# Imaging of Dopamine Transporters with Iodine-123-FP-CIT SPECT in Healthy Controls and Patients with Parkinson's Disease

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Several SPECT studies reported decreased striatal $^{123}$I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([$^{123}$I]FP-CIT) binding in patients with Parkinson's disease. For application in routine clinical studies, information on the reliability and reproducibility of the [$^{123}$I]FP-CIT SPECT technique is critical. This study reports on the reliability and reproducibility of [$^{123}$I]FP-CIT SPECT in healthy control subjects and patients with Parkinson's disease using two different analysis protocols: the conventional region of interest (ROI) protocol and a newly developed, fully automatic, operator-independent volume of interest (VOI) protocol. **Methods:** We performed repeated [$^{123}$I]FP-CIT SPECT scans in 6 healthy control subjects and 10 patients with Parkinson's disease to measure scan-to-scan variations. Scintigraphic data were analyzed 3 hr after injection of the radiotracer. **Results:** In controls, the mean test/retest for the ratio of the striatal-to-nonspecific [$^{123}$I]FP-CIT uptake were (3.79 ± 0.67/3.82 ± 0.74) and (4.16 ± 0.70/4.08 ± 0.97) for the ROI and VOI technique, respectively. No significant differences were measured between test/retest studies. The mean test/retest variability for the ROI technique was low (7.25%) with excellent reliability ($\rho$ = 0.99). In addition, the mean test/retest variability for the VOI technique was also low (7.47%) with very high reliability ($\rho$ = 0.95). In Parkinson's disease patients, we found mean test/retest for the striatal-to-nonspecific [$^{123}$I]FP-CIT ratio of (1.78 ± 0.23/1.79 ± 0.25) and (1.83 ± 0.31/1.85 ± 0.35) using the ROI and VOI technique, respectively. Also in patients, these results did not differ significantly between test/retest studies. The mean test/retest variability for the ROI technique was low (7.90%) with excellent reliability ($\rho$ = 1.00). In addition, the mean test/retest variability for the VOI technique was also low (7.36%) with high reliability ($\rho$ = 0.96). **Conclusion:** Reliable and reproducible results were obtained with the ROI, as well as the VOI technique, for the analysis of striatal dopamine transporters with [$^{123}$I]FP-CIT SPECT in healthy controls and Parkinson's disease patients. The use of an operator-independent method will be a great advantage in routine clinical studies.

**Key Words:** SPECT; reproducibility; dopamine transporter imaging; iodine-123-FP-CIT; cocaine analogs

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Imaging of dopamine transporters using PET or SPECT has been introduced as a valuable tool to evaluate patients with several neuropsychiatric disorders, for example Parkinson's disease (*1,2*). In particular, cocaine analogs have been developed successfully and evaluated in humans as a PET or SPECT probe for imaging dopamine transporters (*2–11*).

The cocaine-like radioligand, $^{123}$I-FP-CIT ([$^{123}$I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane), binds with high affinity to dopamine and serotonin transporters in vitro (*6,12,13*). [$^{123}$I]FP-CIT has been tested as a SPECT probe in rat, monkey and human studies (*7,8,12,14,15*). Animal studies demonstrated that the in vivo striatal activity of [$^{123}$I]FP-CIT is largely associated with dopamine transporters (*15*). In addition, a monkey PET study showed that the striatal binding of the radioligand [$^{11}$C]FP-CIT could be displaced by β-CIT (*16*). Autoradiographic studies performed on the human brain revealed that striatal binding of FP-CIT is specific for the dopamine transporter (*16*). Initial human SPECT studies clearly showed the ability of the [$^{123}$I]FP-CIT SPECT technique to image dopamine transporters in vivo, demonstrating pronounced decline of striatal [$^{123}$I]FP-CIT binding in patients with Parkinson's disease (*10,14,17–19*).

Previous studies already emphasized that, due to the fast kinetics of FP-CIT, the [$^{123}$I]FP-CIT SPECT technique allows use of a 1-day protocol for imaging of dopamine transporters, which is convenient for routine clinical studies (*8,12,14,18*). Information on the reliability and reproducibility of quantitative measurements, both in healthy control subjects and patients with movement disorders is critical, however, to the application of the [$^{123}$I]FP-CIT SPECT technique in routine clinical studies. Moreover, this information is essential to perform power calculation for prospective [$^{123}$I]FP-CIT SPECT studies.

