial}} \) and flow of gray substance (\( F_g \)). 6c and 6d show the relation between \( CBF_{10} \) and \( CBF_x \). In figure 6e the relationship between \( CBF_{\text{initial}} \) and \( CBF_{10} \) is shown. It is a straight line above \( CBF_{10} \) 25 ml/100 gm/min \( (r = 0.98) \). Below this it bends toward the zero point. The percentile over/underestimation of \( CBF_{\text{initial}} \) compared to \( CBF_{10} \) is not constant as seen in figure 6. \( CBF_{10} \) can be estimated from the \( CBF_{\text{initial}} \) value with good accuracy using the regression line (as discussed in the text).
given the false impression that the CBF_{initial} relates more to CBF_{10} than to F_g. With decreasing flow values the white substance will influence the CBF_{initial} increasingly. This might be prevented by using a $\lambda$ which gradually increased with low flow values as suggested by Bassingthwaighte et al. Until a more exact relationship between the various parameters of the cerebral circulation is known, however, the present authors prefer a fixed $\lambda$ value with its known shortcomings. It might be mentioned that if CBF_{initial} is to be correlated to CBF_{10} or CBF_{\infty}, the $\lambda_{g}$ to be used must be corrected for hemoglobin if this is done in the two other calculations.

**Correction for Remaining Activity from Previous Measurements**

This correction is somewhat difficult with the CBF_{initial} measurement because the first part of the clearance curve from the brain can be regarded only as approximately monoexponential, and therefore the theoretically correct equation for a monoexponential curve with an added constant “background” from a previous study cannot be used. Because of these difficulties an empirically derived correction for remaining activity has been established by measuring a number of constructed curves with and without addition of 5% or 10% constant activity. Whether this was done or whether the very slow clearance rate usually observed after 15 minutes was taken into account did not influence the result significantly. The diagram obtained is shown in figure 8. It is used as follows: from the continuously recorded sum of all 35 channels the remaining activity just before a flow measurement is calculated as percent of the peak height. Then the correction factor is found by entering the diagram corresponding to the measured flow value, and the percent remaining activity times the correction factor is added to the calculated flow value. Thus, if the remaining activity is 5% at a measured CBF_{initial} of 70 ml/100 gm/min, $5 \times 1.9 = 9.5\%$ should be added to the flow resulting in a value of 76.6 ml/100 gm/min.
This average correction factor is not completely valid because the amount of remaining activity in different regions is not identical. There will usually be a higher percentage of remaining activity in the temporal region because of the abundant soft tissues here. Furthermore, the error in constructing the diagram was considerable. Therefore, effort should be made to keep the difference in remaining activity below 5% to 10% (by a sufficiently long time interval) for accurate comparisons between flow measurements. The random error due to correction for remaining activity is then probably in the order of 1% to 2%.

**Data Processing with rCBF<sub>Initial</sub>**

With the Polaroid recording system described above both a positive and a negative image is obtained of the first two minutes of the semilogarithmically recorded clearance curves from all regions studied. The negative is transparent and this makes a rapid *semiquantitative evaluation* possible by superimposing the negatives from two subsequent measurements (fig. 4). One takes into consideration whether the curves (as normally) are straight lines, whether the absolute slope of the curves is within normal limits, whether the slopes (as normally) are practically equal all over the hemisphere, and whether any changes have occurred in these parameters from the first to second measurement. In this way a rapid and fairly accurate comparison between the two measurements can be made, and the planned investigations can be modified according to the results. The *correct calculation of the*
The apparatus used in the measurement of rCBF\textsubscript{initial} values from the photographic negatives. One photo has been placed under a movable magnetic frame and the position adjusted so that the four reference lines of the upper part of the photo have slope zero. Under the photo is a turnable glass disk with parallel lines, and looking at one particular clearance curve this disk is turned until one of the parallel lines fits with the slope of the clearance curve using the white handle to the left. The flow value of the region can then be read directly on the scale above the photo—in this case 56 ml/100 gm/min.

rCBF\textsubscript{initial} is done according to equation 5, which shows that the flow is the initial slope of the curve multiplied by a constant.

