Comparative Analysis of Striatal FDOPA Uptake in Parkinson's Disease: Ratio Method Versus Graphical Approach

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Striatal-to-occipital ratio (SOR) and influx constant K_i^{occ} are commonly used as analytic parameters in L-3,4-dihydroxy-6-^{18}F-fluorophenylalanine (FDOPA) PET studies. Both have been shown to be useful in discriminating Parkinson's disease (PD) patients from healthy subjects. We evaluated the relative performance of SOR and influx constant (K_i^{occ}) in the clinical assessment of nigrostriatal dopaminergic function in PD. **Methods:** Twenty-one parkinsonian patients (Hoehn and Yahr scale I–IV; mean age ± SD, 56 ± 9.2 y) and 11 healthy subjects (mean age, 60 ± 16 y) underwent 3-dimensional dynamic FDOPA scanning from 0 to 100 min. After spatial realignment, PET images at each frame were integrated by summing 4 central striatal slices, and time–activity curves (TACs) were generated after placing a standard set of elliptic regions of interest over striatal and occipital structures. SOR and K_i^{occ} values for each subject were then computed from TACs at different times using an input function from the occipital cortex. **Results:** Both SOR and K_i^{occ} showed significant bilateral decreases in striatal dopamine uptake in the PD group compared with the control group. SOR values estimated for 10-min frames between 65 and 95 min are statistically equivalent in group discrimination. In addition, SOR values in the caudate and putamen correlated strongly with K_i^{occ}, especially toward the end of the scanning epoch. Both parameters correlated significantly and comparably with Unified Parkinson's Disease Rating Scale motor scores. **Conclusion:** These results suggest that SOR determined from a single 10-min scan at 95 min is as accurate as K_i^{occ} in separating PD patients from healthy subjects and in predicting clinical measures of disease severity.

Key Words: L-3,4-dihydroxy-6-^{18}F-fluorophenylalanine; PET; ratio method; graphical analysis; Parkinson's disease

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Imaging with PET and L-3,4-dihydroxy-6-^{18}F-fluorophenylalanine (FDOPA) has long been an established procedure to quantify the integrity of dopamine function in the human brain. Both striatal-to-occipital ratio (SOR) and influx constant (K_i^{occ}) have previously been measured noninvasively in dynamic mode using region-of-interest (ROI) approaches (*1–4*). With the use of reference tissue, both parameters computed for putaminal ROIs have been found to separate Parkinson's disease (PD) patients from healthy subjects, but with varying degrees of accuracy. We have consistently shown that SOR is a reliable imaging indicator of disease severity in parkinsonism (*5–7*). Similarly, K_i^{occ} measurements have been used extensively to quantify regional dopamine metabolism (*8,9*) and to estimate the rate of disease progression (*3*).

Both parameters have become popular in recent years because their measurement is simple and does not require taking blood samples. SOR may offer a practical advantage because it can be determined by static data acquisition whereas K_i^{occ} requires dynamic scans over a longer time. A long study in patients with advanced PD not only poses a serious compliance issue but also increases potential bias from subject movement. Thus, the application of a ratio index such as SOR may be useful in quantifying nigrostriatal dopamine function in parkinsonism and related disorders. Two important issues, however, need to be addressed before the broad implementation of ratio methods with FDOPA PET: The first is the dependence of SOR on time after the tracer reaches equilibrium, and the second is the relative merits of SOR and K_i^{occ} as descriptors of nigrostriatal dopaminergic degeneration. In this study, we examined these questions by comparing FDOPA PET data from a set of PD patients and a set of healthy volunteers. Compared with our previous study that compared SOR and K_i^{occ} using 2-dimensional data acquisition (*1*), we have this time used 3-dimensional data acquisition on a more sensitive PET scanner with shorter time frames.

MATERIALS AND METHODS

Subject Characteristics

We investigated 21 patients with moderate PD (13 men, 8 women; mean age ± SD, 56 ± 9.2 y; Hoehn and Yahr stage I–IV; n = 5, 6, 7, and 5 in stages I, II, III, and IV, respectively) (*10*). All

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patients stopped dopaminergic medications 12 h before FDOPA PET. We also selected 11 age-matched healthy volunteers as control subjects (8 men, 3 women; mean age, 60 ± 16 y). All patients and healthy volunteers signed a consent form after receiving a detailed explanation of the clinical protocol, which was approved by the Institutional Review Board at North Shore University Hospital.

