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What Is the Correct Value for the Brain–Blood Partition Coefficient for Water?

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Summary: A knowledge of the brain–blood partition coefficient (λ) for water is usually required for the measurement of CBF with [^{15}O]water. The currently accepted value for whole-brain λ, 0.95–0.96 ml/g, calculated from brain and blood water content data, is incorrect because in the calculation, the blood water content was not adjusted for the density of blood. The correct value is 0.90 ml/g. Variations in brain or blood water content affect λ. Thus, λ changes during development of the brain and varies regionally in it, even among different gray matter structures, owing to variation in brain water content. In addition, λ would be expected to vary with the hematocrit, owing to changes in blood water content. The impact of using an incorrect value for λ will depend on the sensitivity of the CBF measurement technique used to errors in λ. **Key Words:** Cerebral blood flow—Partition coefficient for water—Positron emission tomography.

^{15}O-Labeled water is increasingly used as a radiotracer for the study of the cerebral circulation. It was initially employed for the measurement of CBF using external residue detection of a bolus of tracer injected into the internal carotid artery (Ter-Pogossian et al., 1969; Eichling et al., 1974). More recently, several techniques have been developed to measure regional CBF with positron emission tomography (PET) using [^{15}O]water as the flow tracer (Subramanyam et al., 1978; Frackowiak et al., 1980; Herscovitch et al., 1983; Howard et al., 1983; Huang et al., 1983; Raichle et al., 1983). These techniques involve the use of the brain–blood partition coefficient (λ) for water, and in most cases the value of λ must be specified for the calculation of CBF. Errors in the specified value of λ will lead to errors in calculated CBF, although their magnitude is dependent on the specific model used for flow measurement.

The partition coefficient of a flow tracer, as defined by Kety (1951), is the ratio between the tissue and blood tracer concentrations at equilibrium. The partition coefficient for a variety of CBF tracers, including [^{15}O]water, has been measured in experimental animals according to this definition (Reivich et al., 1969; Sakurada et al., 1978; Ginsberg et al., 1982). For studies in humans, λ for water is calculated from the ratio of brain and blood water contents, using published values (Ter-Pogossian et al., 1969; Jones et al., 1982). This calculation assumes that all brain water is freely exchangeable with that of blood. Since external detection systems cannot measure [^{15}O]water activity or regional CBF in pure gray or white matter, an average brain λ is used (Eichling et al., 1974; Jones et al., 1982; Raichle et al., 1983), calculated from whole-brain water content. Values for gray and white matter λ have also been calculated, principally for use in simulation studies of the accuracy of PET measurements of regional CBF (Lammertsma et al., 1981; Jones et al., 1982; Herscovitch and Raichle, 1983; Herscovitch et al., 1983).

The purpose of this communication is to review the calculation of λ for water from published water content data in order to demonstrate that the value of 0.95–0.96 ml/g currently used for whole-brain λ (Eichling et al., 1974; Jones et al., 1982; Howard et al., 1983; Herscovitch et al., 1983; Lebrun-Grandié

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Abbreviation used: PET, positron emission tomography.

et al., 1983; Raichle et al., 1983) is in fact incorrect. In addition, the effect of physiological or pathological variations in the water content of blood or brain on the value of λ will be examined. These considerations are of importance in the development and use of methods for measuring CBF with [^{15}O]water.

AVERAGE BRAIN PARTITION COEFFICIENT FOR WATER

The brain–blood partition coefficient for water can be calculated from published values of average tissue and blood water contents (Ter-Pogossian et al., 1969; Jones et al., 1982). Values for the partition coefficient of gray matter (λ_g) and white matter (λ_w) are shown in Table 1, calculated from the following data on water contents: blood 80.5 g/100 g (Davis et al., 1953); cerebral cortex 84 g/100 g; and cerebral white matter 70 g/100 g (Randall, 1938; Stewart-Wallace, 1939; Dittmer, 1961). The average whole-brain partition coefficient, $\bar{\lambda}$, calculated either from the mean of λ_g and λ_w or from the value of whole-brain water content, 77 g/100 g (Dittmer, 1961), is 0.96 g/g. Note that the water content values used above were all measured on a percent weight basis, resulting in λ values that are in units of g blood/g brain.