As described above the logarithmically displayed curve is a straight line only for a certain interval of time, and the slope should be measured from this part of the curve and not as the average slope of the first two minutes (see figs. 2-5). In patients with chronic brain disorders (dementia, postapoplectics, etc.) the blood flow is somewhat decreased, and the curve monoexponential for more than two minutes; in normals the logarithmic curve is straight for approximately one and one-half minutes, and in cases of high flow the straight portion is one minute or perhaps even less (figs. 4 and 5). The calculation of the rCBF\textsubscript{initial} is done by placing the negative photograph on a glass plate under which a disk with parallel lines can be turned (fig. 9). When the slope of the curve and the slope of one of the parallel lines fit, the rCBF\textsubscript{initial} value can be directly read on a scale and the correct value is obtained by correction for remaining activity as just described (usually one corrects only the mean rCBF value). With multichannel equipment some detectors are usually so peripheral to the brain that they should not be taken into consideration. These curves are easily recognized by their low counting rate (figs. 2-4).

The error of the slope determination was assessed as follows: Clearance curves were measured on the calculator with a time interval
of some months by a person who was using the instrument routinely. The mean deviation and the error of measurement in a single channel (i.e., in reading the rCBF) was 0.79, SD 2.96%, and the values for the hemispheric mean flow were 0.26, SD 0.90%. Another person read the same curves once. Variation between the readings of the different persons were calculated. The mean difference and error of measurement in a single channel was 0.28, SD 3.29%, and the values for the mean hemispheric blood flow were 0.55, SD 1.12%.

Results
Normal rCBF<sub>initial</sub> values have not been obtained in the strict sense of normality, because normal persons were not subjected to carotid puncture. However, from a large series of patients on whom flow measurements were done in combination with carotid arteriography, a group of eight patients without anamnestic clue to organic brain lesion, without major neurological deficits and with normal carotid angiography were selected to represent normality. Hemoglobin, arterial P<sub>CO<sub>2</sub></sub>, flow data and clinical diagnosis are listed in table 2. The average rCBF<sub>initial</sub> in these patients was 64 ± 9.1 ml/100 gm/min. Thus, with the present method an rCBF<sub>initial</sub> below 46 and above 82 ml/100 gm/min can be regarded as abnormal with a fairly high degree of certainty. The CBF<sub>10</sub> values were 50 ± 5.2 ml/100 gm/min. The interchannel coefficient of variation of rCBF<sub>initial</sub> in the individual patient is seen in table 2. The average of all patients was 5.7 ± 1.6 ml/100 gm/min or 8.2 ± 1.2%.

Repeated resting state rCBF<sub>initial</sub> measurements were performed in 18 patients in whom no focal abnormalities of the rCBF were seen and the reproducibility of the rCBF<sub>initial</sub> was tested in these cases. Between the two resting state studies one or more measurements were usually done with changes of blood pressure or arterial P<sub>CO<sub>2</sub></sub>. It is our experience that such tests slightly decrease the reproducibility of the resting state measurements. With correction for remaining activity as described, only minor changes in rCBF<sub>initial</sub> took place from first to second resting state study. This was the case whether in the next section described the correction for changes in P<sub>CO<sub>2</sub></sub> was carried out or not (average change without correction: +3.5%, S.E. of mean 1.6%; and with correction +0.9%, S.E. of mean 1.7%). Thus the correction for remaining activity based on model analysis as described seems to be fairly accurate.

The experimental error as calculated from the difference between the measurements after correction for remaining activity and P<sub>CO<sub>2</sub></sub> changes was for the mean flow S<sub>region</sub> = 5.1% for one single channel S<sub>region</sub> = 7.6% and for one single channel after subtracting of the average change in hemispheric mean flow S<sub>region, cor.</sub> = 5.5%.

It appears that the experimental error of measurement of the rCBF<sub>initial</sub> is far larger than the error of reading the flow from the clearance curve as described under Methods. This must be explained by small changes of P<sub>CO<sub>2</sub></sub> during the measurement, by small head movements, and by some error in correction for remaining activity. Furthermore, we believe that true variation of the rCBF occurs with time. Thus the regional cerebral blood flow may change during changes of the neuronal activity.

