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Measurement of arterial time-activity curve by monitoring continuously drawn arterial blood with an external detector: Errors and corrections

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Accurate description of the arterial time-activity curve (ATAC) is of paramount importance in quantitative determination of the regional cerebral blood flow (rCBF) using positron tomography following bolus i.v. injection of O-15 labeled water. Frequent manual sampling from an arterial catheter does not permit sampling in less than 5-sec intervals and runs the risk of missing the arrival time or the peak count. A continuous ATAC monitoring system has been developed. This system consists of a single bismuth germanate detector in a lead shield and a constant-flow aspirator. The arterial blood was drawn continuously from a catheter within the brachial artery into an extended tube and its activity was monitored by the detector as the detector time-activity curve (DTAC). Comparison with the manual sampling from the contralateral brachial artery in the same run revealed that the DTAC differed from the manual sampling not only in delayed arrival but also in the shape of the curve, which was dispersed because of viscosity and the width of the detector field of view. However, deconvolution of DTAC using the experimentally obtained system step response provided an accurate arterial time course, which successfully filled in the gaps of the manual sampling. Moreover, water and blood showed different dispersion in the step response, suggesting that the system function should be determined using blood or a fluid of similar hydrodynamic nature.

Key words: Positron emission tomography, Input function, Dispersion, O-15 labeled water

INTRODUCTION

BOLUS INTRAVENOUS INJECTION of O-15 labeled water ($H_2{}^{15}O$) is a useful technique to quantitatively evaluate regional cerebral blood flow (rCBF) using positron emission tomography (PET).[1–3] This method, however, requires determination of the time course of the arterial activity concentration following the administration of the tracer as an input function to the brain.

Frequent manual sampling from the peripheral arterial catheter does not permit sampling in less than 5-sec intervals, even by a skillful person, and runs the risk of missing the arrival time or the peak count rate, which altogether may induce errors of 5–10% in CBF values.[1] Nor can manual sampling be timed to less than 0.5 sec. Moreover, it is troublesome and requires at least 3 or 4 persons including an injector, a sampler, a timer, and an assistant, followed by weighing and measuring the activity of each sample in a well counter.

An arterial time-activity curve (ATAC) monitoring system has been developed in which the arterial blood is drawn continuously from a catheter in the brachial artery into an extended tube and its activity monitored by a single bismuth germanate (BGO) detector as the detector time activity curve (DTAC). This system, however, has two major problems. First, the sensitivity is lower than the well counter. The single detector has a smaller aperture angle than the well counter and a smaller amount of blood within

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the field of view, and a shorter counting time is allotted for each measurement, resulting in greater statistical noise. The second problem is that the DTAC differs from the ATAC not only in delayed arrival but also in the shape of the curve, which is blunted for several reasons. (i) Due to viscosity, the velocity of the fluid running through a tube is not uniform within its cross section but higher at the tube axis than near the inner wall (viscosity effect). (ii) It takes a finite time for the fluid to pass across the detector field of view, which brings about a sort of smoothing (field effect). (iii) Diffusion of the radioactive molecules within fluid (diffusion). Increasing the tube diameter or the length within the field to increase the sensitivity would also increase the dispersion due to field effect, and increasing the aspiration flow to decrease the dispersion would increase the amount of sampled blood volume.

Because of a linear relationship between ATAC and DTAC, DTAC can be expressed as a convolution of ATAC and system impulse response. The system step response can be obtained experimentally and its derivative equals the impulse response. Thus, whatever dispersion may exist, accurate ATAC could be obtained, at least theoretically, by deconvoluting DTAC with the system impulse response, although validity of this correction method has yet to be directly demonstrated. The present study deals with the validity and practicability of this arterial activity monitoring system and its correction technique.

The goals of this study are: (i) to construct a model which describes the system's characteristic function, (ii) to study how the conditions of the system setup affect the system function, (iii) to demonstrate that the deconvolution of DTAC with the system impulse response yields accurate ATAC in a clinical study, and (iv) to find the optimum system conditions to minimize the errors.

MODEL

In this paper we present a simple model to describe the system function.