The quantitative measurement of dopamine transporters using [$^{123}$I]FP-CIT or [$^{123}$I]β-CIT SPECT is routinely based on a ratio-equilibrium analysis in which the ratio of radioactivity concentration in the striatum to that in a nonspecific brain region is used as an index of transporter density (*12,20*). The striatal binding ratio can be assessed by the ROI technique, which is a practical approach. However, this operator-dependent procedure may introduce variability in the final result. To exclude this variability, we developed a fully automated quantification technique using predefined volumes of interest (VOIs), which are registrated to individual scintigraphic data.

In this study, we evaluated the reproducibility and reliability of striatal [$^{123}$I]FP-CIT SPECT binding measurements at 3 hr after a bolus injection of the radioligand in groups of healthy control subjects and patients with Parkinson's disease, using both the ROI and VOI procedures.

## MATERIALS AND METHODS

### Subjects

Six healthy control subjects (all women and free of drugs; mean age 61 yr; range 51–70 yr), with no current or past history of neuropsychiatric disorders, and 10 patients (3 women, 7 men; mean age 67 yr; range 57–77 yr), with clinically established Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank criteria (*21*), were selected for test/retest studies. The mean duration of disease from the time of first symptoms to the first

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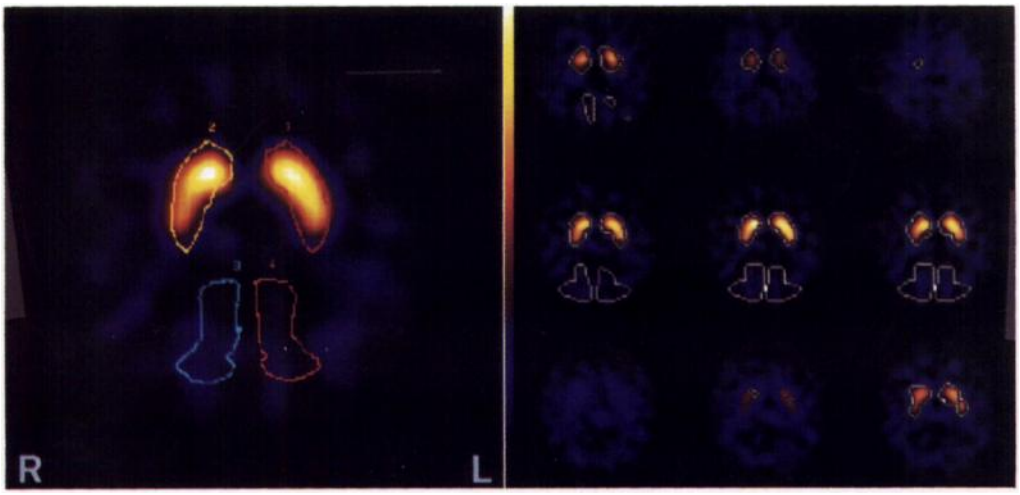


**FIGURE 1.** Iodine-123-FP-CIT SPECT images of 70-yr-old healthy woman. Level of radioactivity is color coded from low (black) through medium (red) to high (white) and scaled to maximum of study. (Left) Transverse slice from brain at level of striatum with overlaid ROIs for striatum and occipital cortex (R = right side of brain, L = left side of brain). (Right) Consecutive transverse slices of striatum with overlaid VOIs. Since VOI template is constructed and positioned in three dimensions, notice that VOIs are not always completely visible in individual slices.

SPECT assessment was 12 yr (range 2–25 yr). A neurological examination of the patients was performed to assess the stage of illness using the Hoehn and Yahr staging scale (*22*), which ranged from II to IV. At the time of acquisition of the SPECT studies, the patients were under dopaminergic medication using either levo-dopa (plus a peripheral decarboxylase inhibitor) and dopamine receptor agonists or only levo-dopa. The medical ethical committee gave permission for this study. All participants gave written informed consent.