Image Acquisition

Dynamic FDOPA PET data were acquired in 3-dimensional mode on an Advance scanner (General Electric Medical Systems, Milwaukee, WI) during the 100 min after injection (*11*). This camera covered the whole brain with an intrinsic resolution of 4.2 mm and a slice separation of 4.25 mm. All subjects had a light breakfast 4 h before the study and were given 200 mg of carbidopa 1.5 h before the scan to inhibit decarboxylation. The FDOPA preparation and imaging protocols have been described in detail elsewhere (*5*). Dynamic scanning started at the time of tracer injection at continued until 100 min after tracer injection. Images were reconstructed with a 6-mm Hanning filter to give a 3-dimensional image resolution of about 8 mm. There were 35 image planes per frame, with a matrix dimension of 128 × 128 and a voxel size of 2.34 × 2.34 mm. Corrections were made for random events, scatter, and electronic dead time, and the photon attenuation effect was corrected using a 10-min transmission scan collected with rotating ^{68}Ge rod sources. These images were then transferred to personal computers running Windows NT (Microsoft, Redmond, WA) and were converted into Analyze format (Mayo Clinic, Rochester, MN).

Image Processing

Dynamic frames were realigned to the image at 55 min using the SPM99 program (Wellcome Department of Cognitive Neurology, London, U.K.). PET images between 40 and 100 min were averaged, and a mean image was created by summing 4 central slices (thickness, 17 mm) covering the striatum. The units of radioactivity for time–activity curves (TACs) were kBq/mL. A set of standard elliptic ROIs (55, 160, and 310 cm^2 for the caudate region, putaminal region, and occipital region, respectively) were placed over the right and left caudates, putamen, and occipital cortex on the mean image. To reduce noise in the occipital TAC, the values for the left and right sides were averaged.

Image Analysis

TACs in the caudate, putamen, and occipital cortex were computed from the corresponding single-slice PET images. Striatal-to-occipital ratio (SOR) values were generated for each structure using bilaterally averaged occipital ROI data. SOR was calculated for each 10-min time frame: 65, 75, 85, and 95 min after injection. K_i^{occ} was also calculated by graphic analysis over 40–100 min using the nonspecific uptake value from the occipital region. SOR and K_i^{occ} data from the left and right caudates and the putamen were averaged. The 2 parameters were correlated within each striatal ROI (caudate, putamen) by computing Pearson product moment correlation coefficients. ROI data from the PD and the healthy groups were analyzed separately and in combination. Caudate and putaminal data from the PD group were compared with control data using discriminant function analysis (F test). In 16 of the 21 PD patients (mean age, 55 ± 8.6 y; mean composite Unified Parkinson's Disease Rating Scale [UPDRS] motor ratings, 33 ± 12), both parameters were correlated with individual motor UPDRS ratings.

RESULTS

We first compared SOR with K_i^{occ} in each structure by combining the data from both the PD group and the healthy group. For the combined group of PD patients and healthy subjects, SOR values at times later than 65 min were strongly correlated with K_i^{occ} in the caudate ($r^2 = 0.75$; $P < 0.0001$) and putamen ($r^2 = 0.92$; $P < 0.0001$) (Fig. 1; Table 1). This criterion was also significant ($P < 0.01$) within each of the 2 groups. This correlation became stronger with time after injection; r^2 increased from 0.82 to 0.92 at times from 65 to 95 min (Table 1). Caudate uptake behaved similarly, although the accuracy of discrimination was generally lower.

Both SOR and K_i^{occ} data in the caudate and putamen were greatly reduced in the PD patients compared with the healthy subjects (Table 2). The magnitudes of reduction in the 2 regions ranged from 21% to 34% for SOR (34%–56% for ratio R, defined as SOR − 1, or the ratio of specific activity in the putamen to occipital activity) and 32%–60% for K_i^{occ}. Figure 2 shows a clear separation in mean values between the 2 groups, with a significance level of $P < 0.0001$. There were fewer miscategorizations (false-negatives) present with SOR than with K_i^{occ}. Moreover, SOR for the putamen reached a higher significance than did K_i^{occ} in the discrimination analysis (F test, Table 1). The decrease in striatal FDOPA uptake and the relative sensitivity of SOR over K_i^{occ} were in line with our results from a different PET scanner (*1*). When we compared PD patients with healthy subjects, the FDOPA uptake indices given by both parameters were significantly lower in the putamen than in the caudate. This finding agrees with early studies reported by several groups (*2*,*8*). In addition, all SOR values at 65, 75, 85, and 95 min after injection were effective in discriminant analysis ($P < 0.0001$, Table 1), although an improving trend with time was evident (F values increasing from 182 to 251, Table 1).