A practice used by most authors is to express λ in units of ml blood/g brain (Lassen and Perl, 1979). This allows λ to be interpreted as the volume of distribution of tracer per unit weight of tissue. The values of $\bar{\lambda}$, λ_g, and λ_w in g/g can be converted to units of ml/g by dividing by the density of blood, 1.06 g/ml (Ashworth and Adams, 1940–41; Van Slyke et al., 1950) (Table 1). This gives a value for $\bar{\lambda}$ of 0.90 ml/g, not the value of 0.95–0.96 ml/g that has been widely used (Eichling et al., 1974; Jones et al., 1982; Lebrun-Grandié et al., 1983; Raichle et al., 1983). The discrepancy results from a failure to appreciate that blood water content was expressed as a percentage by weight (Davis et al., 1953). Thus, one must divide by the density of blood to express λ in units of ml/g.

Some investigators have expressed λ in units of ml blood/ml brain (Frackowiak et al., 1980). The appropriate values of λ, calculated using the value of 1.05 for gray matter and white matter specific gravity (Torack et al., 1976) are listed in Table 1. The $\bar{\lambda}$ of 0.95 ml/ml differs from the value of 1.0 frequently used.

TABLE 1. *Partition coefficients for whole brain ($\bar{\lambda}$), gray matter (λ_g), and white matter (λ_w)*

	Dimensions for partition coefficient values		
	g/g	ml/g	ml/ml
$\bar{\lambda}$	0.96	0.90	0.95
λ_g	1.04	0.98	1.03
λ_w	0.87	0.82	0.86

EFFECT OF HEMATOCRIT ON PARTITION COEFFICIENT

If a tracer is not uniformly distributed between plasma and red blood cells, its partition coefficient will be a function of hematocrit (Rosenblum, 1972). Because the water contents of plasma and erythrocytes differ appreciably (Davis et al., 1953), changes in hematocrit will affect the water content of whole blood and thus λ for water. Thus, variations in large-vessel, peripheral hematocrit will affect λ. In addition, we note that cerebral hematocrit is less than large-vessel hematocrit with values for the ratio of cerebral to large-vessel hematocrit of from 0.69 to 0.92 reported in humans (Larsen and Lassen, 1964; Oldendorf et al., 1965; Lammertsma et al., 1984). However, the use of cerebral rather than peripheral hematocrit to calculate blood water content and λ may depend on the context in which λ is used in any specific tracer kinetic model (see Discussion).

The water content of whole blood, C_{bl} (g/ml), can be calculated from plasma and red cell water contents and densities as

$$C_{bl} = \text{Hct} \cdot d_{rbc} \cdot w_{rbc} + (1 - \text{Hct}) \cdot d_{pl} \cdot w_{pl} \quad (1)$$

where Hct is the hematocrit fraction, d_{rbc} is the density of red cells (1.10 g/ml) (Ashworth and Adams, 1940–41; Van Slyke et al., 1950), d_{pl} is the density of plasma (1.03 g/ml) (Ashworth and Adams, 1940–41; Van Slyke et al., 1950), w_{rbc} is the red cell water content (66 g/100 g) (Stewart-Wallace, 1939; Davis et al., 1953), and w_{pl} is the plasma water content (92 g/100 g) (Davis et al., 1953; Keitel et al., 1955). Substituting these values into Eq. 1 gives

$$C_{bl} = 0.95 \text{ g/ml} - (0.22 \text{ g/ml}) \cdot \text{Hct} \quad (2)$$

Values for C_{bl} for a wide range of Hct and the corresponding λ_g, λ_w, and $\bar{\lambda}$ values are given in Table 2. As hematocrit varies from 25 to 55%, $\bar{\lambda}$ varies from 0.86 to 0.93 ml/g. Plasma and red cell density and water content values used in these calculations are, of course, subject to variation. However, d_{pl} and w_{pl} change by less than $\pm 1\%$ from their mean values over the plasma protein range of 6.0–8.0 g/100 cc (Sunderman, 1936; Van Slyke et al., 1950). Similarly, d_{rbc} and w_{rbc} are relatively constant unless there are appreciable changes in red cell hemoglobin concentration (Ashworth and Adams, 1940–41; Van Slyke et al., 1950; von Bubnoff and Riecker,

