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# Measurement of Human Cerebral Blood Flow with [$^{15}$O]Butanol and Positron Emission Tomography

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**Summary:** Although $H_2{}^{15}O$ is widely used for CBF measurement by positron tomography, it underestimates CBF, especially at elevated flow rates. Several tracers, including butanol, overcome this problem, but the short half-life of $^{15}O$ provides advantages that cause water to remain the tracer of choice. We report the first use and evaluation of $^{15}O$-labeled butanol for CBF measurement. Flow measurements made in a similar fashion with water and butanol at 10-min intervals were compared in normal volunteers under resting and hypercapnic conditions. Regional analysis showed good agreement between the tracers at low flows, and significant underestimation of flow by water relative to butanol in regions of elevated flow. The observed relationship between the tracers and the curve-fitted permeability–surface area product for water (133 ml · 100 $g^{-1}$ · $min^{-1}$) follow the known relationship between water and true flow. These observations indicate that [$^{15}O$]-butanol provided accurate measurements of human regional CBF under conditions of elevated perfusion. We conclude that butanol is a convenient and accurate method for routine CBF determination by positron emission tomography. **Key Words:** [$^{15}O$]Butanol—Regional CBF—[$^{15}O$]Water—Positron emission tomography—Permeability–surface area product correction.

A strong area of application of positron emission tomography (PET) is the noninvasive measurement of human regional cerebral blood flow (RCBF) for both research and clinical applications. The majority of PET determination of RCBF are based on the Kety technique using freely diffusible tracers (Kety, 1960, 1985). Among these tracers, oxygen-15-labeled water has been commonly used. The preference for water is based on its ready availability and on the short half-life (2 min) of oxygen-15. This short half-life has the dual effect of limiting the radiation dose caused by an individual injection and of causing the residual radioactivity to quickly fall to a level permitting a sequential study. The result of these factors is that several RCBF determinations may be made in one individual in a relatively short time. Because many common procedures require several sequential RCBF determinations or require injections of other tracers, this is a distinct advantage.

Water does, however, have one distinct disadvantage. At slightly higher perfusion rates than those commonly found at rest, its low brain permeability limits its extraction. This causes regional perfusion to be significantly underestimated by the model at flow rates >70 ml · 100 $g^{-1}$ · $min^{-1}$ (Eichling et al., 1974; Ginsberg et al., 1985; Go et al., 1981; Herscovitch et al., 1983; Raichle et al., 1976, 1983). Several compounds with higher lipophilicity have been shown to overcome this problem (Dischino et al., 1983; Eklöf et al., 1974). Prominent among them is butanol. Butanol has been labeled with carbon-14 and used as a blood flow tracer with considerable success (Schaefer et al., 1976; Van Uitert et al., 1981; Irwin and Preskorn, 1982; Clark et al., 1982). Labeled with carbon-11, it has been successfully used as a flow tracer in PET (Hersco-

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*Abbreviations used:* PET, positron emission tomography; PS, permeability–surface area product; RCBF, regional cerebral blood flow.

vitch et al., 1985, 1987; Oberdorfer et al., 1982; Takagi et al., 1984, 1987), without any indication of a permeability limitation. In spite of this, [$^{15}$O]water has been routinely selected as the tracer of choice because of both its half-life advantage and the relative difficulty of producing other tracers (Lammertsma and Mazoyer, 1990).

Butanol labeled with oxygen-15, by combining the desirable properties of [C-11]butanol and [$^{15}$O]water, should be an ideal agent for routine RCBF measurements. On the assumption that this would be the case, we developed a preparation of [$^{15}$O]butanol suitable for routine studies (Berridge et al., 1990*a*). The present study examines the use of this tracer for perfusion measurements in normal volunteers under baseline and elevated perfusion (hypercapnia) conditions.

The goal of this work was twofold. First, it was necessary to determine the practicality of butanol as a tracer for routine use. The lower yield and more difficult synthetic procedure, as compared with water, raised questions concerning its applicability for routine, repetitive, clinical studies. Second, the observations noted above clearly would lead one to expect that [$^{15}$O]butanol would be a good tracer for perfusion measurements. However, before such measurements can be done with confidence there is a need (Herscovitch et al., 1987; Lammertsma and Mazoyer, 1990) to demonstrate that these expectations are justified. This study was therefore intended to provide the validation necessary for use of this tracer in human subjects. Because it is not ethical to make microsphere determinations of blood flow in normal human subjects, it was necessary to use another comparison to determine the validity of flows determined by butanol. We chose water as a convenient comparative tracer because it is the tracer most likely to be replaced by butanol, and therefore the comparison is of direct practical interest. Also, the relationship between true RCBF and [$^{15}$O]water measurements of RCBF is known. By comparing the relationship between butanol and water measurements to the known relationship between water and true flow, we are able to deduce the accuracy of quantification with [$^{15}$O]-butanol.