Correlations between FDOPA uptake as measured by SOR or K_i^{occ} and clinical indices of motor disability were evaluated (Table 1; Fig. 3). Decreased uptake in the putamen correlated significantly with composite UPDRS motor scores. Both SOR ($r^2 = 0.46$; $P < 0.004$) and K_i^{occ} ($r^2 = 0.44$; $P < 0.005$) had similar correlations with disease severity. No significant correlations were found between UPDRS motor ratings and either SOR or K_i^{occ} in the caudate ($P < 0.2$).

DISCUSSION

The correlations of SOR and K_i^{occ} were of comparable magnitude to those described previously in patients with early-stage PD (*5*). SOR was based on independent 10-min scans starting at 60 min after injection, whereas K_i^{occ} was based on 40–100 min of dynamic data. The linearity of the

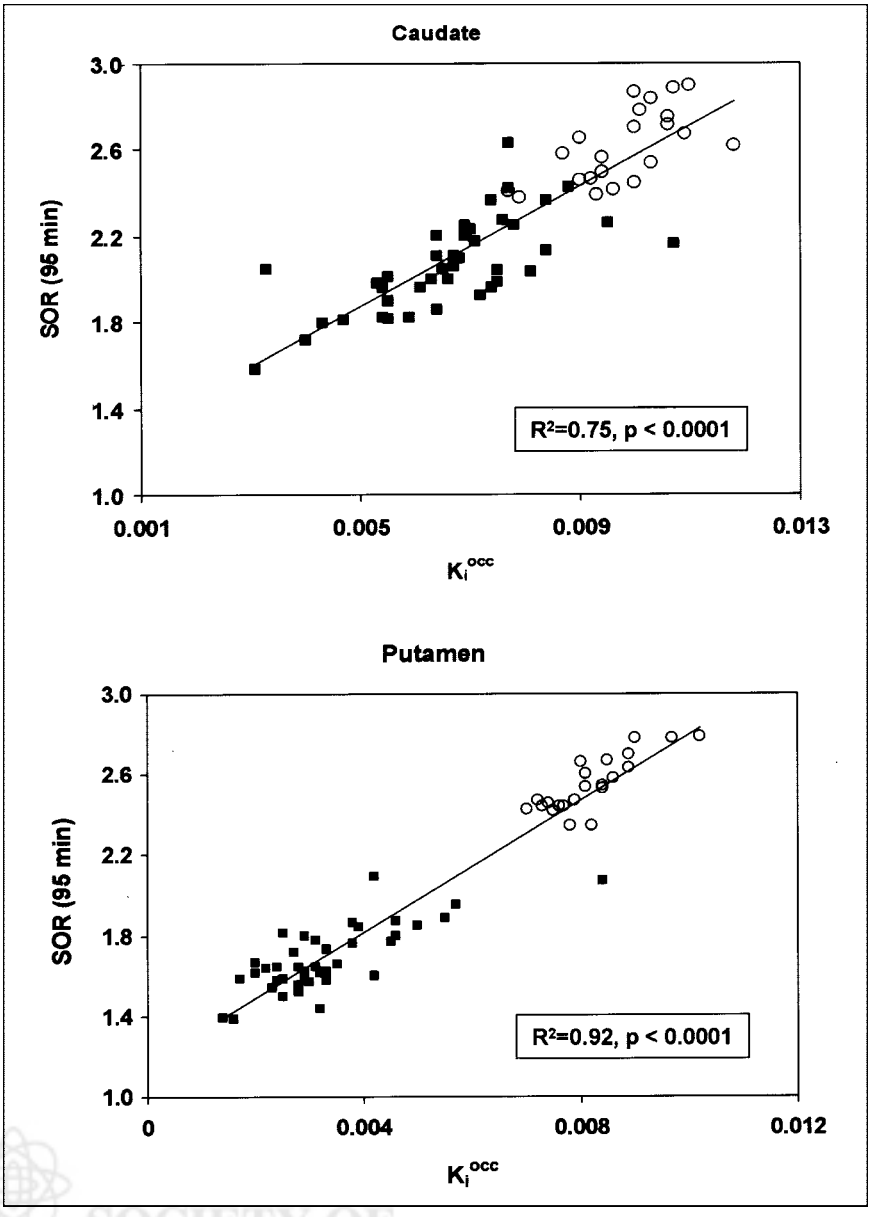

FIGURE 1. Parametric correlation between SOR (95 min) and K_i^{occ} in 2 striatal structures in both PD and control groups.