Correlation between CBF<sub>initial</sub> and other flow parameters: Data from the above-mentioned patients plus data from a group of patients with low flow values due to dementia, brain trauma or barbiturate poisoning were analyzed with the compartmental method using the curve representing the sum of outputs from all 35 channels. The calculated flow of gray and white substance and relative weight of gray substance are listed in table 3. Using the same curve CBF<sub>10</sub> and CBF<sub>∞</sub> were calculated by the stochastic analysis, whereas CBF<sub>initial</sub> was calculated as the average of all 35 regional values from the Polaroid film. Figure 10 shows the relationship between F<sub>g</sub>, F<sub>∞</sub> and W<sub>g</sub> plotted against CBF<sub>initial</sub>. F<sub>∞</sub> seems practically independent of the CBF<sub>∞</sub> value, whereas F<sub>g</sub> increases markedly with increasing CBF<sub>∞</sub>. Above CBF<sub>∞</sub> ~ 20 ml/100 gm/min the relation between F<sub>g</sub> and CBF<sub>∞</sub> is linear.

The W<sub>g</sub> (and consequently also the W<sub>g</sub>/W<sub>∞</sub> ratio) is seen to be fairly constant in the CBF<sub>∞</sub> range from 30 ml/100 gm/min and upward. Below this value the bicompartamental resolution of the curves was difficult or impossible because the curve was almost monoexponential. Figure 6a shows CBF<sub>initial</sub> from individual patients plotted versus F<sub>g</sub>. In figure 6c the CBF<sub>10</sub> is plotted against CBF<sub>∞</sub>. Figures 6b and
TABLE 2

CBF<sub>initial</sub> in "Normal" Man

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Hemoglobin (gm/100 ml)</th>
<th>Clinical data</th>
<th>P&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>CBF&lt;sub&gt;initial&lt;/sub&gt; (ml/100 gm/min)</th>
<th>CBF&lt;sub&gt;o&lt;/sub&gt; (ml/100 gm/min)</th>
<th>Interch. coefficient of variation (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>F</td>
<td>13.2</td>
<td>Idiopathic orthostatic hypotension. No neurological symptoms, PEG normal</td>
<td>41.4</td>
<td>104</td>
<td>56</td>
<td>47</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>F</td>
<td>13.1</td>
<td>Hemicrania, no neurological deficits</td>
<td>41.1</td>
<td>90</td>
<td>63</td>
<td>53</td>
<td>8.4</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>14.1</td>
<td>Two nightly epileptic seizures. EEG focus during sleep</td>
<td>41.8</td>
<td>105</td>
<td>64</td>
<td>49</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>14.0</td>
<td>Mental depression. Maybe slight dementia</td>
<td>40.1</td>
<td>82</td>
<td>71</td>
<td>50</td>
<td>8.8</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>M</td>
<td>16.3</td>
<td>One and six months before study transient attacks of right side dyscoordination. At present no neurological deficits</td>
<td>43.2</td>
<td>90</td>
<td>66</td>
<td>50</td>
<td>8.6</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>M</td>
<td>13.3</td>
<td>During two months, three syncopes. No neurological deficits</td>
<td>43.9</td>
<td>153</td>
<td>52</td>
<td>44</td>
<td>7.5</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>M</td>
<td>15.5</td>
<td>During some months gradually increased dyscoordination in the contralateral arm. No other deficits. PEG shows some cerebellar atrophy</td>
<td>40.2</td>
<td>87</td>
<td>59</td>
<td>44</td>
<td>8.9</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>F</td>
<td>12.8</td>
<td>During two to three years constant right-side headache, paresthesia of changing localization, social unfitness</td>
<td>39.2</td>
<td>63</td>
<td>81</td>
<td>60</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Mean 64 50 8.2
SD 9.1 5.2 1.2
TABLE 3
Influence of PaO₂ on rCBF in Patients Without Focal Flow Abnormalities

