

Quantitation of Regional Cerebral Blood Flow with ^{15}O -Butanol and Positron Emission Tomography in Humans

H. Herzog, *R. J. Seitz, L. Tellmann, E. Rota Kops, F. Jülicher, *G. Schlaug, *A. Kleinschmidt, and H. W. Müller-Gärtner

*Institute of Medicine, Research Center Jülich, and Department of Nuclear Medicine, Heinrich-Heine-University Hospital Düsseldorf, Jülich; and *Department of Neurology, Heinrich-Heine-University Hospital Düsseldorf, Düsseldorf, Germany*

Summary: We describe the implementation and validation of a combined dynamic-autoradiographic approach for measuring the regional cerebral blood flow (rCBF) with ^{15}O -butanol. From arterial blood data sampled at a rate of 1 s and list mode data of the cerebral radioactivity accumulated over 100 s, the time shift between blood and tissue curves, the dispersion constant DC, the partition coefficient p , and the CBF were estimated by least squares fitting. Using the fit results, a pixel-by-pixel parametrization of rCBF was computed for a single 40-s

(autoradiographic) ^{15}O -butanol uptake image. The mean global CBF found in 27 healthy subjects was $49 \pm 8 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$. Gray and white matter rCBF were 83 ± 20 and $16 \pm 3 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$, respectively, with a corresponding partition coefficient p of 0.77 ± 0.18 and $0.77 \pm 0.29 \text{ ml/g}$ in both compartments. The quantitative images resulted in a significantly higher gray matter rCBF than the autoradiographic images. **Key Words:** Regional blood flow— ^{15}O -butanol—Autoradiographic model—Partition coefficient—Positron emission tomography.

Butanol is freely diffusible across the blood-brain barrier (Raichle et al., 1976; Schaefer et al., 1976; van Uiter et al., 1981; Dischino et al., 1983) and has been found suitable for measuring rCBF with positron emission tomography (PET) after labeling with ^{11}C or ^{15}O (Herscovitch et al., 1987; Berridge et al., 1990; Berridge et al., 1991). Due to its complete extraction, ^{15}O -butanol should yield a favorable signal, particularly in areas with high rCBF (Quarles et al., 1993).

Here we describe the implementation and validation of an approach for quantitation of rCBF using ^{15}O -butanol, which combines the tracer dynamics in blood and cerebral tissue and a single autoradiographic uptake scan. We will demonstrate that this

approach yields quantitative rCBF images that are suitable for neurophysiological activation studies.

MATERIALS AND METHODS

Subject Preparations

Twenty-seven normal subjects (20 men, 7 women, 26.4 ± 3.6 years) were enrolled in this study approved by the ethical committee of the Heinrich-Heine-University Düsseldorf. Informed consent was given by each subject.

Prior to the examination, venous and arterial catheters were inserted. The subjects' eyes were patched. The scanner room was totally quiet.

rCBF Measurements

On each subject, six measurements were performed, each 15 min apart, after intravenous bolus injection of $\sim 1,500 \text{ MBq } ^{15}\text{O}$ -butanol automatically prepared as described previously (Crouzel et al., 1993; Herzog et al., 1994). The first and last scans in each subject were acquired during resting wakefulness. During the other scans, different stimuli were applied, which are not detailed here.

Using the camera PC4096-15WB (Rota Kops et al., 1990), emission data were acquired in list mode for 3 min postinjection. Simultaneously, arterial blood was continuously measured at 1-s intervals using an automatic measurement system (Eriksson et al., 1980) cross-calibrated

Received July 25, 1994; final revision received March 14, 1995; accepted November 3, 1995.

Address correspondence and reprint requests to Dr. Hans Herzog, Institute of Medicine, Research Center Jülich, D-52425 Jülich, Germany.

Abbreviations used: GM, gray matter; MT, mixed tissue; PET, positron emission tomography; rCBF, regional cerebral blood flow; ROI, regions of interest; WB, whole brain; WM, white matter.

to the PET camera. The list mode data was framed (a) into 90 sequential frames of 2 s each for two planes at the level of the basal ganglia and the centrum semiovale and (b) into a single (autoradiographic) frame of 40 s starting at the tracer's entry into the brain comprising all 15 image planes. Using measured attenuation correction, the emission data were reconstructed with filtered backprojection [image resolution = 9 mm (full width half maximum)].