TABLE 1
Properties of SOR and K_i^{occ}

Property	Minutes after injection				
	65 (SOR)	75 (SOR)	85 (SOR)	95 (SOR)	40–100 (K_i^{occ})
Coefficient of variation for control group (%)	4.5	5.1	4.8	5.4	9.8
F ratio for control-vs.-PD discrimination	182*	199*	224*	251*	153*
r^2 (SOR vs. UPDRS)	0.29	0.31	0.37	0.46	0.44†
(*P* values)	0.03	0.03	0.01	0.004	0.005
r^2 (SOR vs. K_i^{occ})	0.82*	0.85*	0.90*	0.92*	

*$P < 0.001$.
†r^2 value for K_i^{occ} vs. UPDRS.

TABLE 2
Mean SOR and K_i^{occ} Values in Striatal Structures: Comparison of PD and Control Groups

Parameter	Caudate			Putamen		
	Normal	PD	%Δ	Normal	PD	%Δ
SOR	2.61 ± 0.17	2.06 ± 0.19	−21	2.55 ± 0.14	1.68 ± 0.15	−34
K_i^{occ}	0.0098 ± 0.0009	0.0066 ± 0.0014	−32	0.0082 ± 0.0008	0.0033 ± 0.0012	−60
R	1.61 ± 0.17	1.06 ± 0.19	−34	1.55 ± 0.14	0.68 ± 0.15	−56

%Δ denotes change in PD group relative to control group. Values are given as mean ± SDs. SOR was calculated at 95 min after injection. R is ratio of specific striatal activity to occipital activity and is equivalent to SOR − 1. Units for K_i^{occ} are 1/min.

K_i^{occ} plot improves with time, and the uptake rate is usually calculated from data between 40 and 100 min. SOR, in contrast, reaches a plateau very slowly, and this parameter is better estimated at later times except for increased noise in the occipital counts after about 100 min. The results in Table 1 show that the SOR-versus-K_i^{occ} correlation varied from 0.82 to 0.92 between 65 and 95 min and was highest at 95 min.

Our results demonstrate that both parameters significantly discriminate PD patients from healthy subjects and correlate with independent measures of motor dysfunction in patients as expected on the basis of theoretic considerations. Both