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Pao₂ (mm Hg) Rest</th>
<th>MABP (mm Hg) Rest</th>
<th>CBFinitial (ml 100 gm/min) Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>Encephalitis?, cerebral atrophy</td>
<td>36.5</td>
<td>111</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>Korsakoff’s syndrome</td>
<td>42.4</td>
<td>68</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>Alzheimer</td>
<td>42.6</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>F</td>
<td>Glioblastoma</td>
<td>41.4</td>
<td>115</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>F</td>
<td>Glioblastoma</td>
<td>38.4</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>M</td>
<td>Carotid stenosis two weeks postoperatively</td>
<td>43.9</td>
<td>133</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>F</td>
<td>Idiopathic orthostatic hypotension</td>
<td>41.8</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>Epilepsy</td>
<td>48.2</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>Encephalitis</td>
<td>31.4</td>
<td>90</td>
<td>150</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>F</td>
<td>Glioblastoma</td>
<td>41.7</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>M</td>
<td>Cerebral metastasis</td>
<td>42.0</td>
<td>80</td>
<td>105</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>M</td>
<td>Dementia</td>
<td>38.9</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>F</td>
<td>Migraine</td>
<td>41.1</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>F</td>
<td>Epilepsy</td>
<td>43.8</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>M</td>
<td>Apoplexy</td>
<td>40.3</td>
<td>110</td>
<td>133</td>
</tr>
<tr>
<td>16</td>
<td>75</td>
<td>F</td>
<td>Apoplexy</td>
<td>44.5</td>
<td>115</td>
<td>150</td>
</tr>
<tr>
<td>17</td>
<td>51</td>
<td>M</td>
<td>Apoplexy</td>
<td>37.3</td>
<td>135</td>
<td>160</td>
</tr>
<tr>
<td>18</td>
<td>75</td>
<td>F</td>
<td>Apoplexy</td>
<td>40.7</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>19</td>
<td>63</td>
<td>F</td>
<td>Apoplexy</td>
<td>41.2</td>
<td>97</td>
<td>117</td>
</tr>
<tr>
<td>20</td>
<td>46</td>
<td>M</td>
<td>Apoplexy</td>
<td>39.3</td>
<td>75</td>
<td>78</td>
</tr>
</tbody>
</table>
RELATIONSHIP BETWEEN \( F_g \), \( F_w \), \( W_g \) AND CBF

Figure 10 shows the result of bicompartimental analysis of the mean hemispheric blood flow in 23 patients with varying flow values due to chronic disease and barbiturate poisoning. All lines were drawn by hand. The flow of white substance is relatively constant despite wide variations in CBF. Most or all variation of CBF in these patients was thus due to a depression of flow in gray substance. The relative weight of gray substance is fairly constant at CBF values above 30 ml/100 gm/min. Below this level the bicompartimental analysis becomes difficult in practice and a decreasing weight of the fast component \( W_g \) is observed even in cases without brain damage (barbiturate poisoning). This is illustrated but the lowest \( F_g \) and \( F_w \) values are too uncertain and have been omitted (see table 1).

6d show the percentile relationship between these parameters. Figure 6e shows CBF_{initial} versus CBF_{10}. A very good linear relationship is found between the two parameters above CBF_{10} \( \approx 20 \text{ ml/100 gm/min} \) \( (r = 0.98) \). The regression line does not go through zero, but the experimental values show that the line bends gradually toward zero below CBF_{10} values of 25 ml/100 gm/min. In this range the CBF_{initial} may even be lower than the CBF_{10}. This is so because the curve at these flow levels is almost monoexponential and a lower \( \lambda \) (0.87) is used.
The relationship between CBF
initial and PaCO₂ in various patients. In the upper left diagram CBF
initial is plotted against PaCO₂. Exponential curves seem to give the best fit. This is seen to be the case in the upper left diagram, where log CBF
initial versus PaCO₂ shows a linear relationship. In the lower diagram the "carbon dioxide reactivity" is calculated as Δln CBF
initial/ΔPaCO₂ and related to both the lower (filled circles) and the higher (open triangles) CBF
initial values in each patient. The horizontal line is drawn corresponding to the mean "carbon dioxide reactivity" of 0.041. It is seen that the relative CO₂ reactivity is independent of the height of the blood flow.

for calculating CBF
initial than for CBF₁₀ (\( \lambda = 1.17 \)). The percentile relationship between CBF
initial and CBF₁₀ is shown in figure 6f.

The influence of changes in arterial PaCO₂ tension on the regional cerebral blood flow was studied 22 times in 20 patients with various brain disorders but without extensive focal abnormalities in rCBF. In seven studies the arterial PaCO₂ was increased by breathing an air mixture containing 8% CO₂, 20% O₂, and 72% N₂ for one minute prior to and during the rCBF measurement (see fig. 2). Fifteen studies of 13 patients were performed after one minute of voluntary hyperventilation which was maintained throughout the measurement.