TABLE 2. *Brain partition coefficient of water as a function of hematocrit*

Hematocrit (%)	Water content of blood (g/ml)	λ_g (ml/g)	λ_w (ml/g)	$\bar{\lambda}$ (ml/g)
25	0.895	0.94	0.78	0.86
35	0.873	0.96	0.80	0.88
45	0.851	0.99	0.82	0.90
55	0.829	1.01	0.84	0.93

λ_g, λ_w, and $\bar{\lambda}$, partition coefficients for gray matter, white matter, and whole brain, respectively.

1961). Of note, a similar approach has been used by Frackowiak et al. (1980) to calculate the ratio of whole blood to plasma water content from measured hematocrit and published values of red cell and plasma water contents.

VARIATIONS IN BRAIN WATER CONTENT

Regional brain water content is related, in an inverse fashion, to the amount of lipid and myelin present (Randall, 1938; Katzman and Pappius, 1973). Differences in water content between cerebral gray and white matter are well recognized. However, water contents, and thus λ, can also vary among different gray matter structures and among different white matter regions. The thalamus and caudate have lower water contents than cerebral cortex, whereas the corpus callosum has a higher water content than the centrum semiovale (Randall, 1938; Stewart-Wallace, 1939). The water contents of selected cerebral structures and their corresponding partition coefficients are listed in Table 3. Cerebral edema increases white matter water content (Stewart-Wallace, 1939; Torack et al., 1976) and thus λ_w (Lammertsma et al., 1981), as shown in Table 3. The value of λ will, of course, depend on the degree of edema.

The water content of the neonatal brain, 89 g/100 g (Dittmer, 1961), is greater than that of the adult brain. The neonatal blood water content is 76 g/100 g (Ujsaghy, 1940) and density 1.06 g/ml (Gray and Elliot, 1943). Thus, $\bar{\lambda}$ equals 1.10 ml/g, considerably higher than in adults. This must be taken into consideration when [^{15}O]water is used to measure CBF in the neonate (Volpe et al., 1983).

TABLE 3. *Regional values of the brain partition coefficient of water*

	Water content (g/100 g)	Partition coefficient (ml/g)
Gray matter		
Cerebral cortex	84.3[a]	0.99
Thalamus	75.1[a]	0.88
Caudate nucleus	81.4[b]	0.95
White matter		
Centrum semiovale	70.7[a]	0.83
Corpus callosum	75.7[a]	0.89
Edematous centrum semiovale	81.8[a]	0.96

[a] Data from Stewart-Wallace (1939).
[b] Data from Randall (1938).

DISCUSSION

Most methods for the measurement of CBF with [^{15}O]water employ a value for the mean equilibrium brain–blood partition coefficient for water, $\bar{\lambda}$. The standard value for $\bar{\lambda}$ used by many authors, 0.95–0.96 ml/g, is incorrect. This arose from a failure to realize that blood water content is measured as a percentage by weight (Davis et al., 1953). Thus, a division by the density of blood is required to calculate λ in units of ml/g. The correct value for $\bar{\lambda}$ is 0.90 ml/g. The impact of this error of ~5% in λ on the measurement of CBF will depend on the particular measurement technique used. Methods for measuring CBF with [^{15}O]water differ in their sensitivity to errors in λ. The CBF value calculated using the central volume principle (Eichling et al., 1974) is directly proportional to the assumed value for λ. Thus, a variation in the value of λ results in an equivalent variation in calculated CBF. The adaptation of the Kety autoradiographic method (1960) to the determination of CBF with PET is relatively insensitive to errors in λ (Herscovitch et al., 1983). A given percent variation in λ results in a smaller variation in calculated CBF (Herscovitch et al., 1983; Kanno et al., 1984). In contrast, the $C^{15}O_2$ steady-state technique is more sensitive to error in λ, especially at higher flows (Lammertsma et al., 1981; Herscovitch and Raichle, 1983).