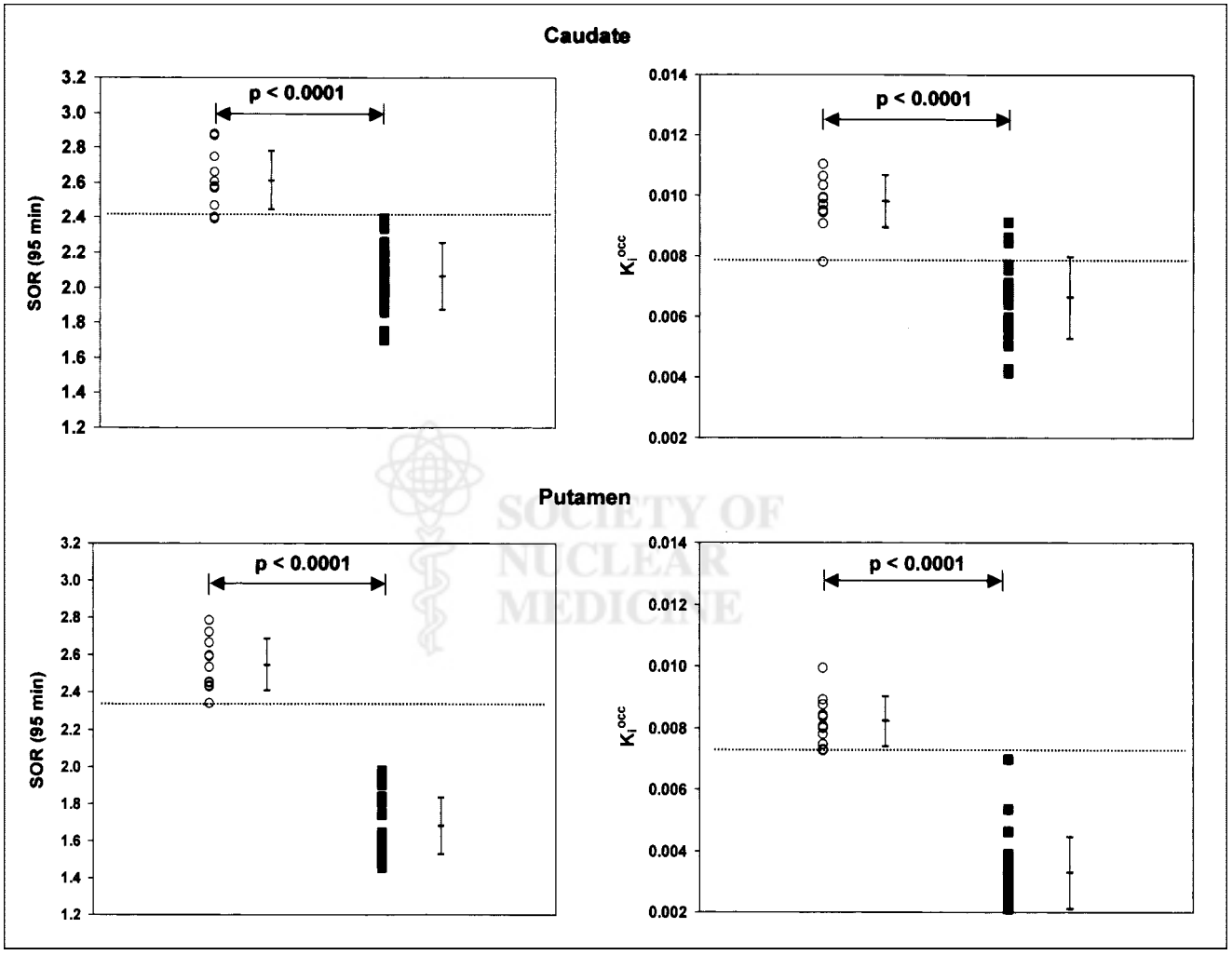

FIGURE 2. Discrimination analysis using SOR (95 min) and K_i^{occ} in 2 striatal structures. SOR and K_i^{occ} give similar separation between PD and control groups. However, SOR is associated with higher discriminant scores (F scores) than is K_i^{occ} (Table 1). Error bars indicate mean and SDs.