Our model describes the system impulse response as a convolution of two functions. The first component is called the "viscosity component," described by a sum of exponentials shifted for a certain time.

$$I_1(t) = \begin{cases} 0 & (0<t<a) \\ \sum_i c_i k_i e^{-k_i(t-a)} \quad (\sum_i c_i = 1) & (t>a) \end{cases}$$

In which k_i's are called dispersion turnover rate. The second component is called the "field component," which is a rectangular function.

$$I_2(t) = \begin{cases} 1/v & 0<t<v) \\ 0 & (t>v) \end{cases}$$

In which v is called the field factor. The field effect is expressed by a time-integration instead of position to simplify further calculation.

Thus the system impulse response is

$$I(t) = GI_1(t) * I_2(t)$$

where G equals sensitivity of the detector and $*$ denotes convolution integral. The implications of the components ($I_1(t)$ and $I_2(t)$) are not restricted to viscosity effect and field effect, respectively, although they are introduced to reflect those effects.

The step response is the integral of $I(t)$ from $t=0$ to t.

$$\int_0^t I(t)dt$$

We fitted this model to the measured step response curve and estimated the parameters. In all cases only one or two exponentials were sufficient for $I_1(t)$ to fit the results within statistical noises.

MATERIALS AND METHODS

System design. The system consists of a single BGO detector contained in an 8-cm thick lead shield and a constant-flow aspirator (Fig. 1). This shielding proved to be sufficient to screen the detector from the activities usually administered in a patient study (20–30 mCi). The BGO detector has a 12 mmϕ × 25.4 mm BGO crystal coupled to a Hamamatsu photo tube and is connected to a single channel pulse height analyzer. The arterial blood was drawn continuously from a catheter inserted within the brachial artery into an extended tube of 2.3 mm in inner diameter and its activity was measured by the

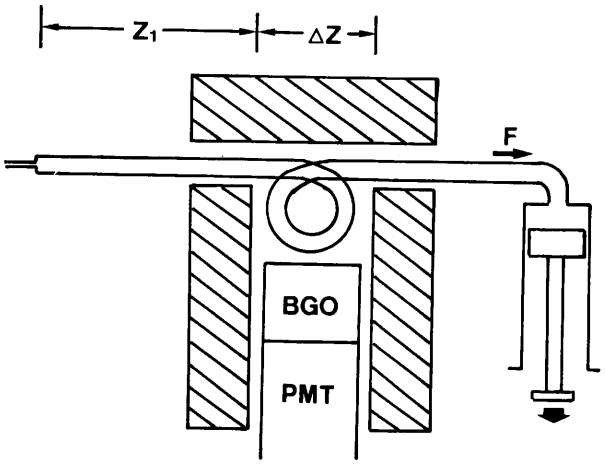

Fig. 1 System design of the arterial activity monitoring system.

detector as DTAC. The sampling time was 0.8 sec per every second (0.2 sec for data transfer). The detector count rate was corrected for dead time and physical decay before being submitted to further data manipulation.

Radionuclides. O-15 labeled water ($H_2{}^{15}O$) and Ga-68 labeled Ga-EDTA were used in the study. $H_2{}^{15}O$ was synthesized by palladium-catalyzed reaction of H_2 and O-15 labeled O_2, which had been produced in an in-house cyclotron. Ga-68 was eluted from a $^{68}Ge/^{68}Ga$ generator.

Sensitivity calibration. Sensitivity of the detector system was calibrated against a well counter, using a Ga-68 solution of known activity concentration filled within the extension tube. The calibration factor between the well counter and the detector system ranged from 8 to 20 cps (well)/ml/cps (detector) depending on the length of the tube within the field of view.

Effect of system conditions on system function. The effect of tube length and aspiration flow on the system function was studied by measuring step responses on various conditions. The tube length from the entrance to the detector (z_1) was 20, 35 or 55 cm. The tube length within the field of view (Δz) was 15 cm or 30 cm. The aspiration flow was 11.9 or 4.8 ml/min. ^{68}Ga-EDTA solution was used in the study.

Discrepancy between water and blood. In order to evaluate the effect of the hydrodynamic properties of the fluid, the step response was measured using water first, then using patient blood, in the same system setup.