## METHODS

### Blood flow measurements

Ten healthy, normal volunteers between the ages of 20 and 44 years were recruited for the study. After giving informed consent, each subject was positioned in the PET scanner. The instrument used was a PETT Electronics (St. Louis, MO, U.S.A.)/Scanditronix (Essex, MA, U.S.A.) Superpett 3000, BaF, time-of-flight, four-ring, seven-slice tomograph. Although the instrument has an optimal resolution of 4.2 mm, reconstruction for this study was done with 12-mm resolution filters. Axial resolution in the low-resolution mode used was similarly 11–13 mm. Positioning was accomplished and maintained with the aid of a rigid thermoplastic half-face mask and two orthogonal cross-hair laser systems. The image slices were oriented parallel to the orbitomeatal line. After the subject was positioned, an attenuation measurement was performed using a 3-mCi rotating Ge-68/Ga-68 source. During the attenuation scan (20–30 min), radial intravenous and intraarterial catheters were inserted to allow injection of tracer and measurement of the tracer concentration in arterial blood. The room was kept dimly lit and quiet during all scans. Scans were acquired with the subject's eyes open and ears unobstructed. List mode data were collected, and a segment of these data was reconstructed as described below.

Before any data were acquired, a sham injection (physiological saline) and scan were performed under resting conditions. This scan was to allow the subject to adjust to the procedure and avoid including the systematic differences in perfusion that we have observed in the first scan of a series. After the sham injection, the first blood flow scan was performed with visual stimulation using [$^{15}$O]water. The subject fixed his attention on a strobe light positioned 50 cm from his eyes and flashing at a rate of 8 Hz. The light was started 30 s before the injection of the tracer and continued flashing until the end of the 2-min acquisition. This scan was not quantitated for the study, but was used for objective definition of unbiased small regions of interest, as discussed below. Eight perfusion scans were then performed at 10-min intervals. The first four were done with resting conditions, and the second four while the subject breathed a mixture of 6–7% carbon dioxide in room air to induce hypercapnia and the associated increase in RCBF. The scans began randomly with either water or butanol and alternated between the two tracers. Therefore, with each experimental condition (rest and hypercapnia), two water scans and two butanol scans were obtained. For the resting scans, the subject was given a 1-min warning that the scan would begin, the injection and a 2-min scan were performed, and 8 min were allowed for the $^{15}$O to decay before the next injection. For the hypercapnic scans, the subject was asked to begin breathing the gas mixture 4 min before the injection of tracer. Subjects were instructed to relax and attempt to breathe normally. The gas was removed at the end of the scan, allowing the subject to rest with room air for 4 min before breathing the gas for the next scan. Subjects reported sensations of shortness of breath and of increased effort to ventilate at the conclusion of each hypercapnic scan, but reported no discomfort or other effects.

### Preparation of tracers

Oxygen-15 was produced by bombardment of a mixture of 0.2% oxygen in nitrogen gas with 6 MeV deuterons. Labeled water was prepared on-line by reacting the oxygen with hydrogen over a platinum wire catalyst (Berridge et al., 1990*b*). The labeled water, 20–25 mCi/μA of beam current, was trapped in sterile saline for injection. Labeled butanol was produced (Berridge et al., 1990*a*) by reacting the oxygen with tri-*n*-butyl borane. The butanol, 5–7 mCi/μA of beam current containing <0.2% labeled water, was taken up in sterile saline containing 5% ethanol. Both tracers were sterile filtered (0.22 μm) before injection and were found by USP procedures to be sterile and pyrogen free.

### Data acquisition

Each data collection procedure was the same regardless of the tracer used. An injection dose (50–100 mCi, 65 median) was chosen by an experienced operator based on the weight of the subject. Each data acquisition was begun at the moment of injection and continued for 2 min. Arterial blood withdrawal at 6 ml/min was begun before each injection and continued through the scan. Arterial radioactivity was sampled in 0.1-s intervals by a multichannel analyzer as the blood flowed through 0.5 mm I.D. polytetrafluoroethylene (Teflon) tubing (Nelson et al., 1990). The true arterial concentration curve was obtained from these data as described below. The blood-counting apparatus was calibrated after each study using a known concentration of a positron emitter dissolved in the collected blood.