### Iodine-123-FP-CIT

The [$^{123}$I]FP-CIT was manufactured by Amersham Cygne (Eindhoven University of Technology, The Netherlands) using the trimethylstannyl precursor of FP-CIT obtained from Research Biochemicals International (Natick, MA) (specific activity >185 MBq/nmol; radiochemical purity >98%; radiochemical yield of the labeling procedure 80%–85%).

### SPECT Imaging

Imaging studies were performed using a high-resolution tomographic neuroSPECT system, the SME 810X (Strichman Medical Equipment Inc., Medfield, MA). The system is equipped with 12 individual crystals, each with a focusing collimator, and is interfaced to a computer. The transaxial resolution of this system is 7.6 mm FWHM of a line source in air (*14*). The energy window was set at 135–190 keV.

Each subject received an intravenous injection of [$^{123}$I]FP-CIT (range 71–122 MBq) and had a second [$^{123}$I]FP-CIT injection (range 69–122 MBq) for retest 3–6 wk later, at the same time of the day, under the same experimental conditions. Before injection of the radioligand, all subjects received potassium iodide (total approximately 270 mg) orally to block thyroid uptake of free radioactive iodide.

Acquisition of the images was always performed at 3 hr postinjection (*14*). Imaging started, after positioning of the head of the subject in the camera, with beams from gantry-mounted lasers oriented parallel to the canthomeatal(CM)-line, by multiSPECT acquisition (150 sec/slice) from the CM-line up to the vertex (interslice distance 5 mm) and lasted approximately 40 min. During the retest scan, all efforts were made to position the subject's head in the camera to conform to the position during the test scan. The distances from the meatuses of the ears and from orbital angles to the position of the laser beams were recorded. Images were attenuation-corrected and reconstructed, as previously described (*14*). The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml as specified by Strichman Medical Equipment Inc.).

### Data Processing ROI

For analysis of striatal [$^{123}$I]FP-CIT binding, the ratio of striatal- (mean left and right side) to-nonspecific binding was calculated by summing two transverse slices representing the most intense striatal binding. A standard template, with regions of interest (ROIs) constructed manually according to a stereotactic atlas and including regions for the striatum and occipital cortex (nonspecific binding), was placed bilaterally on the summed image, as earlier described (*14,18*) (Fig. 1). All analyses were performed by the same experienced investigator.

### Data Processing by an Automatic Algorithm (VOI Technique)

All [$^{123}$I]FP-CIT studies also were analyzed by an automatic algorithm. The essential differences with the manual ROI method are: (a) the algorithm uses volumes of interest (VOIs) instead of ROIs; and (b) VOIs are positioned automatically on the image. For this purpose, we created a VOI template (Fig. 1) containing VOIs for the left and right striatum ($VOI_0$ and $VOI_1$, respectively) and for the left and right occipital cortex ($VOI_2$ and $VOI_3$, respectively). The VOIs of this template were constructed by manual drawing on consecutive slices of a standard stereotactic atlas (*23*). A transformation matrix $T_i$, with rotation and translation parameters, was allocated for each $VOI_i$. Each VOI is positioned automatically on the image by adjusting the corresponding matrix by simplex method to minimize a mathematical cost function $C_i$ (*24*). However, the definition of the cost function for $VOI_{0,1}$ differs from that for $VOI_{2,3}$.

To position $VOI_0$ and $VOI_1$ optimally in an area of striatal radioactivity, the cost function for $VOI_0$ and $VOI_1$ was defined in a way that the total counts in these VOIs were maximized. Therefore, the cost function for these VOIs was defined to equal the negative value of the total counts in $VOI_i$ after translation over the matrix $T_i$:

$$C_{i=0,1} = -\,total\ counts_i = -\sum_{r_{voi_i}} S(T_i r_{voi_i}) \qquad \text{Eq. 1}$$

Where $r_{voii}$ is the list of voxels within the VOI as specified by the template, and $S(T_i r_j)$ represents the value of the study at coordinate $T_i r_j$ in SMUs. The adjustment of the matrices for positioning of $VOI_{0,1}$ was restricted by the demand that $VOI_0$ has to be positioned on the image left of $VOI_1$.

