Detection of Compartmental Slippage in Noninvasive rCBF Measurements

K. Herholz, W.-D. Heiss, G. Pawlik, H. W. Ilsen, and K. Wienhard

Max-Planck-Institut für neurologische Forschung, Ostmerheimer Str. 200, 5000 Köln 91 (Merheim), FRG

Noninvasive measurements of regional cerebral blood flow (rCBF), using the Xe-133 clearance technique and a two-compartment open model for data analysis, may produce false numerical results when distinction between compartments is poor. For rapid detection of error conditions of that kind, we propose a three-dimensional graphic display of the quality of fit to the original clearance curve, based on bivariate simulations of clearance constants. This procedure may follow rCBF computation, irrespective of the main algorithm used. The discriminating power of this method is demonstrated in two characteristic routine rCBF measurements by gradual addition of random noise to the original data.

J Nucl Med 24: 1188–1191, 1983

Noninvasive techniques of measuring regional cerebral blood flow by inhalation or intravenous injection of xenon-133, with external activity monitoring, have become widely accepted diagnostic routines, and various algorithms have been described for estimation of flow from a series of time-activity curves, recorded simultaneously by external detectors, from the patient's respiratory air and a number of regions over his head. Irrespective of the numerical method used—whether data analysis is based on a variable metric approximation (*1*), Taylor series (*2*), Marquardt's algorithm (*3*), or Fourier analysis (*4*)—a bicompartmental model is fitted to the tissue clearance curve. In a variety of pathological conditions, however, discrimination between those two differently perfused compartments is poor, and spurious results are obtained when tissue of the one compartment is counted with the other (*5*), a phenomenon that may be termed compartmental slippage (*6*). Unfortunately, such situations are easily overlooked, since no single statistical standard parameter can define the reliability and significance of both clearance constants and volume fractions of the two compartments. Therefore, a simulation technique was developed and tested in clinical routine applications, permitting a rapid assessment of the quality of the numerical results and recognition of uncertain compartmental separation.

METHODS

The two-compartment open model generally used in noninvasive rCBF measurements with freely diffusible radioactive inert gases is described by

$$Q_{fit}(T) = \sum_{m=1}^{2} p_m \int_0^T C_a(t)\exp[-k_m(T-t)]dt \qquad (1)$$

where

$Q_{fit}(T)$ = calculated regional count rate at time T,
P_m = weighting factor of compartment m,
$C_a(t)$ = arterial blood activity (estimated from end-tidal air activity) at time t,
k_m = washout constant of compartment m.

The quality of fit to the sampled data of the resulting four-parameter clearance function then is defined by the coefficient of determination:

$$r^2 = \frac{\sum_{i=i_o}^{i_n} (Q_{fit}(i) - \bar{Q}_{meas})^2}{\sum_{i=i_o}^{i_n} (Q_{meas}(i) - \bar{Q}_{meas})^2} \qquad (2)$$

where

$Q_{fit}(i)$ = calculated regional count rate at sampling period i,
$Q_{meas}(i)$ = measured regional count rate at sampling period i,
$\bar{Q}_{meas}$ = mean of all sampled count rates in that region,
i_o = index number of sample at start of fit time,
i_n = index number of sample at end of fit time.

Since r^2 is a measure of the global quality of fit only, and does not indicate the error proportion contributed by each subset of parameters p_m and k_m, respectively, we performed computer simulations to describe separately the possible effects of compartmental slippage. In these calculations the clearance constant, k_1, of the more rapidly perfused compartment was varied from 0 to 1.52 min^{-1} in steps of 0.08, concurrently changing k_2 in steps of 0.02 from 0 to 0.36 min^{-1}. All k_1 values less than k_2 were ex-

Received Mar. 21, 1983; revision accepted July 12, 1983.

For reprints contact: Dr. W.-D. Heiss, Max-Planck-Institut für neurologische Forschung, Ostmerheimer Str. 200, 5000 Köln 91 (Merheim), West Germany.