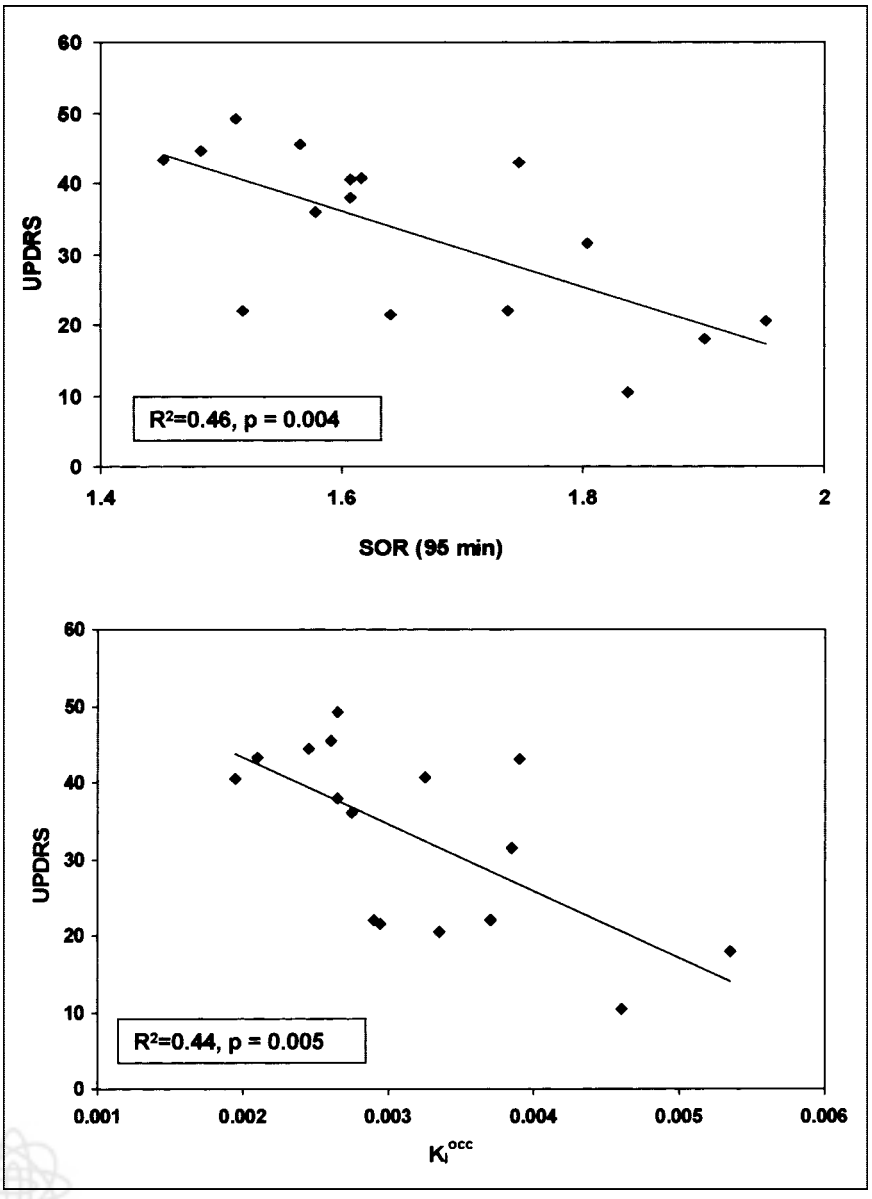

FIGURE 3. Clinical correlation between UPDRS motor ratings and dopamine uptake in putamen as measured by SOR (95 min) and K_i^{occ}.

SOR and K_i^{occ} successfully discriminate PD patients from healthy subjects and are also equally sensitive as descriptors of disease severity. Indeed, we are currently using SOR as an index to statistically map 3-dimensional topographic changes in FDOPA uptake after therapeutic treatments (*7*).

Even though SOR values calculated at 65, 75, 85, and 95 min were statistically equivalent in discriminating healthy subjects from PD patients, the F ratio reflecting the power of discrimination improved with time, from 182 to 251 (Table 1). Moreover, the correlation between clinical severity rating (UPDRS) and SOR improved with time, from 0.29 (at 65 min) to 0.46 (at 95 min, Table 1). This finding is important for longitudinal studies, in which higher sensitivity is required to reduce the number of subjects needed to detect a small change.

The mean percentage differences in K_i^{occ} were equal to or larger than corresponding SOR values; however, the SD in SOR was lower than that in K_i^{occ}, especially for PD patients. We have previously reported differences in the coefficient of variation in SOR and K_i^{occ} using 2-dimensional data from a lower-resolution scanner (*1*).

We have used the average of the left and right sides to establish a conservative estimate (the more affected body side would better discriminate between healthy and PD subjects, but it is often difficult to assign which side is more affected in some individuals. In healthy subjects, averaging the 2 sides to reduce variance is obviously better. Additionally, the discrimination between healthy and PD subjects will dramatically improve if SOR and K_i^{occ} analysis is performed separately on the anterior and posterior parts of the putamen. FDOPA levels have been shown to reveal a distinct anterior–posterior gradient as the disease progresses. It remains to be seen if a similar improvement in correlation between the 2 parameters (SOR and K_i^{occ}) and

UPDRS results if one focuses exclusively on the posterior region of the affected putamen (increased noise in the putaminal signal may, to some extent, counterbalance the expected increased sensitivity and specificity of the regional information).