To position $VOI_2$ and $VOI_3$ optimally in a brain area known to be representative of nonspecific [$^{123}$I]FP-CIT activity, the cost function for $VOI_2$ and $VOI_3$ was defined in a way that the homogeneity of counts within the VOI was maximized. The cost

**TABLE 1**
Variability and Reliability Between Test and Retest in Six Healthy Control Subjects

| Subject | Age (yr) | ROI protocol | | | VOI protocol | | |
|---|---|---|---|---|---|---|---|
| | | Test* | Retest* | Variability† | Test* | Retest* | Variability† |
| 1 | 70 | 3.56 | 3.76 | 5.29 | 4.38 | 4.84 | 10.09 |
| 2 | 51 | 4.88 | 5.19 | 6.33 | 5.29 | 5.45 | 2.91 |
| 3 | 54 | 3.66 | 3.21 | 13.12 | 3.45 | 3.36 | 2.69 |
| 4 | 66 | 2.88 | 3.12 | 8.21 | 3.37 | 2.78 | 18.99 |
| 5 | 59 | 3.63 | 3.78 | 3.88 | 4.23 | 4.09 | 3.25 |
| 6 | 66 | 4.12 | 3.85 | 6.69 | 4.22 | 3.94 | 6.88 |
| Mean ± s.d. | | 3.79 ± 0.67 | 3.82 ± 0.74 | 7.25 ± 3.22 | 4.16 ± 0.70 | 4.08 ± 0.97 | 7.47 ± 6.35 |
| Reliability‡ | | | 0.99 | | | 0.95 | |

*Data expressed as ratio of striatal to nonspecific binding.
†Absolute values of the test/retest difference expressed as percentage of the mean of the test and retest measures.
‡Intraclass correlation coefficient (ρ). ROI = region of interest; VOI = volume of interest.

function for these VOIs, therefore, equals the standard deviation of the counts within the VOI divided by the mean value of the VOI:

$$C_{i=2,3} = \frac{n_i * SD_i}{total\ counts_i} = \frac{\frac{\sum_{rVOI_i} S(T_i r_{VOI_i})^2}{n_i} - \left(\frac{\sum_{rVOI_i} S(T_i r_{VOI_i})}{n_i}\right)^2}{total\ counts_i} \quad \text{Eq. 2}$$

where $n_i$ represents the number of voxels within $VOI_i$.

The adjustment of the matrices for positioning of $VOI_{2,3}$ was restricted by the demand that $VOI_{2,3}$ have to be positioned on the image inferior to $VOI_{0,1}$, and $VOI_2$ has to be positioned left of $VOI_3$. All studies were analyzed by this algorithm with the same parameters and without any user-defined interface.

### Statistical Analysis

The Wilcoxon matched-pairs signed-ranks test was used for statistical comparison between test and retest measures. The within-subject variability between test and retest conditions was calculated as the absolute value of the differences of the test and retest measure divided by the mean of the test and retest and expressed as a percentage. Spearman rank correlation was used to examine the relationship between measures obtained from test and retest studies, as well as to examine the relationship between measures obtained from the ROI and VOI protocol.

One-way analysis of variance was performed to estimate the mean sum of squares between and within subjects. Thereafter, reliability coefficients were estimated. The reliability of the two measurements between test and retest was assessed by calculating the intraclass correlation coefficient, according to the following equation:

$$\rho = \text{MSBS} - \text{MSWS}/(\text{MSBS} + \{k - 1\}\text{MSWS}). \quad \text{Eq. 3}$$

MSBS and MSWS are the mean sum of squares between and within subjects, respectively, and k is the number of within-subject measurements, being 2 in this study. The intraclass coefficient is an estimate of the reliability of the two sets of measurements and varies from 0 (no reliability) to 1 (total reliability).

To estimate the intraobserver variability of the ROI technique, the test as well as the retest studies were reanalyzed after an interval of 3 mo by the same investigator. The intraobserver variability was calculated as the absolute value of the differences of the first and second measure divided by the mean of the first and second and expressed as a percentage.

In case of multiple comparisons, the Bonferroni correction method was used. Statistical significance was defined as $p < 0.05$.