In each subject, the rCBF was adjusted to the PCO_2 of the first scan by linear scaling applying a relative change of rCBF of 4% per 1 mm Hg of change in PCO_2 (Zijlstra, 1981). The exact procedure is detailed elsewhere (Seitz and Roland, 1992).

Data Analysis

Decay-corrected time-activity curves of ^{15}O -butanol were calculated at the level of the basal ganglia for three regions of interest (ROI): an ROI comprising the whole brain slice and considered as representative for whole brain (WB); all areas above 50% of the image maximum, including the cortical ribbon with adjacent white matter, thus representing mixed tissue (MT); two areas bilateral in the temporal operculum at a 60% isocontour level regarded as representative for pure gray matter (GM). In addition, an ROI at the level of semiovale center was drawn manually representing white matter (WM). The average data given in the following are taken from all examinations. The stimuli applied in the 27 subjects had no primary activation center in those planes where the WB-, MT-, and GM-ROIs were defined.

Model

The kinetics of the freely diffusible ^{15}O -butanol can be described by the single-compartment model as introduced by Kety (1960) and Kety and Schmidt (1948) and the equation:

$$\frac{dc_T(t)}{dt} = rCBF \cdot c_A(t) - \frac{rCBF}{p} \cdot c_T(t), \quad (1)$$

with the tissue activity concentration c_T , the arterial blood activity c_A , and the partition coefficient p between tissue and blood.

The solution of this equation yields:

$$c_T(t) = rCBF \int_0^t c_A(t') \cdot \exp(-k(t - t')) dt' \quad (2)$$

with $k = rCBF/p$. c_T is directly accessible by the dynamic PET measurement (c_T^m). Compared to the input function c_A in the carotid arteries, c_A^m as measured by the blood measurement system is dispersed and time-delayed (Grenz, 1956; Iida et al, 1986, 1989). The dispersion can be modeled by a convolution with the function $\exp(-t/DC)$ (Kanno et al., 1987; Meyer, 1989), with DC as dispersion constant. To correct for dispersion and delay t , c_A is substituted:

$$c_A(t - \Delta t) = DC \cdot dc_A^m(t)/dt + c_A^m(t) \quad (3)$$

where the right-hand side is the inversion of the convolution with the exponential function.

The model approach tested here for ^{15}O -butanol combines Eqs. 2 and 3 as follows: A nonlinear regression method (Marquardt, 1963) fitted c_T of Eq. 2 to c_T^m with rCBF, p , and t as fit parameters. DC was used as fixed,

and the fitting was repeated for different DC. That fit was considered as optimum, which yielded the minimum absolute summed squared discrepancy between c_T and c_T^m . The fitting of the tissue curves comprised a period of 100 s after tracer injection, in this way avoiding contamination with metabolites of ^{15}O -butanol (Pawlik et al., 1993). The fitting procedure was performed for the time-activity curves for WB, WM, MT, and GM.

The autoradiographic uptake image of ^{15}O -butanol recorded from T_1 to T_2 is related to rCBF, p , and c_A by

$$c_T(T_1, T_2) = \frac{1}{(T_2 - T_1)} \int_{T_1}^{T_2} \left\{ rCBF \int_0^t c_A(t') \cdot \exp(rCBF/p(t - t')) dt' \right\} dt \quad (4)$$

as shown previously (Herscovitch et al., 1983; Raichle et al., 1983). This equation was used by Herscovitch et al. (1983), with a fixed p and not considering dispersion and delay. In our approach, the measured c_A curve was corrected for dispersion and delay as found by fitting the tissue curve of the MT-ROI. Then a look-up table was constructed: $c_T(T_1, T_2)$ was calculated for rCBF values of 0–300 ml 100 g $^{-1}$ min $^{-1}$ in steps of 0.5 ml 100 g $^{-1}$ min $^{-1}$ applying the fitted p found for the MT-ROI. The use of this ROI mainly comprising cortical tissue is justified, because the cortex is the area of neuronal activation, and the evaluation of this region provided less variance than that of the GM-ROI (Fig. 1). Using the look-up table, the 40-s ^{15}O -butanol uptake images were converted pixel-by-pixel into quantitative images of rCBF.