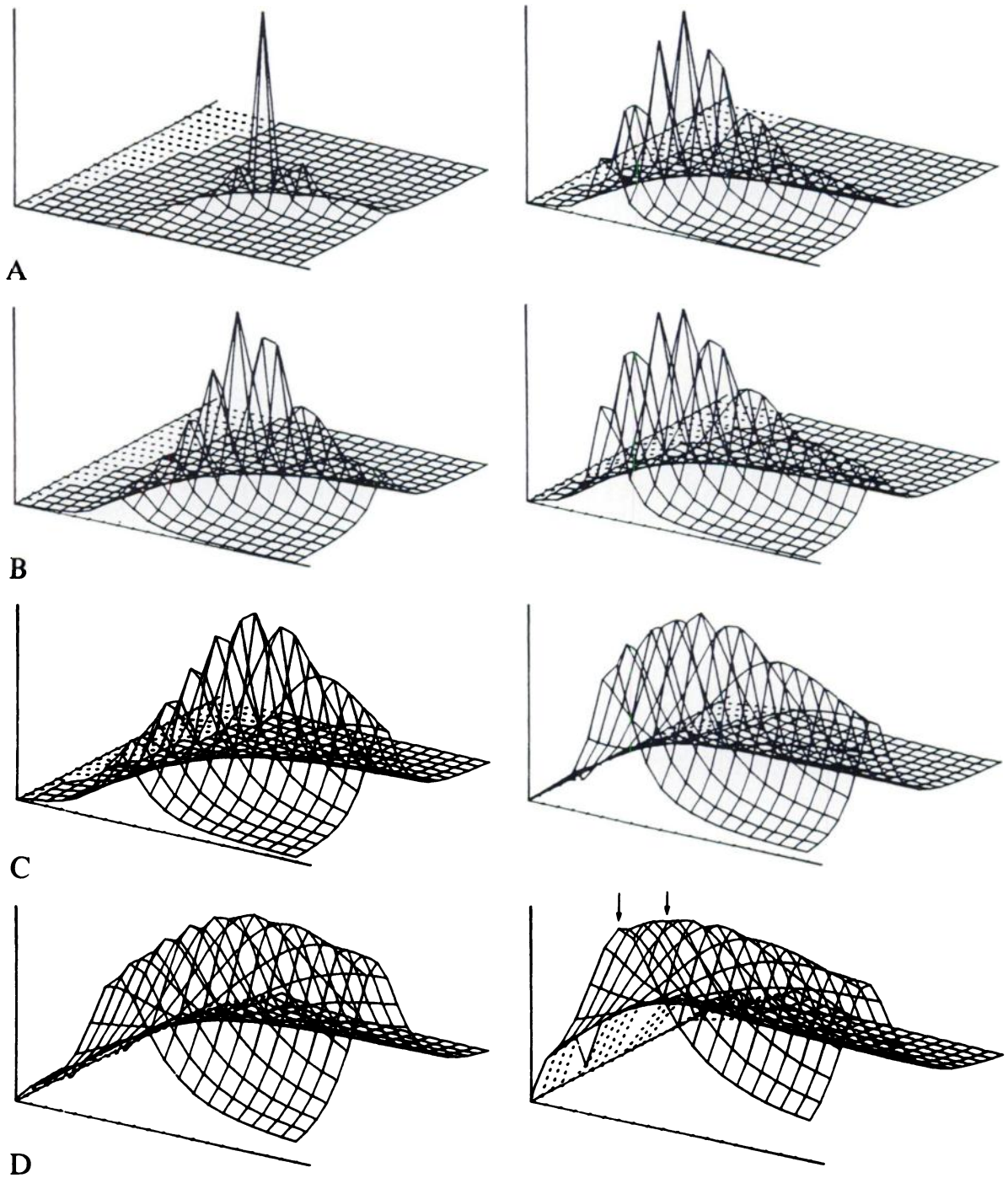

FIG. 1. Computer graphs of quality of fit to Xe-133 clearance data—sampled from healthy control person (Case 1, left column) and stroke patient (Case 2, right column)—of bicompartmental model at simulated combinations of clearance constants. k_1 is plotted along x-axis in steps of 0.08 min^{-1}, k_2 along y-axis in steps of 0.02 min^{-1}, with vertical axis representing $1/(1 - r^2)$ normalized with respect to individual maximum value. Simulation plots based on original activity counts are shown in row A. All other graphs were constructed following superposition of white noise on original data: of 5% of total count rate (row B), 10% (C), and 20% (D).

cluded. Each of the resulting combinations of clearance constants was then inserted into Eq. (1), and a least-squares fit to the time-activity raw data of the patient study was computed with respect to p_1 and p_2, as well as the corresponding coefficient of determination.

