Determination of the Spleen-Blood Partition Coefficient for Water with Oxygen-15-Water and Oxygen-15-Carbon Dioxide Dynamic PET Steady-State Methods

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Methods: Regional splenic blood flow (SBF) was quantified by PET using a steady-state method with ^{15}O-carbon dioxide. SBFs were determined using 104 tomographic planes obtained from 49 patients. **Results:** When the spleen-blood partition coefficient for water (ρ) was ≥0.85, significant correlations ($p < 0.005$) were found between SBF values determined by the steady-state and dynamic methods. The best correlation between SBFs determined by the two methods ($r = 0.571$) was found when $\rho = 0.93$. The best regression line, however, was thought to be the line when $\rho = 0.93$. The regression line between SBF calculated by the steady-state method (y) and SBF determined by the dynamic method (x) was $y = 0.57 \times + 0.03$ with an F ratio of 48.75 (d.f. = 103, $p = 5.0 \times 10^{-8}$%, by ANOVA) when $\rho = 0.92$. **Conclusion:** A quick evaluation of SBF can be made by using the newly defined regression line.

Key Words: positron emission tomography; regional splenic blood flow; spleen-blood partition coefficient

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Following Ter-Pogossian's pioneering studies with ^{15}O to measure cerebral blood flow (*1*), rapid progress has been made in the understanding of cerebral blood flow and oxygen metabolism using the steady-state method (*2*). This method, however, has never been applied to other organs, especially intra-abdominal organs. PET studies enable the exact measurement of the distribution of positron-emitting radioisotopes within the human body and can be used to effectively quantify blood flow in many organs.

We have studied splenic hemodynamics, which change as liver damage progresses (*3,4*), with PET using water and a dynamic-state method. Since splenic hemodynamics are probably important in liver disorders and portal hypertension, PET is a powerful tool to study this relationship.

In this study, we estimated splenic blood flow (SBF) with a steady-state method using ^{15}C-water as well as the reliability of the results in relation to those obtained with the dynamic-state method using ^{15}O-water.

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METHODS

Mathematical Model and Theory

In the steady blood flow state, ^{15}C-water is continuously inhaled and ^{15}O is rapidly converted in the lungs from ^{15}C-water to ^{15}O-water (*5*). Therefore, the following equation holds between the radioactivity in the spleen (Cs(t)), the input function of the aorta (Ca(t)), the total splenic blood flow (F), the volume of the spleen (V), and the spleen-blood partition coefficient for water (ρ):

$$\frac{dCs(t)}{dt} = \frac{F}{V}Ca(t) - \frac{FCs(t)}{V\rho} - \mu Cs(t) = 0, \qquad \text{Eq. 1}$$

where μ is the decay constant of ^{15}O-carbon dioxide. Regional splenic blood flow per 100 g of splenic tissue (SBF) can be solved as follows:

$$SBF = \frac{100F}{DV} = \frac{100\mu}{D\left(\frac{Ca(t)}{Cs(t)} - \frac{1}{\rho}\right)}, \qquad \text{Eq. 2}$$

where D is the specific gravity of the spleen.

Patients

Forty-nine patients [28 males and 21 females, ages range from 32 to 77 yr (mean: 58.1 yr)] were investigated. No patient had hepatic functional disorders.

Materials

The PET system consisted of a whole-body PET scanner and a cyclotron with a gas purifying system. The performance characteristics of the PET system were set as follows: an image resolution of 8.2 mm FWHM and a slice thickness of 11–13 mm FWHM. The matrix size of the image was 128 × 128 with a 2-mm pixel size. The slice interval of the planes was 15 mm. The scan position for each patient was determined using x-ray CT. Emission data for three slices at intervals of 15 mm were collected simultaneously.

One hundred four slices were chosen as having planes which encompassed the spleen and provided regions of interest (ROIs) with full signal imaging. Under steady-state conditions, 5-min PET scanning was performed during continuous inhalation of 185 MBq–370 MBq of ^{15}C-water. Blood samples were collected from