RESULTS

Using Eqs. 2 and 3, satisfying fits were obtained for measured tissue curves of ^{15}O -butanol in the different regions (Fig. 1). The values of rCBF, p , DC, and t that resulted from the fitting procedure are summarized in Table 1. The mean p found in GM and WM were virtually identical at ~ 0.77 ml/g, whereas in heterogenous ROIs, including gray and white matter, a lower p was found, e.g., only 0.63 \pm

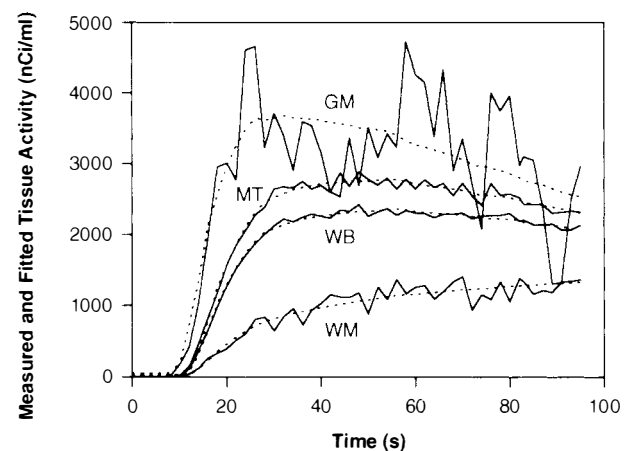


FIG. 1. Measured decay-corrected (straight lines) and fitted (dotted lines) time-activity curves of ^{15}O -butanol in the ROIs of whole brain (WB), mixed tissue (MT), gray matter (GM), and white matter (WM).

0.11 ml/g for WB. When quantitative rCBF images were calculated using a p of 0.77 ml/g, a mean rCBF of 86 ± 17 ml $100\text{ g}^{-1}\text{ min}^{-1}$ was obtained for GM and of 16 ± 3 ml $100\text{ g}^{-1}\text{ min}^{-1}$ for WM.

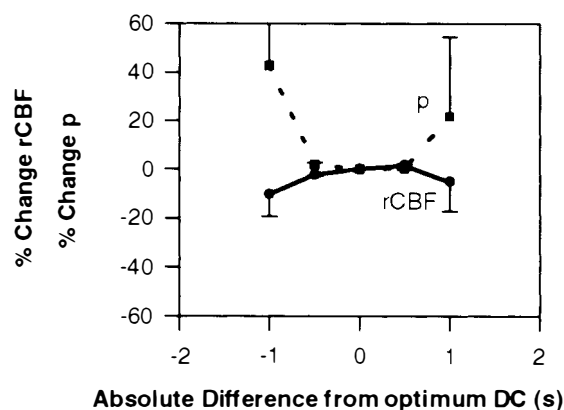
The sensitivity of fitted rCBF and p in respect to errors of DC was tested by the variation of DC in a range ± 1 s around the optimum DC using six data of different individuals. The mean change of rCBF was up to -10% and that of p up to 43%, when DC was offset by 1 s (Fig. 2A). Similarly, variations of rCBF and DC were examined when p deviated from the fitted p . The errors of rCBF and DC were in opposite direction. An underestimation of p by -0.2 ml/g resulted in an underestimation of rCBF by 15% and an overestimation of DC by 35%. rCBF was altered by up to +25% and DC by -17%, when p was offset by +0.2 ml/g (Fig. 2B).

Table 2 compares gray matter rCBF, resulting in quantitative rCBF images with those in autoradiographic uptake images in which the average whole brain radioactivity was set to a global flow value of 50 ml $100\text{ g}^{-1}\text{ min}^{-1}$ (Lassen, 1985). The quantitation produces higher signals than autoradiographic images in the well-perfused gray matter; e.g., the mean rCBF in the gray matter ROI was 29% higher in the quantitative images compared to the autoradiographic images. On the other hand, the variance of the resulting rCBF is increased.

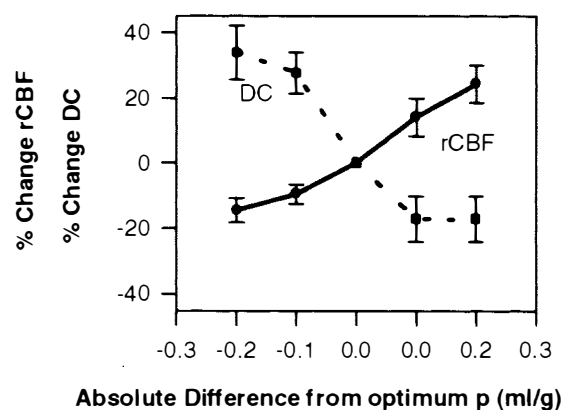
DISCUSSION

Our approach for quantitation of rCBF with ^{15}O -butanol combines the advantages of kinetic parameter estimation with the computationally easy and fast autoradiographic imaging technique.