### Quantification of blood flow

A time–activity curve for one midbrain slice of each scan was constructed from the list mode data. The time of arrival of the tracer bolus in the brain was determined from the derivative of this curve using a computer algorithm. The measured peripheral arterial radioactivity curve was deconvolved to obtain the true arterial activity curve (Eriksson et al., 1988; Muzic et al., 1988; Meyer, 1989). The correction technique relies on an iterative deconvolution algorithm (Schafer et al., 1981) to recover the undispersed input function from the measured dispersed output. This required a characterization of the system response that was obtained by analysis of measured step response data. The deconvolved arterial data were used in an iterative process to calculate an expected tissue activity curve at a global flow value similar to that observed, using an initial assumed flow of 50 ml/100 $g^{-1}$ $min^{-1}$. The same algorithm as was used to determine the brain bolus arrival time was used on this simulated tissue curve to determine the arterial bolus arrival time. Automated reconstruction and quantification was then performed on a pixel basis using the 40-s interval from the bolus arrival in the brain and the arterial data, according to methods previously described (Muzic et al., 1990; Raichle et al., 1983; Snyder et al., 1981). Radioactive decay and the variable deadtime of the tomograph during the study were taken into account. The values used for the partition coefficient ($\lambda$) of water and butanol were 0.956 and 0.77 ml/g, respectively (Herscovitch and Raichle, 1985; Herscovitch et al., 1985, 1987). The resulting images were then used to obtain average blood flow in a variety of regions of interest.

### Region of interest definition

The series of flow images from a single subject was averaged into a composite image, verifying that noticeable motion of the subject did not occur between scans. Anatomic regions were defined on this combined image. The global brain region was first determined using an objective, automated edge detection technique based on morphological processing. A region intended to correspond to cortical matter was defined using the global border as its outer edge with an inner edge defined by a trained nuclear medicine physician and based on the perceived border between the cortex and the white matter. The same investigator then defined regions of interest over the portion of the occipital cortex along the interhemispheric fissure (occiput) and over a subcortical region of increased blood flow thought to correspond to the insula.

Small, nonanatomic regions were defined by applying a threshold to the unquantified visual stimulation scan. All areas in the highest 20% of this scan were taken as preliminary regions of interest. Any extremely small regions (<0.5-cm diameter) were deleted to avoid excessive effects of partial volume, and any very large regions were divided arbitrarily into smaller regions to form the set of final regions. This process resulted in approximately 30 small regions of interest for each subject. The average region size was 2.3 $cm^2$, which represented a volume of approximately 3.3 $cm^3$. The regions were most highly representative of the cortex, and when they were used to analyze the four quantitated scans from each subject in each state (rest and hypercapnia), a good sampling of both high and low blood flows was obtained. This method was used to allow the acquisition of a large number of data points over a large flow range.

### Data analysis

Average blood flow values for each of the regions, defined per subject as noted above, were obtained from each scan. Anatomic regions were analyzed by averaging the results obtained from all subjects based on tracer and scan condition. Paired *t* tests were used to evaluate the observed differences between water and butanol measurements. The flow data measured in each small nonanatomic region of interest by water was plotted against measurements in the same region by butanol under the same conditions (Fig. 1). For these data pairs, all measurements were made within 35 min of each other, with the majority made 10 min apart. Similar plots were made of pairs of water measurements and pairs of butanol measurements to determine the systematic error of the method (Fig. 2). The data were also grouped into ranges of "true" blood flow (Table 1). For butanol measurement, "true" flow was taken to be the measured flow. For water measurements, "true" flow for grouping purposes was calculated from the measured flow using the PS product correction of Eq. 1, below (Fig. 3). A *t* test on the data in each flow region was performed to establish the significance of the observed difference in measured flow as a function of the flow magnitude.

### Correction for PS product

An evaluation was done of a correction of water measurements for incomplete extraction (Kety 1960, 1985). These corrected water values are plotted against measured butanol values in Fig. 3. The correction for the permeability–surface area product (*PS*) of water (Raichle et al. 1983; Herscovitch et al., 1987) was calculated using Eq. 1:

$$F_{(corr)} = F/1 - e^{(-PS/F)} \quad (1)$$

where $F$ is the uncorrected regional average flow measured with water and $F_{(corr)}$ is the resultant corrected value. This is the equivalent of dividing the observed flow value by the Kety $m$. The value of $PS$ that was used in Fig. 3, 133, was determined by a nonlinear regression fit of the corrected water data to the measured butanol data using Eq. 1.