Two earlier studies reported K_i^{occ} to be more powerful than SOR in differentiating PD patients from healthy subjects and in detecting the rate of disease progression (*2*,*3*). Vingerhoets et al. (*12*), in 1994, suggested that SOR may be an appropriate parameter for assessing natural evolution based on its smallest within-subject variation, but K_i (estimated using metabolite-corrected blood data) can permit the use of fewer subjects for drug studies based on larger reliability coefficients. However, in a study dealing with reproducibility and the discriminating ability of FDOPA PET in PD, the same investigators found that SOR and K_i^{occ} were similar in their ability to evaluate progressive changes in nigrostriatal dopaminergic function (*2*). We attribute this finding to the fact that the SOR measure was computed from images acquired in 2 dimensions and integrated over a longer time than was used in this study. Also, the inclusion of the early phase of the scans (from 30 min after injection onward) decreases the sensitivity of the SOR measure (Table 1). We have not directly compared SOR and K_i^{occ} for longitudinal studies, but the correlation between disease severity (UPDRS scores) and the 2 PET-derived parameters (SOR and K_i^{occ}) was similar (0.46 vs. 0.44) at 95 min after injection (Table 1; Fig. 3). Also, the correlation between SOR and K_i^{occ} was 0.92 at 95 min, suggesting that both SOR and K_i^{occ} may be able to reflect disease progression in longitudinal studies in a similar, quantitative manner. Interestingly, we have directly compared SOR with K_i (plasma) in our fetal transplant study that included moderately advanced PD patients and found that SOR was superior to K_i (plasma) for longitudinal changes (*7*).

In longitudinal studies, R is the preferred parameter because it reflects changes specifically in striatal uptake rather than in total uptake. SOR and R have similar information and can easily be derived from each other (R is simply SOR − 1).

The present findings have been derived from several patients with mild to advanced PD. It is still necessary to analyze patients with a wider range of motor severity to confirm the superior discrimination capability of SOR over K_i^{occ}. Such an analysis can offer a good opportunity to further validate SOR and K_i^{occ} correlations with components of UPDRS motor scores in PD at different stages, as well as to compare the rate of change of these measures over time at different disease stages.

Traditionally, the multiple-time graphical approach (Patlak plot) has been used to estimate parameters of interest for FDOPA PET studies (*13*,*14*). The influx transport rate of FDOPA is given by the slope of the line when the ordinate is $C_{striatum}(t)/C_{plasma}(t)$ and the abscissa is $\int_0^t C_{plasma}(\tau)d\tau/C_{plasma}(t)$. A rigorous derivation of the mathematic relationship has been previously published (Eq. 4 (*15*)). A simplified treatment to show the relationships between K_i^{FD}, K_i^{occ}, and SOR follows:

$$\frac{C_{striatum}(t)}{C_{plasma}(t)} = K_i^{FD}\frac{\int_0^t C_{plasma}(\tau)d\tau}{C_{plasma}(t)} + V_o, \quad \text{Eq. 1}$$

for $t > t^*$, where t^* is defined as the time at which radiotracer activity in reversible tissue compartments reaches an effective steady state with that in the plasma pool.

V_o is a volume of distribution that includes tracer-exchangeable space and the plasma volume. Multiplying both sides of the equation by $C_{plasma}(t)/C_{occipital}(t)$, we get:

$$\frac{C_{striatum}(t)}{C_{occipital}(t)} = K_i^{FD}\frac{\int_0^t C_{plasma}(\tau)d\tau}{C_{occipital}(t)} + V_o\frac{C_{plasma}(t)}{C_{occipital}(t)}. \quad \text{Eq. 2}$$

The plasma time–activity curve (TAC) refers to FDOPA only, whereas the occipital TAC includes both FDOPA and its metabolite 3-*O*-methyl-6-^{18}F-fluoro-L-DOPA.

Multiplying the first term on the right-hand side by $\int_0^t C_{occipital}(\tau)d\tau/\int_0^t C_{occipital}(\tau)d\tau$ and rearranging the terms, we get:

$$SOR(t) = K_i^{occ}\frac{\int_0^t C_{occipital}(\tau)d\tau}{C_{occipital}(t)} + V_o\frac{C_{plasma}(t)}{C_{occipital}(t)}, \quad \text{Eq. 3}$$

$$\text{where} \quad K_i^{occ} = K_i^{FD}\frac{\int_0^t C_{plasma}(\tau)d\tau}{\int_0^t C_{occipital}(\tau)d\tau} \quad \text{Eq. 4}$$

and SOR is simply defined as the left-hand side of Equation 2 (some investigators prefer to use the ratio R(t), defined as the ratio of specific uptake in the striatum [total striatal activity minus occipital activity] divided by the occipital activity, which is equivalent to SOR − 1). Equation 3 has traditionally been used to estimate K_i^{occ} and has the advantage of not requiring any blood sampling (*16*). Both FDOPA and its metabolite methyldopa cross the blood–brain barrier, and after a sufficiently long time (approximately 20–30 min after injection of FDOPA), $C_{plasma}(t)$ and $C_{occipital}(t)$ follow each other closely (both can be approximated by very slow changing of exponential functions or linear functions). Therefore, their ratio becomes approximately constant. Plots of $C_{plasma}(t)$ and $C_{occipital}(t)$, as well as their integrals, are shown in Figure 4 and empirically confirm the theoretic assumptions. Equations 3 and 4 show the relationship of the 3 parameters SOR, K_i^{occ}, and K_i^{FD} and emphasize that these parameters are related to each other linearly.