CBF
initial, MABP and PaCO₂ values are reported in table 1. The flow values represent the mean of 35 regional flow determinations. The relationship between cerebral blood flow and arterial carbon dioxide tension is shown in figure 11a. The experimental values seem to fit an exponential curve. In figure 11b the logarithm to the CBF values is plotted versus the PaCO₂ and a linear relationship is now seen. To demonstrate that the percent flow change per mm Hg change in PaCO₂ is independent of the height of the blood flow, the slope of the lines connecting two experimental values from the individual patient in figure 11b was calculated and plotted versus the blood flow (figure 11c). It is seen
that the slopes, i.e., the relative carbon dioxide reactivity, are independent of the height of the blood flow. The mean slope of the ln CBF/\(\text{Pa}_{\text{CO}_2}\) relationship was 0.041 ± 0.011. This means that correction of a flow value obtained at one \(\text{Pa}_{\text{CO}_2}\) (\(\text{Pa}_{\text{CO}_2}^1\)) to the \(\text{Pa}_{\text{CO}_2}\) value of a previous study (\(\text{Pa}_{\text{CO}_2}^2\)) should be carried out according to the equation:

\[
\text{rCBF} (\text{Pa}_{\text{CO}_2}^1) = \text{rCBF} (\text{Pa}_{\text{CO}_2}^2) \cdot e^{0.041 (\text{Pa}_{\text{CO}_2}^1 - \text{Pa}_{\text{CO}_2}^2)}
\]

Since \(e^{0.041}\) is very close to 1.04, the correction could be performed as 4% change per mm Hg change in \(\text{Pa}_{\text{CO}_2}\) when the \(\text{Pa}_{\text{CO}_2}\) difference is not too large.

**Example of Correction for \(\text{Pa}_{\text{CO}_2}\)**

If CBF\(_{\text{initial}}^1 = 25\) at \(\text{Pa}_{\text{CO}_2}^1 = 40\) is to be compared with CBF\(_{\text{initial}}^2 = 30\) at \(\text{Pa}_{\text{CO}_2}^2 = 43\), then CBF\(_{\text{initial}}^2\) may be reduced by 12% resulting in CBF\(_{\text{initial}}^2 = 26.4\). If the difference in \(\text{Pa}_{\text{CO}_2}\) is relatively large, corrections should be carried out using the exponential equation: If \(\text{Pa}_{\text{CO}_2}^2\) had been 50 the simple percent calculation would indicate that the CBF\(_{\text{initial}}^2\) should be reduced with 40%, but the correct calculation would give 0.66, i.e., a reduction of only 34%. Even this correction is valid only for \(\text{Pa}_{\text{CO}_2}\) within the range of 25 to 60 mm Hg. Furthermore, the variability in the response of different patients is relatively large (4.1 ± 1.1%) and, even with the correction described, two flow values are hardly comparable if the difference in \(\text{Pa}_{\text{CO}_2}\) is more than 5 to 10 mm Hg, when the \(\text{CO}_2\) reactivity of that particular patient is not directly measured.

If acute focal or global brain damage is present, the \(\text{CO}_2\) reactivity is markedly decreased and paradoxical reactions may even be seen.\(^{11,16}\)

**Discussion**

**NORMAL MATERIAL**

Since almost all kinds of brain damage result in a decrease of the CBF, a "normal material" consisting of patients in whom a carotid angiogram is indicated is apt to show flow values lower than those found in normal volunteers. The CBF\(_{10}\) reported here fit, however, with those in young volunteers found with the nitrous oxide method.\(^2\) The human volunteers investigated with the intra-arterial \(^{38}\)Xe injection method showed average CBF\(_{10}\) = 49.7, also comparing well with the present findings.\(^27\) However, the CBF\(_{\text{initial}}\) was not measured. In a material of patients selected according to the same criteria as in the present study a slightly lower CBF\(_{\text{initial}}\) value of 60 ml/100 gm/min was found.\(^19\)

**ADVANTAGES AND DISADVANTAGES OF THE rCBF\(_{\text{initial}}\) METHOD**

In most questions of diagnosis or therapy the flow of gray matter is more important than that of white matter and consequently also than average brain blood flow. This was clearly demonstrated in the present study, in which only or mainly the flow of gray matter was decreased due to disease or poisoning. Because of its high metabolism, the gray substance is much more easily damaged due to decreased blood flow or hypoxia. For these reasons the CBF\(_{\text{initial}}\) which represents mainly flow in gray matter is perhaps in some cases more interesting than the average brain blood flow (CBF\(_{10}\)).