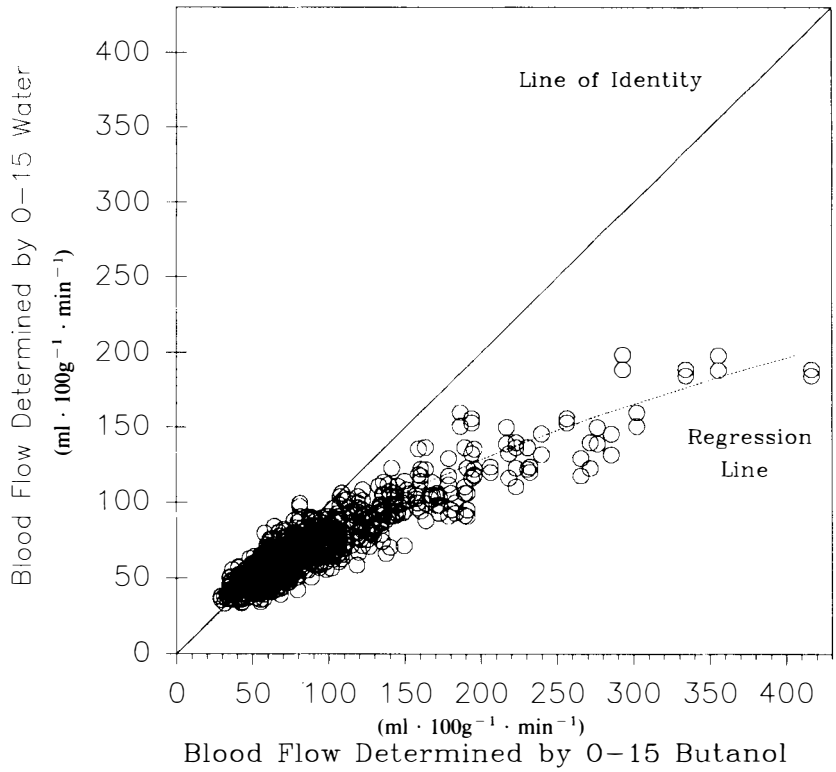



**FIG. 1.** Butanol versus water regional measurements: butanol measurements plotted against paired identical water measurements (951 data points).

## RESULTS

### Routine use of butanol

One of the main goals of this work was to determine the suitability of [$^{15}$O]butanol for routine research and clinical use. By following the procedure as described (Berridge et al., 1990*a*), the reliability of the butanol tracer delivery, on time and in sufficient amount, was ~90%. In the event of a failed delivery, a replacement dose was generally obtained with a delay to the study schedule of ~5 min.

For most of the subjects studied, the injected tracer dose was the same for each scan of the study. However, during early studies it was noticed that butanol scans tended to produce more system coincidence counts, especially during the hypercapnic series of scans. For two of the subjects, therefore, the butanol dose was lowered with respect to the water dose by 15%.

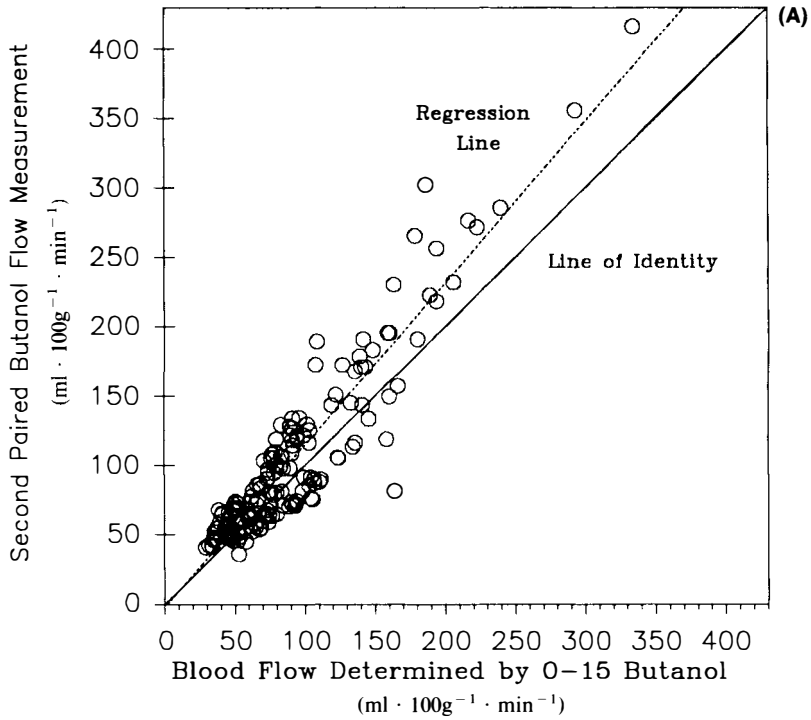
### Regional data

Anatomic regional data are shown in Table 2. In all regions in the resting state, average flows correspond well to the expected values. At rest, butanol gives consistently, although not significantly, higher values. Under hypercapnic conditions, a significant increase in regional flow is expected, and is observed, with both tracers. The increase measured by butanol is also significantly greater than that measured by water.