The kinetic analysis taking into account the individual time shift and dispersion provided a global brain CBF of 49 ± 8 ml $100\text{ g}^{-1}\text{ min}^{-1}$, which agrees with values found by others (for example, see Lassen 1985; Berridge et al., 1991). The ratio of gray matter rCBF (83 ± 20 ml $100\text{ g}^{-1}\text{ min}^{-1}$) and white matter rCBF (16 ± 3 ml $100\text{ g}^{-1}\text{ min}^{-1}$) was



(a)



(b)

FIG. 2. Changes of fitted rCBF and p or DC, relative to their values for the optimum fit, when DC (A) or p (B) were varied by ± 1 s or ± 0.2 ml/g, respectively, around the p and DC values found for the optimum fit.

5.04:1, exceeding former estimations using H_2^{15}O (Frackowiak et al, 1980; Baron et al., 1981; Lenzi et al., 1981; Kanno et al., 1987), but being consistent with recent data reported by Berridge et al. (1991) for ^{15}O -butanol and Lammertsma et al. (1992) for

TABLE 1. Results of dynamic fitting analysis of time-activity curves in different cerebral ROIs obtained in 27 subjects with six measurements each^a

ROI	rCBF (ml/100 g/min)	p (ml/g)	DC (s)	Δt (s)
WB	48.6 ± 8.0	0.633 ± 0.108	9.58 ± 1.32	9.8 ± 2.1
WM	16.4 ± 3.1	0.769 ± 0.291	9.58 ± 1.70	9.8 ± 2.2
MT	57.9 ± 10.1	0.692 ± 0.137	9.51 ± 1.43	9.7 ± 2.1
GM	82.6 ± 20.0	0.772 ± 0.176	9.67 ± 1.62	8.6 ± 2.4

^a WB, whole brain slice at the level of the basal ganglia; WM, a white matter ROI in a plane at the level of semiovale center; MT, a mixed tissue ROI at an isocontour level of 50% in the plane of the basal ganglia including the cortical ribbon and adjacent white matter; GM, a bilateral ROI with an isocontour level of 60% in the temporal opercular cortex representing gray matter; rCBF, regional cerebral blood flow; p , partition coefficient; DC, constant for dispersion correction (according to Eq. 3); Δt , time shift between tissue and blood curves.

TABLE 2. Comparison of autoradiographic and quantitative rCBF data

ROI	rCBF (ml/100 g/min)			
	Autoradiographic images		Quantitative images	
	Mean	Max	Mean	Max
Cortex (MT)	57.8 ± 2.34 ^a	99.6 ± 10.8 ^b	68.5 ± 11.3 ^a	154 ± 40.5 ^b
GM	74.8 ± 8.24 ^c	94.8 ± 11.8 ^d	96.3 ± 20.1 ^c	139 ± 34.3 ^d

^{a-d} The comparisons *a-d* were evaluated with a paired *t* test. Using the Bonferroni correction for multiple tests (*n* = 6) in the single subjects, all comparisons showed a significant difference with *p* < 0.02.

H₂¹⁵O. The gray/white matter ratio obtained in our study is still <5.7:1, which results from a rCBF of 131 ml 100 g⁻¹ min⁻¹ in gray matter and 23 ml 100 g⁻¹ min⁻¹ in white matter measured with ¹³¹I-labeled CF₃I in conscious rats (Sokoloff, 1961).

Our average *p* found in GM and WM were practically identical, being 0.77 ml/g. The same values were obtained by Gjedde et al. (1980) in rats. The lower values found in mixed tissue can be explained by the effect of applying a single compartment model to heterogenous tissue (Iida et al., 1989; Lammertsma et al., 1990; Herzog et al., 1993).

Greater signals of gray matter rCBF were found in quantitative rCBF images compared to autoradiographic uptake images scaled linearly to a whole brain activity of 50 ml 100 g⁻¹ min⁻¹ (Table 2). This is of considerable importance for neurophysiological activation studies, as a better delineation of activated areas could be expected in quantitative rCBF images. We observed that, in spite of the increased variance of the rCBF data in the quantitative rCBF images (Table 2), the specifically activated cortical and subcortical areas were significant in quantitated images, whereas they failed in autoradiographic images. For example, simple finger flexion movements were not found by t-map analysis using autoradiographic image data (Seitz et al., 1993), whereas the quantitated images of the same experiment rendered significant activation areas in the contralateral motor cortex, frontomesial cortex, and ipsilateral cerebellum (Seitz et al., 1995).