The CBF\(_{\text{initial}}\) method is only minimally influenced by recirculating tracer. It is also rather independent of the input function of the tracer in contrast to the height over area method, which requires instantaneous arrival of the tracer to the brain.\(^{28}\) The reproducibility is good and the interchannel coefficient of variation low. Using a computer technique the error of measurement is minimized, and with such technique it was shown that the CBF\(_{\text{initial}}\) calculation was superior to CBF\(_{10}\) or CBF\(_{\text{infinity}}\) with respect to reproducibility and interchannel coefficient of variation.\(^{29}\)

The easy handling of data with the rCBF\(_{\text{initial}}\) method has made measurements with multiple detectors possible. It could be shown that raising the number of channels from 8 to 16 improved the resolution of the method.\(^19\) Increasing the number to 35 has proved advantageous in the practical work. Thus, it has been possible to demonstrate a sometimes very local increase in rCBF during work with the contralateral hand (fig. 4).\(^{26}\) With 16-channel and 35-channel equipment ischemic and hyperemic areas have been demonstrated in patients with apoplexy—also when the angiogram was normal\(^{26,30}\) and in tumor patients in whom abnormal rCBF is seen in more than 90% of all cases\(^{16}\) (unpublished data by the author) (fig. 3).
To estimate the effect of functional tests (changes in MABP and PaCO₂) and of drugs, a steady state regarding drug effect, MABP, PaCO₂ and mental activity is necessary. An advantage of the rCBF_initial in this respect is the short time of measurement. The equipment used in the present study provides all data on a negative Polaroid photograph which allows a rapid and fairly accurate estimate of regional flow changes during subsequent measurements (fig. 4). This was found to be important in the study of vasomotor function and of the effects of vasoactive drugs on the human cerebral circulation.

Using the rCBF_initial method some abnormalities of cerebral blood flow have been described in patients with focal cerebral disease which were not seen with the Kety technique or with the [133Xe] method using calculations to ten minutes or infinity. These abnormalities consist of early bending of the curves (tissue peaks), i.e., of the finding of curves which are multiexponential in the first two minutes of clearance (fig. 3). The reason why such abnormalities are reflected only slightly or not at all in the CBF_initial or CBF values is that they may constitute only a small percent of the total initial height of the clearance curve and that they affect the area under the curve only minimally. Furthermore, the abnormal curves which initially are steeper than the normal curves later in the clearance may be slower, and therefore a highly pathological curve and a normal curve may have the same area and total height, i.e., the same CBF_initial. This is frequently observed in cases of brain tumor and following head trauma. In most cases with such pathological configuration of the clearance curves only a semiquantitative evaluation of flow is possible, but changes in the flow from one measurement to another are easily observed. The CBF_initial gives a good impression of the pathological, high flow component but does not tell anything about the slow flow components seen in the curves. For this reason the CBF_second minute has been suggested as a semiquantitative measure. It is a value calculated like the CBF_initial but using the slope of the second minute of the clearance curve. A more complicated calculation has also been suggested (the two-minute flow index—TMFI). To the present authors the monoexponential fits to the curve necessary for this last calculation seem too uncertain to justify the complicated calculation.

In conclusion, the rCBF_initial method is especially suitable for the determination of interregional differences in flow and for the study of flow changes within a single patient. However, for the study of interindividual flow variations its value is somewhat limited, and rather large flow deviations are necessary to conclude that a CBF_initial value is beyond the limits of normality. For such a purpose the CBF_10 or CBF∞ calculation is better, and also the Kety method, which allows simultaneous determination of cerebral arteriovenous differences, is more suitable. With the last method, however, only hemispheric mean flow can be calculated.