Results obtained from the small nonanatomic regions are shown in Fig. 1. Flow measured in each region by water is plotted against the flow measured by butanol in the same region, under the same conditions, and in the same subject. The plot shows a pronounced underestimation of flow by water with respect to butanol over the range of 70–400 ml · 100 $g^{-1}$ · $min^{-1}$. Although Fig. 1 shows that below ~70 the points cluster around the line of identity, paired and unpaired tests show a significant difference between water and butanol at all flow values except 45–60 (Table 1). Above this range, the flow difference and the significance of that difference increase. Below 45 ml · 100 $g^{-1}$ · $min^{-1}$, the butanol values were slightly lower than the water values were.

### Study controls and PS product correction

To control for any systematic errors, curves were generated for pairs of water scans and pairs of butanol scans. Each plot is similar to that in Fig. 1; however, regions on water scans (Fig. 2B) are plotted versus a corresponding water scan in the same subject, and butanol data are similarly paired in Fig. 2A. It may be noted that although the fit of data lies close to the line of identity in both cases, the fit from the water data is better than with the butanol. There are two reasons for this. First, as noted in Fig. 1, the range of the butanol data is larger and the



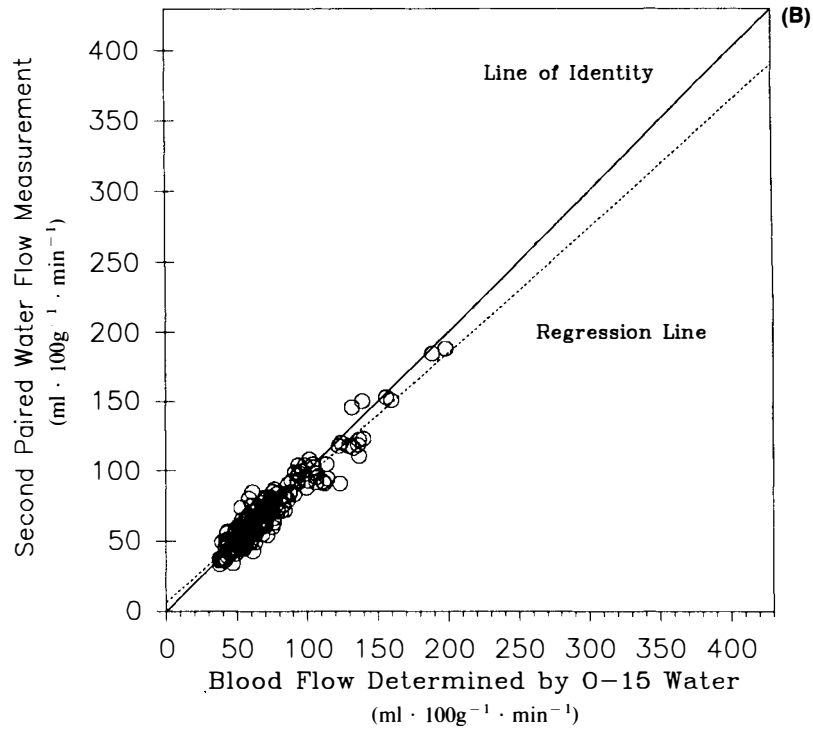




**FIG. 2.** Paired control plots. **A:** Butanol measurements plotted against paired identical butanol measurements (177 data points). **B:** Water measurements plotted against paired identical water measurements (195 data points).

relative compression of the water data will necessarily result in less scatter of the points. Second, the success of the volunteers in achieving high blood flow through hypercapnia was variable between volunteers and from scan to scan, as shown by several regions in which clusters of points originate from one individual. These plots probably demonstrate both the variability of the PET measurement

**TABLE 1.** *Method comparison: statistics are shown for water and butanol measurements within selected ranges of "true" flow (see text); for each flow range, the number of observations, corresponding water and butanol measurements mean and SD, and the p value obtained for the difference between the water and butanol are given*