We note that the "standard" values for $\bar{\lambda}$, λ_g, and λ_w (Table 1) may not always be appropriate. The higher water content of neonatal or edematous brain results in a higher λ. Furthermore, deep gray matter structures have a lower λ than the cerebral cortex, whereas the corpus callosum has a higher λ than hemispheric white matter. These regional variations will assume more importance as the resolution of PET imaging devices improves.

In addition, changes in blood water content due to variations in hematocrit may affect the value of λ for water. This effect has been noted for other flow tracers that do not distribute uniformly between plasma and erythrocytes (Veall and Mallett, 1965). Variations in peripheral hematocrit can easily be taken into account, as shown above. However, the incorporation of the cerebral hematocrit, which is less than the peripheral hematocrit, into the calculation of λ for water is conceptually less straight-

forward. One must consider the context in which λ is defined. The autoradiographic method for the measurement of CBF (Kety, 1960) as well as methods using PET and $H_2{}^{15}O$ (Subramanyam et al., 1978; Herscovitch et al., 1983; Huang et al., 1983) assume that instantaneous equilibration of the flow tracer occurs between any brain tissue element and its venous effluent. Thus, the term for the venous outflow concentration, C_v, is replaced by the ratio C_b/λ, where C_b is the local brain tracer concentration. Although this implies that $\lambda = C_b/C_v$, in practice λ is measured using peripheral arterial blood (Reivich et al., 1969; Sakurada et al., 1978; Ginsberg et al., 1982). Thus, in the context of Kety's autoradiographic model (1960), as well as one-compartment models for measuring CBF with PET and $H_2{}^{15}O$ that make a similar substitution for C_v, an adjustment of the value of λ to reflect the average cerebral hematocrit may be inappropriate. (We do note that the assumption is made that cerebral venous hematocrit equals large-vessel hematocrit.) However, in more complex tracer kinetic approaches using multicompartmental or distributed models to describe the behavior of inert flow tracers such as water, it may be appropriate to account for cerebral hematocrit.

Huang et al. (1983) have implemented a one-compartment model to measure both CBF and the volume of distribution of tracer, i.e., λ, with [^{15}O]water and PET. Values obtained for λ_g and λ_w were 0.85 and 0.76 ml/g, respectively. For a blood water content of 79%, the calculated brain water contents were 67% for gray matter and 60% for white matter. However, since the blood water content (79%) is in units of percentage weight, one must multiply the brain water contents quoted by the density of blood, 1.06 g/ml, to obtain the correct units. The resultant gray and white matter water contents of 71 and 64%, respectively, by weight are still lower than brain water contents measured in vitro. Similar findings were also noted by Depresseux et al. (1983), in a preliminary report, using a different tracer kinetic model. A possible explanation for these observations is that not all brain water is freely exchangeable (Huang et al., 1983). If this hypothesis were true, the duration of PET data acquisition might be important depending on the rate of exchange of tracer with the slowly exchanging water pool. In addition, as the use of a one-compartment model involves considerable simplification of the underlying biology, estimates of λ based on such models may be only approximate.

In contrast to these in vivo data, Ginsberg et al. (1982) measured whole-brain λ for [^{15}O]water in rat brain according to the standard definition (Kety, 1951). They obtained a value of 0.956 ml/g, which is in fact somewhat higher than the value of 0.91 ml/g calculated from published water content data (rat brain water 78 g/100 g; blood water 81.6 g/100 g; blood density 1.054 g/ml) (Dittmer, 1961). This would suggest that in rat brain, [^{15}O]water distributes approximately in proportion to tissue and blood water contents. Further studies are needed to reconcile these in vitro data with the in vivo PET measurements of λ.

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