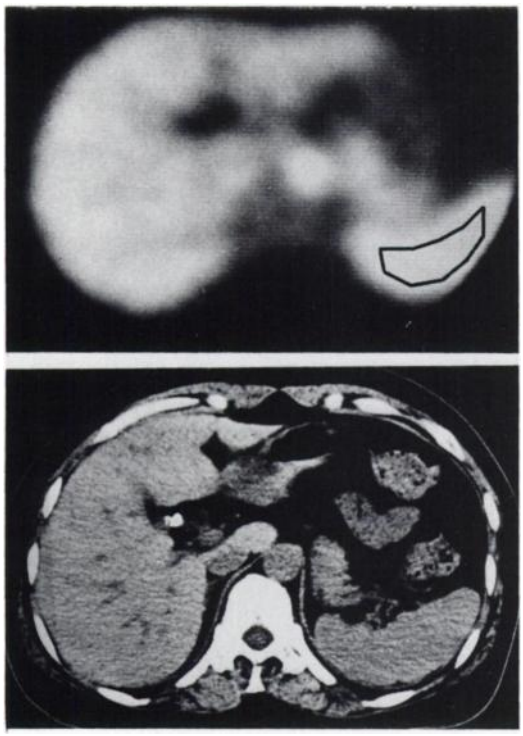

FIGURE 1. PET and x-ray CT images of a patient with normal liver function.

the left brachial artery in the first and last minutes of the scan session, and the average count in the two samples was taken as Ca(t).

Directly after finishing the steady-state experiment, PET scanning using the dynamic method was performed. Determination of blood flow requires that ρ is known, although this parameter cannot be obtained with the steady-state method. Consequently, a value of ρ was taken, which made the SBF derived from the steady-state method correlate most closely with the SBF derived from the dynamic method. Details of the theory and the actual methods pertaining to the dynamic state method have been described in a previous report (*3*), which is based on the method for regional cerebral blood flow (*1*).

The specific gravity of the spleen was taken as one, which closely approximates the mean specific gravity of 1.029 for 15 surgically removed spleens.

Brace's method (*6*) was used to calculate the correlation and the regression line between the dynamic and steady-state methods. Because both the dependent and the independent variables have measurement errors, corrections were made by multiplying each y by the standard deviation of x and dividing the result by the standard deviation of y. F-test analysis (ANOVA) was applied to determine the significance of linear relationships.

RESULTS

A typical PET image with a ROI and x-ray CT images are shown in Figure 1. With the dynamic method, SBF per 100 g of splenic tissue (SBF = F/V) ranged from 46.0 to 347.9 ml/min/100 g (mean: 163.9, s.e.: 6.6). The mean spleen-blood partition coefficient was 0.74.

When ρ derived from the dynamic method was used for the steady-state method or ρ was ≤ 0.84, no significant

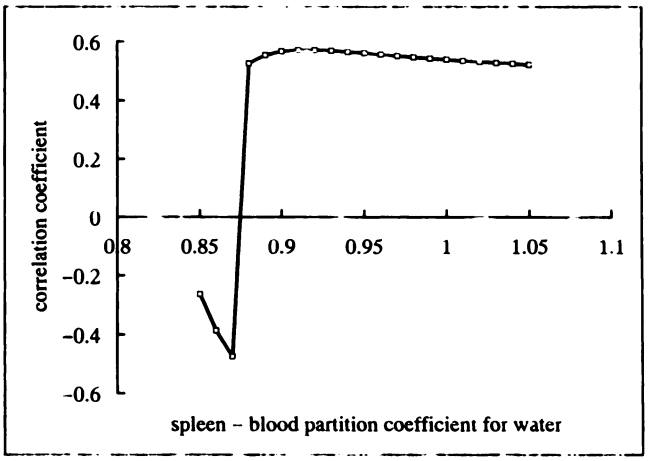

FIGURE 2. Correlation coefficient (r) between SBF determined by the dynamic and steady-state methods when different spleen-blood partition coefficients for water (ρ) were applied to the steady-state method. The r value was the highest amount (0.571) when ρ for the steady-state method was 0.92.

correlations were found between the SBFs obtained during the dynamic and steady states. As ρ increased from 0.85, the correlation coefficient (r) between SBFs determined using the two methods increased and reached a maximum [$r = 0.571$, $y = 0.76\,x - 16.5$ after Brace's correction (*6*)] when ρ was 0.92. Conversely, r gradually decreased as ρ increased beyond 0.92. In all cases where significant correlations were found, the p value was less than 0.005. The relation of r to ρ is shown in Figure 2, and the regression lines for each change in ρ are plotted in Figure 3.