Clinical study. Six cases were studied. The arterial catheter was inserted into the bilateral brachial artery. Our ATAC monitoring system was connected to the left brachial catheter. The arterial pressure was monitored to confirm that the pulse pressure wave of both sides were in complete agreement to exclude the possibility that any stenotic lesions existed in the subclavian or brachial artery, so that both brachial arteries should have the same time activity curve. Following bolus injection of 20–30 mCi of $H_2{}^{15}O$, arterial blood was sampled manually from the right brachial artery every 5–7 sec, and its activity concentration was measured in the well counter. At the same time the blood was drawn from the left brachial artery and its activity was monitored continuously using the system described above (DTAC). Independently, the system response was measured on the same system setup using the patient's blood. Our model was fitted to the measured step response to estimate the parameters. The patient's DTAC was deconvoluted with the system impulse response, which was described with the estimated parameters, using a point-by-point method.[4] The deconvoluted curve was compared with the ATAC obtained by manual sampling.

Simulation of deconvolution errors. A simulation study was performed to evaluate the errors involved in the deconvolution technique and to search for the optimum system condition. The true ATAC was assumed to be

$$A_0(t) = a(t-d)e^{-b(t-d)} + c(1-e^{-b(t-d)})$$

in which a=10,000 (cps/ml), b=0.15 (sec^{-1}), c=1,000 (cps/ml), and d=10 (sec). This curve represents a typical ATAC following bolus intravenous injection of $H_2{}^{15}O$. The system impulse response was described using our model.

$$I(t) = I_1(t) * I_2(t)$$

$$I_1(t) = \begin{cases} 0 & (0<t<a) \\ c_1k_1e^{-k_1(t-a)} + c_2k_2e^{-k_2(t-a)} & (t>a) \end{cases} \qquad (c_1+c_2=1)$$

$$I_2(t) = \begin{cases} 1/v & (0<t<v) \\ 0 & (t>v) \end{cases}$$

Where a=5 (sec), and v, k_1, k_2 and c_2 are variable parameters. The expected DTAC should be the convolution of ATAC and the system impulse response.

$$D_0(t) = A_0(t) * I(t)$$

In the actual measurement, however, a statistical noise is added to $D_0(t)$.

$$D(t) = D_0(t) + N(t) = A_0(t) * I(t) + N(t)$$

$N(t)$ is the Gaussian noise, the mean of which equals zero and the variance equals $D_0(t)$/Cf. Cf denotes the calibration factor and is inversely proportional to v, because widening the field of view decreases both Cf and the statistical noises. The deconvolution of $D(t)$ with $I(t)$ gives estimated ATAC, $A(t)$. The sum of the squares of deviation between $A_0(t)$ and $A(t)$ was evaluated in various system parameter values.

RESULTS

Effect of system setup on the system function. Table 1 shows the parameter estimates of the system functions on various system setup conditions obtained by curve fitting of the step responses using Ga-68 EDTA solution. In every case the acquired curve was well fitted using our model equation with mono-exponential $I_1(t)$. The arrival time (a) approximately proportional to the tube length (z_1) and was considered to be the tube length divided by the maximum velocity. The maximum velocity (velocity at the axis) thus estimated was much faster than the mean velocity derived from cross section and flow. The field factor

Table 1 Effect of system setup conditions on parameter estimates of system function described using our model with mono-exponential $I_1(t)$.

System conditions			Parameter estimates		
Tube length z_1 (cm)	Field Δz (cm)	Flow (ml/min)	a (sec)	v (sec)	k (sec^{-1})
20	15	4.8	5.2	2.9	0.14
35	15	4.8	10.4	3.5	0.13
55	15	4.8	16.5	4.6	0.08
20	30	4.8	6.2	4.1	0.11
55	30	4.8	15.7	10.5	0.08
20	15	11.9	1.9	1.7	0.44
35	15	11.9	3.7	1.6	0.31
55	15	11.9	6.0	2.3	0.22
20	30	11.9	2.2	1.8	0.28
55	30	11.9	6.6	3.9	0.21

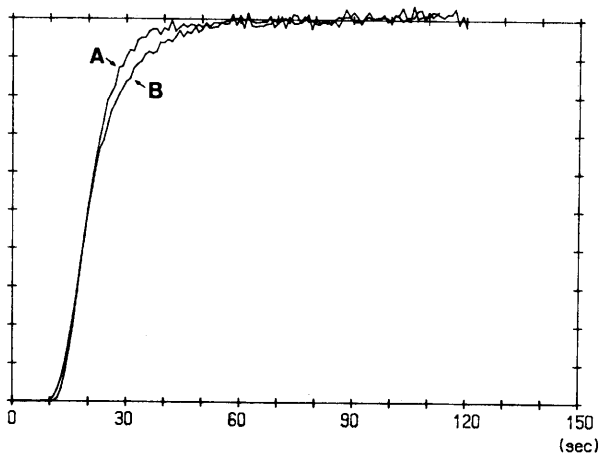

Fig. 2 Step responses of the monitoring system measured with water (A) and blood (B) in the same system condition.