| Flow range selected | n | Butanol flow (ml · 100 $g^{-1}$ · $min^{-1}$) | Water flow (ml · 100 $g^{-1}$ · $min^{-1}$) | p value |
|---|---|---|---|---|
| 15–45 | 68 | 39.2 ± 10.4 | 44.0 ± 6.2 | <0.05 |
| 45–60 | 210 | 52.5 ± 10.1 | 52.0 ± 7.1 | NS |
| 60–70 | 148 | 65.0 ± 14.2 | 58.0 ± 7.9 | <0.001 |
| 70–80 | 136 | 75.4 ± 15.0 | 64.0 ± 8.6 | ≪0.001 |
| 80–90 | 80 | 84.5 ± 17.0 | 67.0 ± 10.1 | ≪0.001 |
| 90–105 | 88 | 96.0 ± 18.6 | 73.0 ± 9.5 | ≪0.001 |
| 105–120 | 55 | 111.0 ± 27.1 | 78.0 ± 12.9 | ≪0.001 |
| 120–135 | 42 | 127.5 ± 25.2 | 85.0 ± 9.0 | ≪0.001 |
| 165–180 | 16 | 172.2 ± 33.2 | 105 ± 9.9 | ≪0.001 |
| 225–240 | 6 | 233.9 ± 27.8 | 130 ± 9.9 | ≪0.001 |
| >300 | 12 | 331.1 ± 44.6 | 165 ± 22.4 | ≪0.001 |

itself and the variability of true cerebral blood flow in the course of this experiment.

Figure 3 shows butanol-determined flow values plotted against the corresponding water-determined values that have been corrected by Eq. 1. The figure demonstrates the much more linear character of the relationship after the correction. Although the *PS* product is a function of flow (Herscovitch et al., 1987), for simplicity we chose a constant value for this correction. The value shown in Fig. 3, 133 ml · 100 $g^{-1}$ · $min^{-1}$, was determined by fitting Eq. 1 to these data with a nonlinear regression ($R^2$ = 0.85). Other reasonable values of *PS* resulted in similarly linear relationships with varying slopes, as would be expected. Also, other methods of evaluation of the correction's "fit" to the data resulted in different values for *PS*. The value of *PS* that produced a linear-regression slope for Fig. 3 closest to the line of identity was 120. However, application of Eq. 1 with any *PS* product value in the range 100–150 gave a great improvement in the agreement between the water and butanol data, and differences between members of this family of curves were minor.

## DISCUSSION

### Routine use of butanol

The success rate of 90% for tracer delivery compares well with many synthesized tracers, although it is poorer than that for water (98.2%). Most failures occurred when an aging borane reagent cartridge, used in the synthesis, caused a low yield of butanol. The reliability of tracer delivery is expected to improve to at least 95% because cartridges older than 1 week are no longer used for human studies. In the case of synthesis failure, it was possible to obtain the dose with a delay to the study of <5 min. This was accomplished by use of

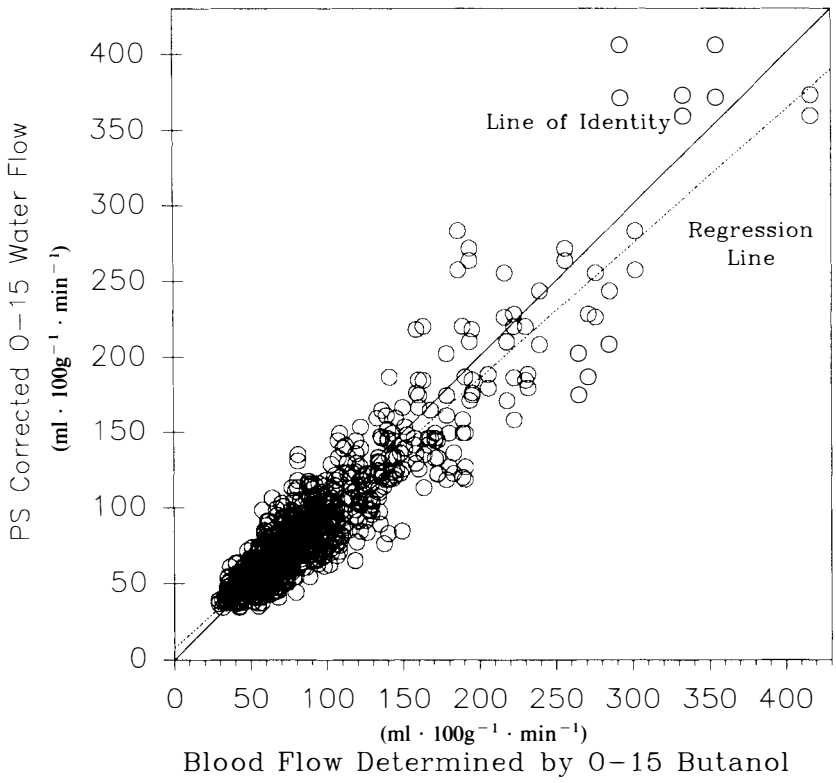



**FIG. 3.** Permeability–surface area (PS) produce correction: butanol measurements plotted against paired identical water measurements. The water measurements have been corrected for incomplete extraction as described in the text. The regression line shown is from a linear regression fit of the data (951 data points).