Following all simulation fit procedures, a perspective three-dimensional graph was constructed showing k_1 (x-axis) and k_2 (y-axis) as independent variables, with the z-axis representing the standardized quality of fit. In order to accentuate the region of best fit, the reciprocal of the coefficient of nondetermination $1/(1 - r^2)$ rather than the coefficient of determination itself, was plotted on the z-axis as the dependent variable. The discriminating power of this iterative simulation technique was tested by superimposing various levels of uniformly distributed random noise on the original patient time-activity series.

Patient studies were performed using a scintillation camera and

TABLE 1. PERCENT CHANGE FROM ORIGINAL VALUE AND CORRELATION OF k_1 AND k_2 FOLLOWING SUPERPOSITION OF RANDOM NOISE

		k_1 (% of original value)	k_2 (% of original value)	r
Case 1: $k_1 = 1.011$, $k_2 = 0.134$.				
Random noise:	5%	−1.4 ± 2.5	−5.2 ± 2.8	0.888
	10%	−1.6 ± 4.9	−9.7 ± 5.3	0.816
	20%	−2.5 ± 10.2	−20.2 ± 11.3	0.814
Case 2: $k_1 = 0.622$, $k_2 = 0.077$.				
Random noise:	5%	+1.1 ± 4.8	−2.6 ± 8.8	0.930
	10%	−0.3 ± 10.0	−11.7 ± 21.0	0.915
	20%	+3.5 ± 23.2	−19.5 ± 50.0	0.880

a custom-built detector/infrared spectrometer unit for continuous activity counting and CO_2 monitoring of the respiratory air. Following a slow intravenous bolus injection of 20–30 mCi Xe-133 in up to 2 ml of normal saline solution, time-activity data were collected both from one side of the patient's head and from his exhaled air, stored in the memory of a minicomputer, and processed utilizing the Gamma-11 software as well as user-written Fortran routines based on the algorithm described by Obrist et al. (*1*). Results were displayed on a graphic terminal connected to a hard-copy unit.

RESULTS

Application of the above methods is demonstrated in two characteristic cases (Fig. 1) selected from a large series of patients referred to this laboratory for routine rCBF measurements.

Case 1. A 22-yr-old female without signs of cerebrovascular disorder; mean regional count rate during an 11-min recording period 53,510 cpm, regional peak count rate 152,830 cpm, $k_1 = 1.011\ min^{-1}$, $k_2 = 0.134\ min^{-1}$.

Case 2. A 36-yr-old male with ischemic infarct in territory of middle cerebral artery following thrombotic occlusion of the ipsilateral internal carotid; mean regional count rate 20,130 cpm, regional peak count rate 41,650 cpm, $k_1 = 0.622\ min^{-1}$, $k_2 = 0.077\ min^{-1}$.

Remarkable differences in the shape of the quality-of-fit plane are apparent in the bivariate simulation graphs of these two cases. If simulations performed with the original data of the patient's time series (Fig. 1A) show a well-defined isolated peak, as in Case 1, a reliable estimate of the parameters of the bicompartmental model may be assumed, and the numerical results for flow and weight of the two compartments probably do not suffer from poor determination. This is in contrast to the second case, where compartmental slippage of some degree cannot be absolutely ruled out.

Upon superposition of an increasing proportion of random noise, the peak flattens out and becomes broad-based, thus indicating uncertain definition of the best curve approximation—i.e., even pairs of k_1 and k_2 that are rather distant from each other yield a similar quality of fit. The latter extreme condition is demonstrated in Fig. 1D, Case 2, which shows no difference in the *minimized* least-squares fit for $k_2 = 0$ and $k_2 = 0.08$ (arrows). Note especially that $k_2 = 0$ does not mean a monoexponential clearance curve with a single exponent k_1, but a compartment with zero flow, i.e., tracer accumulation only, as determined by the algorithm.