## RESULTS

Tables 1 and 2 summarize the individual values of the striatal to nonspecific [$^{123}$I]FP-CIT ratios for the test/retest studies obtained in groups of healthy control subjects and patients with Parkinson's disease. As expected, the striatal-to-nonspecific [$^{123}$I]FP-CIT ratios from the test studies were statistically

**TABLE 2**
Variability and Reliability Between Test and Retest in Ten Patients with Parkinson's Disease

| Subject | Age (yr) | ROI protocol | | | VOI protocol | | |
|---|---|---|---|---|---|---|---|
| | | Test* | Retest* | Variability† | Test* | Retest* | Variability† |
| 1 | 76 | 2.02 | 2.07 | 2.51 | 2.34 | 2.30 | 2.07 |
| 2 | 71 | 1.43 | 1.35 | 5.45 | 1.37 | 1.31 | 4.62 |
| 3 | 68 | 1.60 | 1.56 | 3.06 | 1.57 | 1.43 | 9.51 |
| 4 | 57 | 1.77 | 1.90 | 7.13 | 1.77 | 1.91 | 7.81 |
| 5 | 68 | 2.21 | 2.09 | 5.69 | 2.20 | 2.27 | 3.40 |
| 6 | 65 | 1.88 | 1.95 | 3.52 | 2.07 | 2.17 | 4.47 |
| 7 | 71 | 1.66 | 1.57 | 5.35 | 1.68 | 1.72 | 2.19 |
| 8 | 57 | 1.79 | 1.62 | 9.94 | 2.03 | 1.84 | 10.03 |
| 9 | 63 | 1.56 | 2.02 | 26.00 | 1.61 | 2.02 | 22.95 |
| 10 | 77 | 1.94 | 1.75 | 10.34 | 1.64 | 1.54 | 6.52 |
| Mean ± s.d. | | 1.78 ± 0.23 | 1.79 ± 0.25 | 7.90 ± 6.89 | 1.83 ± 0.31 | 1.85 ± 0.35 | 7.36 ± 6.16 |
| Reliability‡ | | | 1.00 | | | 0.96 | |

*Data expressed as ratio of striatal to nonspecific binding.
†Absolute values of the test/retest difference expressed as percentage of the mean of the test and retest measures.
‡Intraclass correlation coefficient (ρ). ROI = region of interest; VOI = volume of interest.

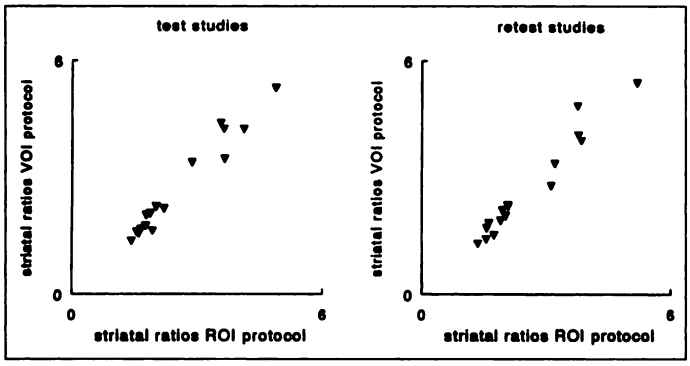


**FIGURE 2.** Correlation between striatal-to-nonspecific [$^{123}$I]FP-CIT binding ratios as obtained by ROI and VOI protocol for test (left) and retest (right) studies for individual subjects.

significantly and positively correlated with those ratios from the retest studies, using the ROI (r = 0.98) as well as the VOI protocol (r = 0.98).

For the controls, the mean values of the test/retest studies using the ROI protocol were 3.79 and 3.82, respectively, and were not significantly different between the studies (Table 1). The mean test/retest variability was low (7.25%) with excellent reliability ($\rho$ = 0.99). The mean values of test/retest studies using the VOI protocol were 4.16 and 4.08, respectively, and these measurements also were not significantly different between the studies. Again, the mean test/retest variability was low (7.47%) with high reliability ($\rho$ = 0.95). Although analysis of the data of the study using the ROI protocol resulted in a somewhat lower mean test/retest variability than the VOI protocol, there were no statistically significant differences in variability between these measurements due to the relatively large intersubject variation in variability (Table 1).

For the patients, the mean values of the test/retest studies using the ROI protocol were 1.78 and 1.79, respectively, and these measures were not significantly different between test/retest studies (Table 2). The mean test/retest variability was low (7.90%) with excellent reliability ($\rho$ = 1.00). The mean values of test/retest of the VOI protocol were 1.83 and 1.85, respectively, and these measures were not significantly different between test/retest studies. Again, the mean test/retest variability was low (7.36%) with high reliability ($\rho$ = 0.96).