**TABLE 2.** *Anatomic regional data: mean and SD for 10 subjects for each anatomically defined region are shown*

| Region | Water flow (ml · 100 g$^{-1}$ · min$^{-1}$) | Butanol flow (ml · 100 g$^{-1}$ · min$^{-1}$) | p value |
|---|---|---|---|
| Resting | | | |
| Global | 45 ± 9 | 49 ± 14 | 0.12 |
| Cortical matter | 47 ± 11 | 50 ± 16 | 0.18 |
| Occipital | 57 ± 17 | 61 ± 25 | 0.28 |
| Insular | 65 ± 15 | 68 ± 13 | 0.13 |
| Hypercapnic | | | |
| Global | 66 ± 18 | 83 ± 37 | 0.035 |
| Cortical matter | 70 ± 22 | 82 ± 42 | 0.086 |
| Occipital | 84 ± 36 | 111 ± 79 | 0.12 |
| Insular | 94 ± 25 | 118 ± 39 | 0.003 |

a small, inexpensive radiation detector (Posimeter, Polytech Lab, Houston, TX, U.S.A.) to monitor the radioactivity initially trapped on the reagent as an early indicator of a failure. The procedure was aborted when a failure was detected and the cartridge was replaced. Because of this potential for unanticipated low yield, 100–150 mCi was usually produced and then allowed to decay to the desired level. Injectable doses up to 250 mCi could be reliably delivered. There was no difficulty encountered in injecting doses of butanol at 10-min intervals.

The observation that more coincidence counts were obtained with butanol is probably due to its complete equilibration at higher flows. The increase was observed during baseline scans, but became much more pronounced during hypercapnic scans. In the extreme cases, this effect limited the dose that could be injected. For a given injected dose, we have found that the whole-body and regional radiation dosimetry of [$^{15}$O]butanol is very similar to that of [$^{15}$O]water. Although this did not affect the radiation dose to volunteers in this study, it may be possible to lower total radiation doses to future patients and research subjects if consistently lower tracer doses can be given.

### Choice of partition coefficients

The values used for the partition coefficients (λ) of water and butanol were 0.956 and 0.77 ml/g, respectively (Herscovitch and Raichle, 1985; Herscovitch et al., 1985, 1987). Although this choice of λ for butanol represents the best estimate currently available and is generally accepted, we expect that the optimum value for use in human RCBF studies will be the subject of future investigations. Our choice of λ for water is at the high end of the range of λs that have been used by other investigators. The reason for this is partly historical, in that it is the value that has been used in this institution in the past and allows direct comparison with previous studies. It is also more heavily weighted toward the λ for gray matter, which has been estimated at values between 0.9 and 1.01 (Herscovitch et al., 1985). This study is intended to concentrate on regions of relatively high RCBF. It was likely that the data that would contribute the most weight to the results would be derived from tissue in which gray matter was overrepresented in comparison with whole brain. The results seem to support this assumption, and therefore the use of a relatively high λ seems appropriate. As has been pointed out by others (Herscovitch et al., 1983, 1987) and verified for this study by our own calculations, the effect of changes in λ within this range have a relatively small effect (3–11% over flows from 40 to 150 ml · 100 g$^{-1}$ · min$^{-1}$ measured with water) on the measured blood flow values.

### Region selection and quantitation

The difficulty encountered in gathering data for this study was to obtain a sufficient representation of elevated perfusion values. Normal brain scans contain large areas with relatively low perfusion (ventricles, white matter) in which very little discrimination between blood flow tracers is expected. For this reason, region of interest selection was intentionally biased toward the cortex and particular regions of high flow. In addition to the global CBF measurement, a "cortical matter" region including most of the cortex; an occipital region including the visual cortex; and the insula, a relatively small and potentially well-perfused region, were chosen. We have used the automated method for global CBF measurement extensively in previous studies (Bednarczyk et al., 1990*a,b;* Gardner et al., 1990; Green et al., 1990) and obtained good reproducibility (coefficient of variation = 5% on test–retest, different days).