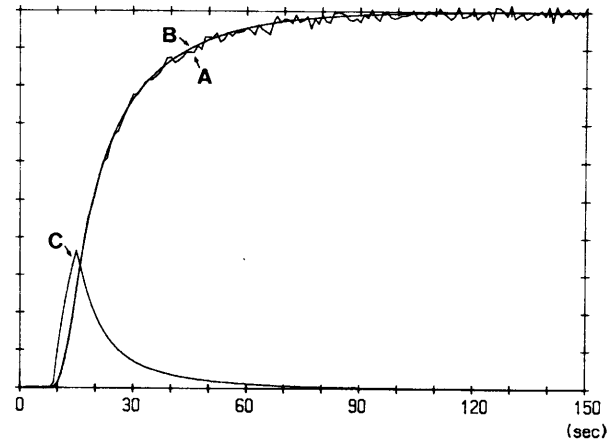

Fig. 3 A: Measured step response. B: Fitted curve. C: Derivative of curve B.

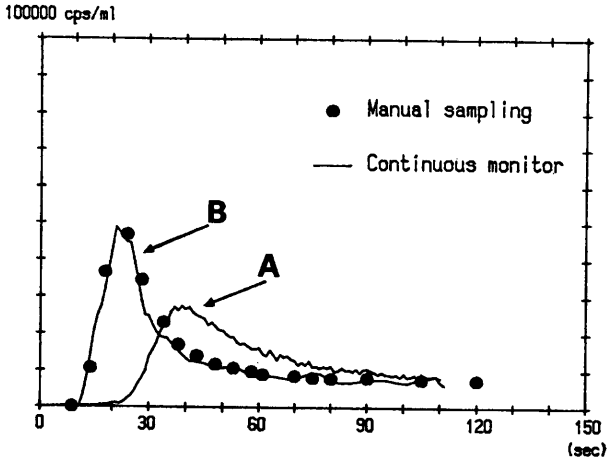

Fig. 4 Arterial time activity curves (ATAC) in a clinical study. A: Original BGO detector curve (DTAC). B: Estimated ATAC obtained by deconvolution of curve A with the system impulse response. Symbols indicate the activity concentration of the samples manually drawn from the contralateral brachial artery.

(v) was comparable to the field length divided by maximum velocity except for a few cases. The estimates of v increased as flow rate decreased or field (Δz) increased.

Discrepancy between water and blood. Fig. 2 compares the step responses obtained with water or blood as fluid material. The results indicated a significant discrepancy between water and blood, demonstrating the effect of the hydrodynamic nature of the fluid on dispersion.

Clinical study. Fig. 3 and Fig. 4 show the results of one of the clinical studies. In Fig. 3, the acquired step system response was fitted using the model, and its derivative was calculated to obtain the impulse response. In Fig. 4, the DTAC was deconvoluted with the impulse response to obtain the ATAC to compare with the ATAC obtained by manual sampling from the contralateral brachial artery. The deconvoluted curve corresponded well to the manual sampling and filled in the gaps of the latter. Similar results were observed in the other cases.

Simulation studies. Table 2 describes the results of the simulation studies regarding the deconvolution errors. In general, accuracy increased as field factor (v) decreased or viscosity turnover (k) increased. Significant increases in deconvolution errors were observed in $v=10$ sec while less increase was indicated in $k=0.05\ sec^{-1}$. The attempt to decrease the noise by increasing the field resulted in decreasing the accuracy.

DISCUSSION

Quantitative evaluation of regional organ function using a tracer kinetic model has been one of the