The striatal-to-nonspecific [$^{123}$I]FP-CIT ratios, calculated using both the ROI and VOI protocol, were much lower in the patient compared with the control group and showed no overlap (Tables 1 and 2). The relationship between the striatal-to-nonspecific [$^{123}$I]FP-CIT ratios obtained using the ROI and VOI protocol was statistically significant for the test (r = 0.94) and retest (r = 0.97) studies (Fig. 2). The intraobserver variability of the [$^{123}$I]FP-CIT studies, using the ROI protocol, was 2.39% ± 1.34% (mean ± s.d.).

## DISCUSSION

We showed that the [$^{123}$I]FP-CIT SPECT measurements are reliable and reproducible both in healthy control subjects and patients with Parkinson's disease. In healthy subjects, the [$^{123}$I]FP-CIT SPECT technique yield intraclass correlation coefficients ranging from 0.95–0.99, depending on the method of analysis. These results were comparable with those found in patients with Parkinson's disease (0.96–1.00). This finding was unexpected, since it was anticipated that the reliability of the [$^{123}$I]FP-CIT SPECT technique may be lower in patients compared with controls due to the lower striatal signal from the diseased striatum and movements of the patients. Vingerhoets and coworkers (*25*) demonstrated that the reliability of scintigraphic studies is affected by the size of the ROI. The use of large compared with small ROIs resulted in decreased relative variation in the counts within the ROI, less degeneration of data by movement of the subject and less sensitivity to small differences in repositioning. Moreover, they showed that the use of large ROIs indeed resulted in comparable reliability of the [$^{18}$F]DOPA measurements in controls and patients (*26*). Therefore, the comparable reliability of the [$^{123}$I]FP-CIT SPECT measurements in controls and patients, in this study, might be explained partly by the fact that we also used large ROIs and VOIs comprising the whole striatum. In addition, other studies reported PET measurements of [$^{11}$C]raclopride binding to be highly reliable in both controls with a low $D_2$ receptor occupancy (favorably high striatal-to-nonspecific ratio) as well as in patients with a high $D_2$ receptor occupancy (*27,28*). This indicates that a low striatal contrast will not necessarily result in a relatively low reliability, provided that sufficient counts are obtained.

Previous SPECT studies reported a small overlap between striatal [$^{123}$I]FP-CIT ratios obtained in controls and patients with Parkinson's disease (*14,17,18*). The data of this study, however, revealed no overlap of striatal-to-nonspecific [$^{123}$I]FP-CIT ratios in the control compared with the patient group. Nevertheless, the patients in this study were not comparable to those presented previously. All patients in this study were treated with dopaminomimetics and had a long disease history (mean duration of disease 12 yr), whereas previous studies also included parkinsonian patients that were less advanced (i.e., disease duration less than 5 yr). Data obtained in patients with recent onset of the disease probably caused the overlap of striatal [$^{123}$I]FP-CIT measures between patients and healthy controls.

For diagnostic purposes, subjects will be evaluated mostly by [$^{123}$I]FP-CIT SPECT in the early phase of the disease. Strictly, in this study the reliability and reproducibility of striatal [$^{123}$I]FP-CIT data were not evaluated in that phase of the disease. However, since the results of this study demonstrated that the reproducibility and reliability of the [$^{123}$I]FP-CIT technique is comparable in patients and controls, it is likely that this technique also will be highly reproducible in parkinsonian patients in the onset of the disease.

A source of possible confounding, in the data of this study, lies in the fact that all patients received dopaminomimetics at the time of imaging. It cannot be excluded that direct or indirect effects of this medication could have interfered with [$^{123}$I]FP-CIT binding to the dopamine transporter. However, the results of a recent study performed in baboons demonstrated that acute administration of a large dose of levo-dopa had no significant influence on specific striatal [$^{123}$I]$\beta$-CIT binding (*20*). Moreover, recent studies in rats showed that neither acute nor chronic administration of dopamine $D_2$ agonists had any influence on binding of radiotracers to the dopamine transporter (*29,30*). It is reasonable to assume, therefore, that treatment with levo-dopa and dopamine $D_2$ agonists will not influence significantly the in vivo binding of [$^{123}$I]FP-CIT to dopamine transporters in Parkinson's disease patients.