Acknowledgment: We thank W. Hamkens for routine production of ¹⁵O-butanol and C. Tarras and E. Theelen for their technical assistance during the studies. We appreciate the help of Dr. S. M. Qaim in preparing the manuscript of this article. This study was supported by the Deutsche Forschungsgemeinschaft (DFG), SFB 194.

REFERENCES

- Baron J, Steinling M, Tanaka, et al. (1981) Quantitative measurement of CBF, oxygen extraction fraction (OEF) and CMRO₂ with ¹⁵O continuous inhalation technique and positron emission tomography (PET): experimental and evidence and normal values in man. *J Cereb Blood Flow Metab* 1:S5-S6
- Berridge MS, Cassidy EH, Terris AH (1990) A routine, automated synthesis of ¹⁵O butanol for positron emission tomography. *J Nucl Med* 31:1727-1733
- Berridge MS, Adler LP, Nelson AD, et al. (1991) Measurement of human cerebral blood flow with [¹⁵O]butanol and positron emission tomography. *J Cereb Blood Flow Metab* 11:707-715
- Crouzel C, Clark JC, Brihaye C, et al. (1993) Radiochemistry automation for PET. In: *Radiopharmaceuticals for Positron Emission Tomography* (Stöcklin G, Pike VW, eds), Dordrecht, Kluwer, pp 45-89
- Dischino DD, Welch MJ, Kilhourn MR, Raichle ME (1983) Relationship between lipophilicity and brain extraction of C-11-labeled radiopharmaceuticals. *J Nucl Med* 24:1030-1038
- Eriksson L, Bohm C, Kesselberg M, Holte S (1988) An automated blood sampling system used in positron emission tomography. *Nucl Sci Appl* 3:133-143
- Frackowiak RSJ, Lenzi GL, Jones T, Heather JD (1980) Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ¹⁵O and positron emission tomography: theory, procedure and normal values. *J Comput Assist Tomogr* 4:727-736
- Gjedde A, Hansen AJ, Siemkowicz E (1980) Rapid simultaneous determination of regional blood flow and blood-brain glucose transfer in the brain of rat. *Acta Physiol Scand* 108:321-330
- Greitz T (1956) A radiologic study of the brain circulation by rapid serial angiography of the carotid artery. *Acta Radiol [Suppl]* 140:1-123
- Herscovitch P, Markham J, Raichle ME (1983) Brain blood flow measured with intravenous H₂¹⁵O. I. Theory and error analysis. *J Nucl Med* 24:782-789
- Herscovitch P, Raichle ME (1983) Effect of tissue heterogeneity on the measurement of cerebral blood flow with the equilibrium C¹⁵O₂ inhalation technique. *J Cereb Blood Flow Metab* 3:407-415
- Herscovitch P, Raichle ME, Kilbourn MR, Welch MJ (1987) Positron emission tomographic measurement of cerebral blood flow and permeability-surface area product of water using [¹⁵O] water and [¹¹C]butanol. *J Cereb Blood Flow Metab* 7:527-542
- Herzog H, Seitz RJ, Tellmann L, et al. (1993) Measurement of cerebral blood flow with PET and ¹⁵O-butanol using a combined dynamic-single-scan approach. In: *Quantitation of Brain Function. Tracer Kinetics and Image Analysis in Brain PET* (Uemura K, et al., eds), Amsterdam, Elsevier, pp 161-168
- Herzog H, Seitz RJ, Tellmann L, et al. (1994) Pharmacokinetics and radiation dose of oxygen-15 labelled butanol in rCBF-studies in humans. *Eur J Nucl Med* 21:138-143
- Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K (1986) Error analysis of a quantitative cerebral blood flow measurement using H₂¹⁵O-water autoradiography and positron emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metab* 6:536-545
- Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K (1989) A determination of the regional brain/blood parti-