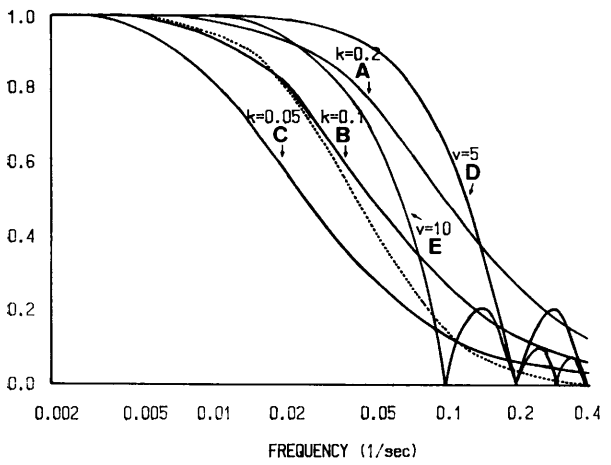

Fig. 5 Transfer function of $A_0(t)$, $I_1(t)$ and $I_2(t)$ in the simulation study. Curves A, B and C represent $I_1(t)$ when $k=0.2$, 0.1 and 0.05 sec^{-1}, respectively. Curves D and E represent $I_2(t)$ when $v=5$ and 10 sec, respectively. Dotted curve shows $A_0(t)$.

Table 2 Effect of parameter values of system function on deconvolution errors evaluated with sum of squares of deviation (SSD) in simulation studies.

v	k_1	k_2	c_2	Cf	SSD
2.5	0.2	0.02	0.5	40	5.2×10^6
5	0.2	0.05	0.5	20	1.5×10^7
10	0.2	0.05	0.5	10	7.8×10^7
5	0.05	0.02	0.2	20	3.1×10^7
5	0.1	0.05	0.2	20	2.5×10^7
5	0.3	0.05	0.2	20	1.0×10^7

major dimensions of nuclear medicine, especially now that the development of the PET instrument has allowed the *in vitro* measurement of regional activity more accurately than ever. Given the appropriate radioactive tracer and its model which describes its kinetics, the regional physiological parameters such as blood flow and metabolic rate can be estimated *in vivo*.[1,2] Such a technique, however, requires determination of the tracer input function to the organ or the arterial time activity curve (ATAC) following the administration of the radionuclide. Measurement of regional CBF with PET and radioactive water, for instance, involves intravenous injection of the radionuclide followed by PET measurement of regional cerebral activity, and successive simultaneous arterial blood sampling to acquire the ATAC. A manual sampling method has several disadvantages including the risk of missing the arrival time or the peak, inaccurate clocking and personnel requirements.

Hutchins et al designed a continuous input function detector using a plastic scintillator and an aspirator, and succeeded in monitoring the activity of the drawn blood.[5] Theoretically, deconvolution of the monitored activity curve with the system impulse response should yield an accurate ATAC, although they failed to demonstrate it directly. The plastic scintillator is one of the beta-ray detectors which has the advantage of high sensitivity if 511 keV gamma rays and scatter from the patient are eliminated, and may be appropriate for positron-emitting radionuclides. Their system,[5] however, requires special equipment and manufacturing process, and it cannot be applied to single photon-emitting radionuclides.

We have made a similar system using a BGO detector, which is a gamma-ray detector. In contrast to the beta detector, the field of view had to be widened to compensate for the low sensitivity, and lead blocks had to be used for shielding. Our results indicated, however, that the gamma ray detector could also be utilized for an ATAC monitoring system. There has been a growing shift in radiopharmaceutical chemistry from positron emitters to lower energy single photon emitters such as ^{99m}Tc or ^{123}I. Our results suggested that a single NaI detector could also be applied to the ATAC monitoring system for those single photon emitters if appropriate tracers and kinetic models were developed.

A wide discrepancy was observed between the monitored detector time-activity curve (DTAC) and the true arterial time-activity curve (ATAC), possibly due to dispersion of the blood within the fluid, the field of view and diffusion. Because a linear relationship holds between ATAC and DTAC, DTAC can be expressed as a convolution of ATAC and the system impulse response, which on the other hand can be obtained as the derivative of experimentally obtained system step response. Therefore, deconvolution of DTAC with the impulse response would, at least theoretically, generate the ATAC. However, large errors are induced if differentiation and deconvolution are executed numerically because noises are magnified in both processes. A certain mathematical modeling and curve fitting to it are advisable. It is possible to model the viscosity effect for a laminar flow of a Newtonian fluid theoretically using the Hagen-Poiseille equation.[5] But it could not be applied to our system probably because of (i) the non-Newtonian behavior of blood, (ii) the possibility of tubular flow, (iii) diffusion, and (iv) the nonuniform contribution of tube segments. For practical purposes, however, a model without appropriate theoretical basis is permissible just to decrease the noise. We developed a model which describes the system impulse response as a convolution of two components, viscosity component and field component, although these terms do not necessarily imply their exact nature. The results of our study indicated that

the system function was well described using our model in a system setup for clinical use (Fig. 3).