The anatomically defined regions were of interest from a clinical point of view. However, they were too few to give good statistical data from a reasonable number of volunteers and too large in size to give average flows that reflect the higher values present in stimulation studies. For these reasons it was necessary to define small regions in areas likely to give good representation of the higher flows attained in the brain. Initial attempts at using threshold methods were not successful. Regions obtained from any scan or combination of scans were biased toward that type of scan (baseline, hypercapnic, visual), or to the scan type that carried the most weight in an average. Normalization before averaging did not remove the bias, it only changed it because of the differences in the dynamic range of the

different scans. The bias was evidenced by good linear regression correlation coefficients (0.6–0.9) from plots of water versus butanol data using regions defined on dissimilar scans, but the same scan data plotted using regions defined on similar scans gave scatter plots with very poor correlations (0.001–0.2). We found that an unquantitated water scan done with visual stimulation would give 18–30 threshold regions of a desirable size well distributed throughout the cortex and unbiased with respect to the data scans. Use of these regions gave consistent data from all water and butanol scans.

**Regional flow comparisons**

A small but consistent excess of butanol-determined values over water was observed in resting scans (Table 2). This is expected, because in the normal resting flow range, water is known to give a very good estimation of true blood flow. The differences observed are probably due to the presence of smaller areas within each region that have flow rates high enough to produce a water–butanol difference. Under hypercapnic conditions, the butanol measurements significantly exceed the water measurements. In each region, there is a noticeable change in the p value toward increased significance between the baseline and the hypercapnic scans. This is consistent with the expectation that water progressively underestimates flow as flow increases.

The small nonanatomic regions represent no particular or consistent portion of the brain. They also represent a continuum of blood flow values from 30 to 420 ml · 100 $g^{-1}$ · $min^{-1}$. The best form of analysis of these data is the graphic display shown in Fig. 1. At the lowest flows, <40, butanol-measured flows are slightly, but with marginal statistical significance, less than corresponding water-measured values. It is probable that low flow values arise from regions of predominantly white matter, in which our assumed value for the partition coefficient of water (0.956) is likely to be higher than the true value. There is also a possibility of error in the $\lambda$ for butanol. Although these possibilities could create the observed difference, we have no evidence to explain the observation. There is a near identity of the butanol and water data at flows up to 50, 60, or 70 ml · 100 $g^{-1}$ · $min^{-1}$, depending on how much deviation from the line of identity one is willing to tolerate. Above that level the deviation from the line of identity becomes dramatic. The underestimation by water is 50 and 100% at butanol flows of 150 and 300 ml · 100 $g^{-1}$ · $min^{-1}$, respectively. Regardless of the ultimate accuracy of [$^{15}$O]butanol measurements, this difference would have a significant effect on the results of both quantitative and qualitative PET studies involving elevated regional flows. The errors in $\lambda$ mentioned above could also have an effect in this region of the curve. However, our calculations using these same data files have shown that errors in $\lambda$ >10% would only account for a small part (10–15%) of the observed difference between the tracers. The relationship we observe between butanol and water measurements is very similar to the relationship between true flow and water measurements observed in adult baboons by Raichle et al. (1983). The value we obtained for the *PS* product (133 ml · 100 $g^{-1}$ · $min^{-1}$) is greater than the value obtained by them (*PS* = 104). However, as pointed out by them, this is due to a species brain permeability difference, which led them to predict an average human *PS* product value of 144. A reference tracer (butanol) that does not accurately represent true flow would result in a measured *PS* value for water that is too high (Clark et al., 1981). We conclude that there is reasonable cause to believe that the values measured in this study by the [$^{15}$O]butanol technique represent true RCBF.

Because the *PS* product is itself a function of flow, the proper application of a *PS* correction requires independent measurement of the tracer extraction. The large volume of paired flow measurements in this study is an ideal data set for testing the hypothesis that an extraction correction may permit routine correction of values measured with water. As shown in Fig. 3, a very simple correction that uses no other input than the uncorrected water-measured flow can generate a good agreement with the butanol-measured values. The implication is that this simple correction could be used to obtain improved, if not strictly accurate, blood flow values in a setting in which butanol is not available. The different values we and others (Raichle et al., 1983; Herscovitch et al., 1987; Preskorn et al., 1982) have obtained for the *PS* product under varying conditions point out its variability and the difficulty in choosing a value for general use. The effects of experimental conditions, pathology, and drug treatment on *PS* must be considered if this correction to water data is used in place of butanol.

## CONCLUSION

This work has shown that the [$^{15}$O]butanol method for RCBF determination gives measured values that may be expected to accurately reflect true RCBF. The method is technically no different from the widely used [$^{15}$O]water method. Although the preparation of the tracer is not as simple as preparation of labeled water, tracer preparation presents no disadvantage of reliability or conve-

nience in performing routine clinical and research protocols. We have also shown that although [$^{15}$O]butanol is preferable to [$^{15}$O]water for routine RCBF determination, [$^{15}$O]water RCBF data can be corrected using a simple expression to give improved agreement with butanol-obtained values.

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