- tion coefficient of water using dynamic positron emission tomography. *J Cereb Blood Flow Metab* 9:874–885
- Kanno I, Iida H, Miura S, et al. (1987) A system for cerebral blood flow measurement using an H_2^{15}O autographic method and positron emission tomography. *J Cereb Blood Flow Metab* 7:143–153
- Kety SS, Schmidt CF (1948) The nitrous oxide method for quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J Clin Invest* 27:476–483
- Kety SS (1960) Measurement of local blood flow by the exchange of an inert, diffusible substance. *Methods Med Res* 8:228–236
- Lammertsma AA, Cunningham VJ, Deiber MP, et al. (1990) Combination of dynamic and integral methods for generating reproducible functional CBF images. *J Cereb Blood Flow Metab* 10:675–686
- Lammertsma AA, Martin AJ, Friston KJ, Jones T (1992) In vivo measurement of the volume of distribution of water in cerebral grey matter: effects on the calculation of regional cerebral blood flow. *J Cereb Blood Flow Metab* 12:291–295
- Lassen NA (1985) Normal average value of cerebral blood flow in younger adults is $50 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$. *J Cereb Blood Flow Metab* 5:347–349
- Lenzi G, Frackowiak RS, Jones T, et al. (1981) CMRO₂ and CBF by the oxygen-15 inhalation techniques: results in normal volunteers and cerebrovascular patients. *Eur Neurol* 20:285–290
- Marquardt DW (1963) An algorithm for least-square estimation of nonlinear parameters. *J Soc Indust Appl Math* 11:431–441
- Meyer E (1989) Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the H_2^{15}O autoradiographic method and dynamic PET. *J Nucl Med* 30:1069–1078
- Pawlik G, Fink GR, Bauer B, et al. (1993) Comparative PET study of dynamic and autoradiographic rCBF measurements using O-15 labeled butanol and water in cerebrovascular diseases: effect of butanol metabolism. *Ann Nucl Med* 7:A27–A28
- Quarles RP, Mintun MA, Larson KB, Markham J, MacLeod AM, Raichle ME (1993) Measurement of regional cerebral blood flow with positron emission tomography: a comparison of [^{15}O]water to [^{11}C]butanol with distributed-parameter and compartmental models. *J Cereb Blood Flow Metab* 13:733–747
- Raichle ME, Martin WRW, Herscovitch P, Mintun MA, Markham J (1983) Brain blood flow measured with intravenous H_2^{15}O . II. Implementation and validation. *J Nucl Med* 24:790–798
- Raichle ME, Eichling JO, Straatman MG, Welch MJ, Larson KB, Ter-Pogossian MM (1976) Blood–brain permeability of ^{11}C labelled alcohols and ^{15}O -labelled water. *Am J Physiol* 230:543–552
- Rota Kops E, Herzog H, Schmid A, Holte S, Feinendegen LE (1990) Performance characteristics of an eight-ring whole-body PET scanner. *J Comput Assist Tomogr* 14:437–445
- Schaefer JA, Gjedde A, Plum F (1976) Regional cerebral blood flow in rat using n-[^{14}C]butanol. *Neurology* 26:394–399
- Seitz RJ, Roland PE (1992) Variability of the regional cerebral blood flow pattern studied with [^{11}C]fluoromethane and positron emission tomography (PET). *Comput Med Imag Graph* 16:311–322
- Seitz RJ, Knorr U, Schlaug G, Huang Y, Weder B, Herzog H (1993) Comparison of intersubject averaging and individual response identification for mapping of motor function in the human brain with positron emission tomography (PET). In: *Quantitation of Brain Function. Tracer Kinetics and Image Analysis in Brain PET* (Uemura K, et al., eds), Amsterdam, Elsevier, pp 561–568
- Seitz RJ, Schlaug G, Knorr U, Steinmetz H, Tellmann L, Herzog H (1996) Neurophysiology of the human supplementary motor area: positron emission tomography. In: *The Supplementary Sensorymotor Area. Advances in Neurology* (Lueders HO, ed), New York: Lippincott-Raven, pp 167–175
- Sokoloff L (1961) Local cerebral circulation at rest and during altered cerebral activity induced by anesthesia or visual stimulation. In: *The Regional Chemistry, Physiology and Pharmacology of the Nervous System* (Kety SS, Elkes J, eds), Oxford, Pergamon Press, pp 107–117
- Van Uiter RL, Sage JL, Levy DE, Duffy TE (1981) Comparison of radio-labeled butanol and iodoantipyrine as cerebral blood flow markers. *Brain Res* 222:365–372
- Zijlstra WG (1981) Physiology of cerebral circulation. In: *Cerebral Blood Flow: Basic Knowledge and Clinical Implications* (Minderhoud JM, ed), Amsterdam, Excerpta Medica, pp 34–55