It is theoretically evident that deconvolution of DTAC with impulse response yields ATAC although direct demonstration has not been reported. We compared the deconvoluted DTAC with manual sampling from the contralateral brachial artery to demonstrate the accuracy of the theory and validate the deconvolution technique. The results indicated that the deconvoluted curve was in agreement with manual sampling and successfully filled in the gaps of the latter (Fig. 4).

We also studied the effect of the hydrodynamic nature of the fluid by comparing water and patient blood. A significant discrepancy was observed, indicating that the system response must be determined using blood or a fluid of similar hydrodynamic nature (Fig. 2). Since the blood viscosity depends on the packed cell volume, the most appropriate fluid could be the anti-coagulated patient blood of that study.[6]

A simulation study was performed to search for the optimum condition to minimize the errors. Increasing the field factor (v) to 10 sec significantly increased the deconvolution errors in spite of a decrease in statistical noise due to an increase in sensitivity. A similar increase in errors was observed, though to a less degree, when the viscosity turnover (k) was decreased to 0.05 sec^{-1}. Fig. 5 shows the transfer function (absolute value of Fourier transform) of $A_0(t)$, $I_1(t)$ and $I_2(t)$. Since convolution is equivalent to multiplication in Fourier transform, decreasing k in $I_1(t)$ or increasing v in $I_2(t)$ would decrease high frequency components of $I(t)$. And when $A_0(t)$ and $I(t)$ are convoluted to make $D_0(t)$, high frequency components of $A_0(t)$ would be abolished. In such cases, it is speculated that $A_0(t)$ could not be recovered accurately by deconvolution.

There is a relationship among sensitivity, field length, cross-sectional area and flow,

$$\begin{aligned}(\text{sensitivity}) &\propto (\text{sensitive volume})\\ &= (\text{cross-sectional area}) \times (\text{field length})\\ &= (\text{flow}) \times (\text{transit time})\end{aligned}$$

and field factor (v) largely reflects transit time. Therefore, when a system suffers low sensitivity, the flow should be increased without increasing the transit time to maintain the deconvolution accuracy.

Thus, this study presented and validated a useful means of determining the arterial time-activity curve with less sampling volume, less manpower and higher sampling frequency than manual sampling, and will contribute to the assessment of regional organ function using single photon or positron-emitting radionuclides.

Apart from the dispersion within the extension tube (external dispersion), there also exists a dispersion within the artery down to the punctured site (internal dispersion).[7] When there is a discrepancy between dispersion to the cerebral arterioles and to the brachial artery, some errors will be introduced if the brachial ATAC is used as the input function to the brain.[8] We will further investigate the effect of internal dispersion to correct this.

REFERENCES

1. Herscovitch P, Markham J, Raichle ME: Brain blood flow measured with intravenous $H_2{}^{15}O$. I. Theory and error analysis. *J Nucl Med* 24: 782–789, 1983
2. Raichle ME, Martin WR, Herscovitch P, et al: Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 24: 790–798, 1983
3. Herscovitch P, Raichle ME: Effect of tissue heterogeneity on the measurement of cerebral blood flow with equilibrium $C^{15}O_2$ inhalation technique. *J Cereb Blood Flow Metabol* 3: 407–415, 1983
4. Gamel J, Rousseau WF, Katholi CR, et al: Pitfalls in digital computation of the impulse response of vascular beds from indicator-dilution curves. *Circ Res* 32: 516–523, 1973
5. Hutchins GD, Hichwa RD, Koeppe RA: A continuous flow input function detector for $H_2{}^{15}O$ blood flow studies in positron emission tomography. *IEEE Trans Nucl Sci* 33: 546–549, 1986
6. Chien S, Vsami S, Taylor HM, et al: Effects of hematocrit and plasma proteins on human blood rheology at lower shear rates. *J Appl Physiol* 21: 81–87, 1966
7. Iida H, Kanno I, Miura S, et al: Error analysis of a quantitative cerebral blood flow measurement using $H_2{}^{15}O$ autoradiography and position emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metabol* 6: 536–545, 1986
8. Senda M, Nishizawa S, Shibata T, et al: Effect of arterial blood dispersion on the measurement of cerebral blood flow using PET and O-15 water. *J Nucl Med* 28: 656, 1987, (abstr)