When ρ was 0.93, the regression line relating the SBFs for the two methods passed on the origin. Figure 4 shows the correlation between SBFs for the two methods. The regression line relating SBF estimated by the steady-state method (y) to SBF determined by the dynamic method (x) was $y = 0.57\,x + 0.03$ with an F ratio of 48.75 (d.f. = 103, $p = 5.0 \times 10^{-8}$%, by ANOVA). The relationship between

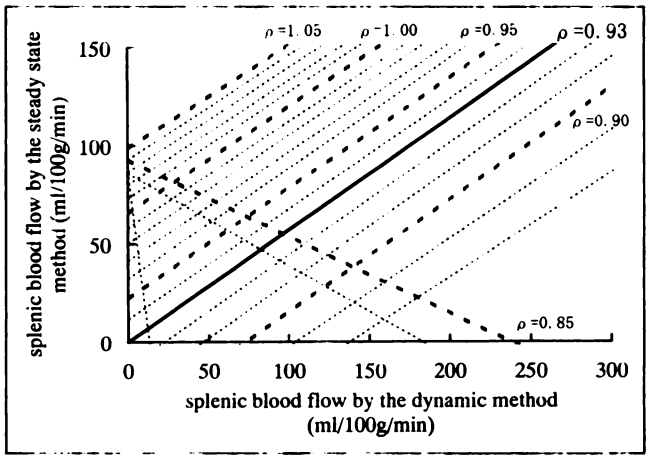

FIGURE 3. Calculation of regression lines with Brace's method for SBF determined by the steady-state and dynamic state methods for different spleen-blood partition coefficients for water (ρ) are shown.

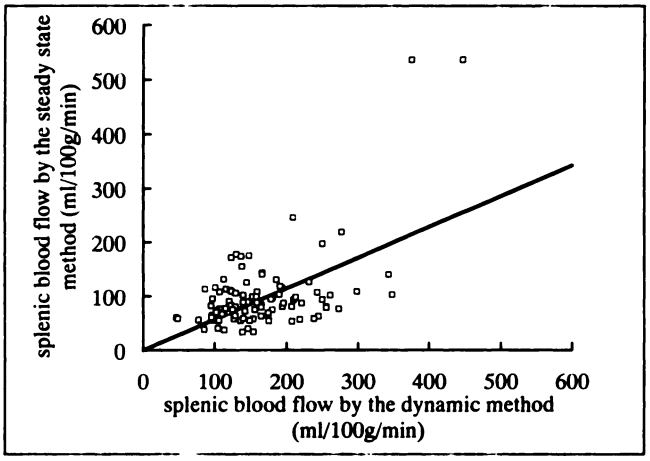

FIGURE 4. Correlation between SBF estimated by the steady-state method with $\rho = 0.93$ (y) and SBF calculated with the dynamic method (x). $y = 0.57 \times + 0.03$ ($r = 0.569$, d.f. = 103, F ratio = 48.75, $p = 5.0 \times 10^{-8}$). ρ: spleen-blood partition coefficient for water.

mean SBF and ρ at steady state is shown in Figure 5. The mean SBF estimated by the steady-state method was 99.9 (s.e.: 7.3) ml/100 g/min.

When ρ was 1.00, r, the regression line relating SBFs estimated by two methods, and mean SBF by the steady-state method were 0.539, y = 0.54 x + 66.0, and 77.6 ml/100 g/min.

DISCUSSION

We have described a technique for quantifying SBF by PET using ^{15}O-water and a dynamic state method. The merits of this approach have been previously discussed (*3,4*). With the steady-state method, the procedures and calculations required to obtain blood flow measurement are simpler and easier than those used in the dynamic method. The steady-state method requires only one scan and there is no need to perform serial arterial blood sampling in order to acquire an input function, as is the case with the dynamic method. A great deal of time is spent in determining SBF with the dynamic method as many scans must be analyzed and the flow can only be calculated by using minimizing nonlinear regression analysis.

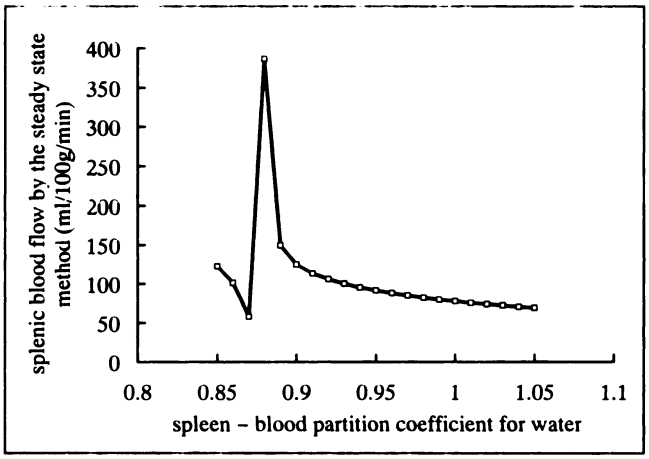

FIGURE 5. Relationship between the splenic blood flow estimated by the steady-state method and the spleen-blood partition coefficient for water.