Correlation Between CBF_initial and Other Flow Parameters

The present study demonstrated that the variation in average brain blood flow (CBF_w) among a group of normocapnic patients with various diseases was almost entirely due to variation in flow of gray substance, whereas the flow of white substance largely was constant. This means that the shape of the clearance curve changes from being clearly biexponential at normal CBF_w toward a monoexponential configuration at low CBF_w values (<25 ml/100 gm/min) (fig. 5c). If F_g in these cases decreased to the same level as F_w, a biexponential curve still would be observed, because the difference in partition coefficients (λ_g = 0.87, λ_w = 1.63) yields a slope of the gray component almost being the double of the slope of the white component. When, as seen in severe barbiturate poisoning, the curve becomes almost monoexponential, this indicates that F_g may be even lower than F_w. In such cases the bicompartamental model of the cerebral blood flow breaks down. The decreased weight of gray substance also observed at these low flows indicates the same: some parts of the gray tissue now have the same clearance rate (but lower flow) as the white substance. It must be mentioned that the weight estimate of these cases is difficult. It may be concluded that the two compartments observed at low flow values represent flow values but do not relate to anatomy. In cases with brain damage (trauma, apoplexy) an almost monoexponential clearance curve has been observed by others.
When the CBF is changed in man by altering the arterial $P_{CO_2}$, flow of white and gray substance changes almost proportionally. On the other hand, flow of white substance was percentilly less changed than the flow of gray substance in anesthetized man and in animal experiments. Thus the pH effect of CO$_2$ seems to affect both compartments of cerebral tissue in contrast to changes due to altered neuronal function as mentioned above.

The correlation between CBF$^{initial}$ and CBF$^{10}$ reported here as linear above CBF$^{10} = 20$ could, with even better accuracy, be described as exponential over the whole flow range according to Boysen. Boysen's CBF$^{initial}$ values were slightly lower than ours, however; this might be due to the anesthesia.

**CARBON DIOXIDE REACTIVITY**

Regarding the response of the cerebral vessels to changes in $P_{CO_2}$, the following parameters are of interest: The shape of the curve describing the CBF-$P_{CO_2}$ relationship, i.e., the mode or quality of the reactivity and the quantitative (how much does the CBF change per mm Hg $P_{CO_2}$ change).

The shape of the CBF-$P_{CO_2}$ curve in animal experiments was found to be a sigmoid when including rather extreme $P_{CO_2}$ value. Using only the interval 20 to 60 mm Hg, it has been found to fit a straight line with reasonable accuracy in animals and normal man.

However, in other animal experiments a better fit was found with an exponential function in the $P_{CO_2}$ interval mentioned, and definite bending of the curve was also found in another recently animal study. Previous data from unanesthetized man and the data of the present study show the same. Thus, the literature seems to indicate that the carbon dioxide reactivity usually is best described by an exponential curve in the physiological range of $P_{CO_2}$ changes in animals as well as in man.

Even when calculated in this way (see Results), the quantitative reactivity of the CBF upon $P_{CO_2}$ changes, however, is different in previous reports. In normal unanesthetized young men, Kety found a change of approximately 4.5% per mm Hg. Wilkinson and Browne as well as Alexander et al. found lower values during anesthesia. The latter author explained the difference between his and Kety's findings as due to the halothane anesthesia which caused a low blood pressure with an almost maximally dilated cerebral vascular bed as reflected in a low cerebral vascular resistance. In animal experiments a somewhat lower reactivity to changes in $P_{CO_2}$ compared to data from unanesthetized man has usually been found. As indicated above this may be due to the anesthesia and to surgical trauma. It is a great advantage that an exponential relationship between CBF and $P_{CO_2}$ has been established in nonanesthetized man. This makes comparisons between CO$_2$ reactivity possible even if the resting flow values are different (e.g., demented patients compared to normal patients). As indicated by the discussion above the experimental technique must be identical, however, to allow such comparisons.

No previous studies deal with comparison of the response in different groups of patients. The present study indicates that the shape of the CBF-$P_{CO_2}$ curve is identical in different groups of patients even quite severely ill, if patients with focally abnormal resting state CBF and patients with increased intracranial pressure are excluded, and that this relation in unanesthetized man is best described by an exponential equation. The figure of 4% CBF change per mm Hg $P_{CO_2}$ change found in these patients compared well with the findings of Kety. The importance of the present findings is that a basis has been set up for better description of regional abnormalities in CBF response, and that it makes better corrections for $P_{CO_2}$ changes possible. Thus, in studies of drug effects, correction for spontaneous changes in $P_{CO_2}$ can be carried out with 4% of the actual flow value per mm Hg $P_{CO_2}$ change without regard to the diagnosis of the patient or to the height of the CBF if focal abnormalities of rCBF or increased intracranial pressure are not present. It must be pointed out, however, that quite large differences were found between the carbon dioxide reactivity in different patients as reflected in a standard deviation of 1.1% per mm Hg, although this variation was at random and independent of the flow level. Thus, correction for larger changes in $P_{CO_2}$ is still subject to considerable error if the $P_{CO_2}$ reactivity is not directly measured in the individual patient.

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