Recent studies, performed in rats, have shown that the dopamine transporter density fluctuates during the female estrous cycle (*31*). Also, acute estradiol treatment increased dopamine transporter density in ovariectomized rats (*32*). A similar effect was observed in rats treated with chronic estradiol and/or progesterone (*33*). We studied women (6 controls and 3 Parkinson's disease patients) who were all postmenopausal without estradiol and/or progesterone treatment. It remains to be established whether the analysis of dopamine transporters with

[$^{123}$I]FP-CIT SPECT also is highly reproducible in groups of young women, or women treated with estradiol and/or progesterone. In addition we are not able to confirm whether the reproducibility of the [$^{123}$I]FP-CIT SPECT technique is comparable in men and women controls, since we only studied women controls. Future studies should address these issues since Parkinson's disease affects both men and women.

Recently, the reproducibility of SPECT measurements of benzodiazepine receptor, dopamine $D_2$ receptor and dopamine transporter binding has been reported in healthy control subjects. The test/retest variability of [$^{123}$I]iomazenil and [$^{123}$I]IBF distribution volume ratios ranged from 5%–8% and 4.4%–9.4%, respectively, depending on the scan protocol used (*12,34*). Seibyl et al. (*35*) reported a test/retest variability of the specific to nonspecific striatal [$^{123}$I]β-CIT of approximately 7%, whereas Tiihonen et al. (*36*) reported a reproducibility of their striatal [$^{123}$I]β-CIT ratios in the range of −16%–8%. Although there are major differences in imaging and data analysis as well as part of the neurotransmission system studied, the reproducibility results of these SPECT studies are in good agreement with the results of this study obtained in healthy volunteers. However, one has to keep in mind that the ratios of striatal-to-nonspecific [$^{123}$I]FP-CIT binding do not necessarily reflect a direct relationship with the density of dopamine transporters.

The test/retest reproducibility of dopamine $D_2$ receptor binding and nigrostriatal dopaminergic integrity using [$^{11}$C]raclopride PET and [$^{18}$F]DOPA PET, respectively, has recently been reported in control subjects (*25,27*). The mean variability in the distribution volume ratio of [$^{11}$C]raclopride was 5.2%, whereas the standard deviation within subjects of the [$^{18}$F]DOPA striatal-to-background ratio represents only 3.3% of the mean. Despite the significant differences in methodology between their studies and the present one, and the higher sensitivity of the PET in comparison with the SPECT technique, the results of both imaging techniques are comparable.

In this study, images were analyzed with the ROI technique by an experienced investigator, which resulted in a low intraobserver variability. Measurement of striatal dopamine transporters with [$^{123}$I]FP-CIT SPECT, using the ROI protocol, proved to be highly reproducible and reliable. However, for clinical routine studies, it is desirable to analyze studies without introducing intra- or interindividual variability in the final result. The results of this study show that a newly developed operator-independent, fully automated quantification technique proved to be as reliable as the ROI technique to analyze the content of striatal dopamine transporters with [$^{123}$I]FP-CIT. This technique may be of value in routine clinical studies and be especially useful in longitudinal studies. Prospective studies will focus on the development of this VOI technique to assess the size of the functional defects in the dopaminergic nigrostriatal system in neurodegenerative diseases (*37*).

## CONCLUSION

The results of this study indicate reliable and reproducible results with the ROI, as well as the VOI technique, for the analysis of striatal dopamine transporters with [$^{123}$I]FP-CIT SPECT in healthy control subjects and Parkinson's disease patients. The use of an operator-independent method will be to great advantage in routine clinical studies.