The close relationship between the shape of the peak in the simulation graph of the quality of fit, and the inaccuracy of the results due to compartmental slippage, are demonstrated in Table 1. One hundred estimates of k_1 and k_2, respectively, were obtained in the two cases of Fig. 1 for each level of random-noise superposition using Obrist's algorithm, and the differences from the original values of these results and their respective standard deviations were computed. It is clearly seen that there is an increase in variance of both clearance constants at higher proportions of random noise. There is also a substantial decrease in their mean values, k_2 being more sensitive to random influences than k_1 ($p < 0.01$) for all variance ratios in a two-way analysis of variance. Correlation coefficients greater than 0.8 demonstrate that both parameters usually deviate in the same direction.

DISCUSSION

Compartmental slippage is assumed when repeated rCBF measurements of the same patient under different test conditions result in different values of the compartmental weights (*7–10*). In these instances poor distinction between tissues belonging to different compartments has been explained as an effect of heterogeneity within one compartment resulting in an overlap of the respective k values. Therefore, changes of blood flow may cause such tissue volumes to "slip" mathematically from one compartment to the other. The higher statistical fluctuation and the increased recording noise inherent in noninvasive rCBF measurements represent another source of errors in the discrimination between compartments (*6*). Some authors made an attempt to reduce the considerable variance in their calculated flow values by using "noncompartmental" parameters, e.g., the initial flow index (*11*) or total flow recorded as CBF_{15} and CBF_{∞} (*6*). However, exclusive use of these parameters would waste the information that can be obtained by properly estimating all the parameters of the bicompartmental model.

Conventional error calculations are hardly feasible in case of a convolution integral introducing the recirculation curve. The proposed method of constructing a three-dimensional diagram of the quality of curve-fitting to individual patient data represents a readily applicable approach for assessing ambiguities in compartment analysis—particularly for the detection of possible compartmental slippage. Moreover, the described procedure is independent of the algorithm actually used and can be adapted to any method of rCBF calculation. Its overall approach can be extended to any type of fitting problem in an exponential model.

REFERENCES

1. OBRIST WD, THOMPSON HK, WANG HS, et al: Regional cerebral blood flow estimated by ^{133}xenon inhalation. *Stroke* 6:245-256, 1975
2. MERIC PH, SEYLAZ J, CORREZE JL, et al: Measurement of regional cerebral blood flow by intravenous injection of Xe^{133}. *Med Progr Technol* 6:53-63, 1979
3. PITKÄNEN MA, KUIKKA JT, KIILIÄINEN H, et al: Comparison of two optimizing algorithms for cerebral blood flow analysis using the intravenous ^{133}Xe wash-out method. *Int J Biomed Comput* 13:213-220, 1982
4. JABLONSKI T, PROHOVNIK I, RISBERG J, et al: Fourier analysis of 133-Xe inhalation curves: Accuracy and sensitivity. *Acta Neurol Scand* 60: Suppl 72, 216-217, 1979
5. REIVICH M: Observation on exponential models of cerebral clearance curves. In *Research on the Cerebral Circulation.* Meyer GS, Lechner H, Eichhorn O. Springfield, CC Thomas, 1969, pp 135-141
6. OBRIST WD, WILKINSON WE: The noninvasive Xe-133 method: Evaluation of CBF-indices. In *Cerebral Circulation and Neurotransmitters.* Amsterdam-Oxford-Princeton, Excerpta Media, 1980, pp 119-124
7. WALTZ AG, WANEK AR, ANDERSON RE: Comparison of analytic methods for calculation of cerebral blood flow after intracarotid injection of ^{133}Xe. *J Nucl Med* 13:66-72, 1972
8. ILIFF L, ZILKA E, BULL JWD, et al: The effect of changes in cerebral blood flow on compartmental weight. In *Cerebral Circulation and Metabolism.* Lonfitt T, McHenry L, Reivich M, Wollman H, eds. Berlin-New York, Springer-Verlag, 1975, pp 145-147
9. BRUCE DA, SCHUTZ H, VAPALAHTI M, et al: Pitfalls in the interpretation of xenon CBF studies in head-injured patients. In *Cerebral Circulation and Metabolism.* Lonfitt T, McHenry L, Reivich M, Wollman H, eds. Berlin-New York, Springer-Verlag, 1975, pp 406-408
10. HEISS WD, ZEILER K, TURNHEIM M, et al: Flow and compartmental weight in relation to the course of stroke. *Stroke* 7:399-403, 1976
11. RISBERG J, ZENAB A, WILSON EM, et al: Regional cerebral blood flow by ^{133}xenon inhalation. *Stroke* 6:142-148, 1975