In many other respects, however, the dynamic method is far superior to the steady-state method. Error amplification is substantially reduced when calculations are made with absolute values of blood flow; thus the raw datasets are more linearly related to actual blood flow. The dynamic method is also less affected by a loss in sensitivity if more than one compartment is analyzed and patients are not needlessly irradiated. Furthermore, the partition coefficient, which is derived with the dynamic method, is a very useful parameter that is closely related to disease progress. In contrast, a constant value must be given for the partition coefficient with the steady-state method. Finally, repeated measurements are possible with the dynamic method and changes in physiological behavior can consequently be evaluated.

Even though the steady-state method is inferior to the dynamic method in quantifying SBF, since ρ cannot be determined, it is nonetheless very useful for assessing a patient's condition. For example, if an upper abdominal PET scan is performed on the liver (*7*) and the pancreas (*8*), blood flow in the spleen can be qualitatively estimated from the PET image. A rough estimate of SBF is possible if ρ is known, although caution is needed in interpreting the estimated values since ρ, which reflects liver function (*4*), may change as the liver disorder progresses. After due consideration of the faults with the steady-state method, a rough calculation of SBF using a universal partition coefficient (ρ) should not be considered meaningless. Furthermore, when the oxygen extraction fraction of the spleen will be measured in the near future, steady-state scans using ^{15}C-water ^{15}C-carbon dioxide, $^{15}O_2$ and C^{15}O will be required. In this case, if the spleen-blood partition coefficient for water is known, the splenic metabolic rate of oxygen can also be calculated from the results of these PET scans alone, because SBF can be measured by a ^{15}C-water steady-state scan.

In the steady-state method, Ca(t) was approximated by the average count of arterial blood samples taken in the first and last minutes of the scan. The accurate radioactive concentration of the arterial blood, Ca, is given as:

$$Ca = \frac{1}{T}\int_0^T Ca(t)\,dt, \qquad \text{Eq. 3}$$

where T is the time at which PET imaging is completed. There is an error between the actual and approximated values when the patient's breathing pattern is not stable. Yamaguchi et al. reported this error to be less than 5% to 6% (*9*).

To derive SBF with steady-state PET imaging, the ρ value has to be evaluated appropriately because the steady-state method does not provide the ρ value. Initially,

ρ values obtained with the dynamic method were used, although it soon became apparent that ρ can have a wide range of values, which if low can yield a negative blood flow to the spleen. Therefore, $\rho \geq 0.85$ was needed to maintain significant correlations between SBF determined using the two methods. In the current study, the highest correlation coefficient between the two methods (0.571) was found when $\rho = 0.92$, although if ρ was assumed to be 1.00, the correlation coefficient was only slightly less (0.539). Thus, assuming $\rho = 1.00$ may be adequate for calculating SBF by the steady-state method. In another study, Lammertsma reported that if the partition coefficient increased above one, there would be only a small over- or underestimation of cerebral blood flow (*10*). Thus, many investigators of cerebral blood flow and oxygen metabolism that use the steady-state method (*11,12*) assume that $\rho = 1$. Despite these arguments, however, it may not necessarily follow that setting $\rho = 1$ will provide reliable estimates of SBF. We found that with $\rho = 1$ the regression line for dynamic and steady-state evaluations of SBFs intersected the axis for SBF by the steady state method on 66.0 ml/100 g/min (Fig. 3). By setting $\rho = 0.93$, the regression line relating SBFs determined by the two methods passed on the origin. This line was thought to be the best one.

The spleen-blood partition coefficient for water, ρ, derived from the steady-state method was higher when compared to the value from the dynamic method. In the dynamic method, ρ can have a wide range of values as mentioned above because it is determined using the nonlinear least squares method. In the steady-state method, however, ρ can have only a very narrow range of values and must be close to one, since ρ is a denomination of one in the second equation. This also explains why organ blood flow derived from the steady-state method is inaccurate.

Because the patients in our study have neither hepatic nor splenic disorders, these results are applicable to them. Data from a previous study (*4*) suggest significant correlation between the spleen-blood partition coefficient for water and hepatic function. This perspective on partition coefficients in patients with liver disease requires further study.

In conclusion, we have established a relationship between dynamic and steady-state methods for measuring SBF. A quick evaluation of SBF can be made with the following regression line: y (SBF by the dynamic method) = 0.57 x (SBF by the steady-state method with ρ at 0.93) + 0.03.

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