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# Fluorine-18-Fluoro-L-DOPA Dosimetry with Carbidopa Pretreatment

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This article presents dosimetry based on the measurement of fluoro-DOPA activity in major tissues and in the bladder contents in humans after oral pretreatment with 100 mg carbidopa. **Methods:** Bladder activity was measured continuously by external probe and calibrated using complete urine collections. Quantitative dynamic PET scans provided time-activity curves for the major organs. Bladder wall dosimetry was calculated using the methods of *MIRD Pamphlet No. 14*. Effective dose was calculated as described in *ICRP Publication 60*. **Results:** Mean absorbed dose to the bladder wall surface per unit administered activity was 0.150 mGy/MBq (0.556 rad/mCi) with the realistic void schedule used in our studies. The dose was 0.027 mGy/MBq (0.101 rad/mCi) to the kidneys, 0.0197 mGy/MBq (0.0728 rad/mCi) to the pancreas, and 0.0186 mGy/MBq (0.0688 rad/mCi) to the uterus. Absorbed doses to other organs were an order of magnitude or more lower than the bladder, 0.009–0.015 mGy/MBq. The effective dose per unit administered activity was 0.0199 mSv/MBq (0.0735 rem/mCi.) **Conclusion:** Urinary excretion of fluoro-DOPA was altered significantly by pretreatment with carbidopa. In general, any manipulation of tracer metabolism in the body should be expected to produce changes in biodistribution and dosimetry. The largest radiation dose was to the bladder wall, for which our estimate was one-fifth of that from the original report. The methods used reflect realistic urinary physiology and typical use of this tracer. The principles of *MIRD Pamphlet No. 14* should be used in planning studies using tracers excreted in the urine to minimize the absorbed dose.

**Key Words:** fluorine-18-DOPA; fluoro-DOPA PET; bladder dosimetry; medical internal radiation dose

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The original published dosimetry for [$^{18}$F]−6-fluoro-L-3,4-dihydroxy-phenylalanine ($^{18}$F-DOPA, fluoro-DOPA) dates from 1985 (*1*), very early in the use of this tracer for PET imaging of brain dopaminergic systems (*2*). Viewed from more than a decade later, this foundation work has several limitations. First, in the absence of continuous bladder activity data the authors chose to base their calculations on the assumption that all the activity that appeared in the bladder by approximately 4 hr after injection was present instantaneously at the time of the injection. In addition, a relatively large postvoid urine residual value was used (20%.) These calculations, therefore, intentionally represented a very conservative *upper limit* estimate of bladder wall absorbed dose. Second, differential tissue activity estimates are based on data from two dogs, with no corroborating human evidence. Third, these measurements were made before the institution of oral carbidopa pretreatment, which is now a universal adjunct to $^{18}$F-DOPA PET imaging (*3–6*). This drug blocks peripheral aromatic L-amino acid decarboxylase (AAAD); its administration markedly improves imaging by preventing the early decarboxylation of $^{18}$F-DOPA to $^{18}$F-dopamine outside the brain. Since this also causes changes in the time course of $^{18}$F-DOPA metabolism and the relative amounts of the various labeled metabolites, the use of carbidopa has an effect on renal excretion and, therefore, on dosimetry for the bladder and other organs. Fourth, the original dosimetry calculations were based on the International Commission on Radiological Protection (ICRP) *Standard Man* model, which has a static urinary bladder. Over the last two decades methods have been developed for more accurate estimation of absorbed dose from bladder contents, leading to the revision of bladder dose calculations published in *MIRD Pamphlet No. 14* from the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (*7*). Two published articles (*8–9*), a doctoral thesis (*10*) and two abstracts (*11–12*) in recent years have addressed some, but not all, of these concerns.

The original published data demonstrated that the upper limit of absorbed dose from $^{18}$F-DOPA administration was within a tolerable range for human use, but more accurate human absorbed dose estimates are needed for several reasons. First, modern targets (*13*) and syntheses (*14*) have made it possible to produce fluoro-DOPA in amounts not readily obtainable in earlier years; radiation dosimetry has, therefore, become the limiting factor in the dose administered. Second, initial dosimetry estimates allow only small administered doses of fluoro-DOPA (*9,12*), leading to severely count-limited studies. Such noisy data have limited sensitivity to the changes brought about by disease and limit the ability to correlate PET data with clinical parameters of disease progression. Third, as PET evaluations of the nigrostriatal system have progressed and more tracers have become available, it is more common for an experiment to require multiple tracer injections. Many pharmacologic or pathophysiologic experiments require the administration of $^{18}$F-DOPA on two or more occasions, or its use in conjunction with markers of dopamine postsynaptic receptors

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