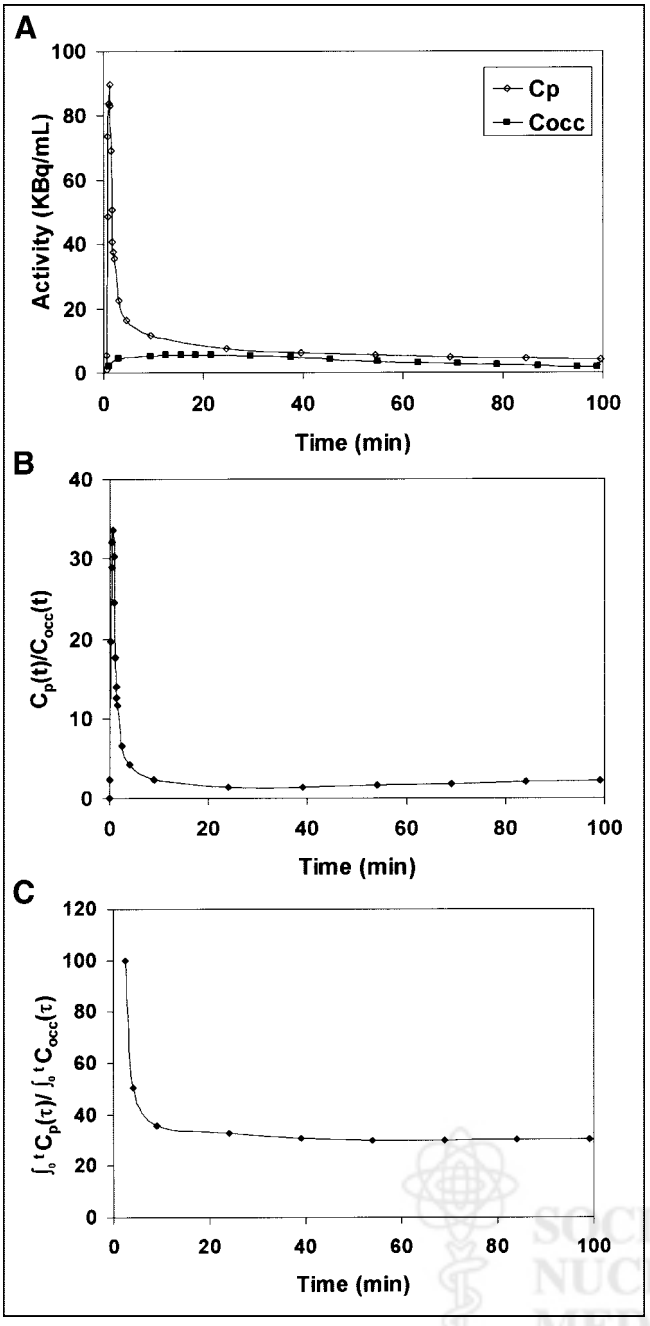

FIGURE 4. (A) Time–activity curves for plasma FDOPA and occipital radiotracer concentration (combined FDOPA and its metabolites) are shown on same scale. (B) Ratio of plasma to occipital activity as function of time. (C) Ratio of integral of plasma activity to integral of occipital activity. occ = occipital; p = plasma.

CONCLUSION

In this study, we have compared the clinical usefulness of SOR and K_i^{occ} in the accurate diagnosis of PD using PET and FDOPA. SOR is generally more sensitive than K_i^{occ} in distinguishing PD patients from healthy subjects while giving a comparable correlation with objective measures of motor deficit. A single short scan at 95 min after tracer injection is sufficient in a clinical research environment dealing with patients with movement disorders. This simplification offers a powerful and economical alternative for investigating the disease mechanism and clinical correlation in longitudinal experiments.

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