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Narrow Energy Window on a Large Field CZT Camera Allows 20% Further Time Reduction Compare to 2020 EANM/SNMMI Guidelines for Dopamine Transporter Visual and Semi-Quantitative Imaging

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ABSTRACT

Background: Single photon emission computed tomography (SPECT) imaging of the dopaminergic system with 123I-Ioflupane (IFP, 123I-FP-CIT, DaTSCANTM, General Electric, UK) improves the management of Parkinsonian syndrome patients. According to international recommendations, a minimum of 1,5M counts is required in a standard Anger gamma-camera thus indicating an acquisition time between 30-45 min for an administered activity of 111-185 MBq. Large field cadmium-zinc-telluride (CZT) cameras should allow a substantial reduction of the acquisition time and/or the administered activity with no impact on the image quality. The present study is aimed at evaluating the minimal dose activity time needed to preserve semi-quantitative analysis (185 MBq as reference) evaluating the impact of the acquisition time reduction of 123I-IFP SPECT in a CZT camera on semi-quantitative analysis and its clinical consequences.

Methods: A retrospective analysis of a consecutive series of patients addressed for a 123I-IFP SPECT between September 1, 2016 and April 1, 2017 (n=199) has been conducted. A 30 min list-mode acquisition was performed following 185 MBq IV administration of 123I-IFP. Raw data were then reconstructed in five our series of: 30, 24, 18, 15 and 12 and 15 min. Striatal Specific Binding Ratios binding ratios (SBR) were automatically measured for each series using DaTQUANTTM (GE Healthcare, Little Chalfont, United Kingdom). 123I-IFP SPECT were classified either as normal or pathological. A visual analysis supplemented by semi-quantification results was carried out for 30 and 15 min series by two independent readers.

Results: Mean number of counts for the 30, 24, 18, and 15and12 min acquisitions were respectively 2M (+/- 0.49), 1.63M (+/- 0.42), 1.31M(+/- 0.33) and 1.02M (+/- 0.29) and X M (+/-0. X). SBR correlations were all ≥ 0.97 till 15 min. At 15 min, relative measurement biases of the pathological 123I-IFP SPECT were: 1.6% and -2.9% for the right and the left striata respectively. A significantly different SBR was estimated in only 10 patients (six left, four right). Kappa coefficient between 15and 30 min series were equal to one. At 12 min, measurements biases was

Conclusion: As for the patients with Parkinsonian syndromes, a 123I-IFP-SPECT performed after administration of 185 MBq of 123I-IFP in a CZT camera, permits the reduction of the acquisition time up to 15 min, with the mean number of counts of 1M with no influence on visual nor semi-quantitative analysis. Therefore, it is feasible to reduce the acquisition time in clinical practice using a large field CZT camera when required according to the patient's condition. Alternatively, a reduction of the injected dose as low as 90 MBq for a 30 min acquisition time still maintain the diagnostic power based on visual and semi-quantitative analysis (DatQuant) both on normal and pathological studies.

Introduction

Assessment of dopaminergic pathway by 123I-Ioflupane (123I-IFP) SPECT, improves the diagnosis and clinical management of Parkinsonian syndromes patients [1]. It confirms the presence of Parkinson's or Lewy body diseases in patients with uncertain diagnosis [2,3]. International EANM/SMMI 2020 recommendations based on experts' consensus suggest use of a minimum of 1.5M counts using in a standard double head Anger gamma-camera, indicating a total acquisition time of 30-45 min for a 123I-IFP dose of 111-185 MBq [4]. Interpretation is conducted through a visual analysis, which is supplemented by a semi-quantitative analysis, in order to improve the inter-observer reproducibility [5-7]. Practical issues related to patient's movements, discomfort and dose limitation to avoid radiation exposure led to reduce the acquisition time and/or the administered activity in certain patients. In 2016, The Discovery NM/CT 670 CZT (General Electric Healthcare, Haifa, Israel) gamma-camera was a large field of view camera equipped with pixelated Cadmium Zinc Telluride (CZT) detectors launched onto the market. The improved energy resolution of CZT detectors, combined with the smaller frame head dimensions reducing the distance to the patient, makes it possible to consider the acquisition time reduction without altering image quality. To the best of our knowledge, at present there is no published study evaluating the impact of the acquisition time reduction on the reproducibility of the semi-quantification at 123I-IFP SPECT, neither on Anger nor on CZT camera. Est ce qu'on considere Bailly frontiers la dedans? the present study aims to assess the minimumaximal impact of the acquisition time reduction of 123I-IFP SPECT usingin a CZT camera with optimized parameters (reference 185 MBq dose as reference) which guarantee the diagnostic standard both on visual andon a semi-quantitative analysis on normal and pathological scans and its clinical consequences.

Patients and Methods

The local ethical committee approved this study. IRB en attente.

Patients

A retrospective analysis of a consecutive series of patients addressed for a 123I-IFP SPECT between September 1, 2016 and April 1, 2017 has been conducted. No selection criterion was applied.

Preparation of Patients

To avoid interactions, all medicines that could potentially alter the uptake of 123I-IFP were stopped at least a week before the exam was conducted. All patients were intravenously administered with 185 MBq of 123I-IFP at the bend of the elbow, followed by a flush of saline solution.

Image Acquisition and Reconstruction

The acquisitions were performed three hours after 123I-IFP administration in a double head camera Discovery NM/CT CZT 670 during 30 min and recorded using the list mode. The camera acquisition protocol was set at the "step and the shoot mode" with automatic adaptation of the distance to the patient and a field of view including the whole head. The camera was equipped with a parallel 45mm collimator matched on a matrix of CZT detectors of 2.46 mm. A single asymmetrical energy window 159 keV -5%, +4% was used. Energy window spectrum ranged from 153 to 163 keV whilst reconstruction matrix was set at 128 x 128. A diagnostic CT also used for attenuation correction was also performed (50 mA, 120 kV, 1 mm). Brain trans axial slices were reconstructed, using an iterative algorithm Ordered Subset Expectation Maximization (OSEM: two iterations, ten subsets) and post-filtered (Butterworth: 0.6 cut off, factor 10).

Creation of Series

In order to simulate a reduction of the acquisition time, the list-mode raw data for each patient were truncated by reduction of the acquisition duration for each pair of projections. Subsequently, they were reconstructed and treated under the same condition to create four series of data: 30 min (reference), 24 min, 18 min and 15 and 12 min.

Semi-Quantitative Analysis

Semi-quantitative analysis was conducted using DaTQUANTTM, a semi-automatic semi-quantification software approved by the Food and Drugs Administration (FDA) [8]. After automatic

registration of the reconstructed images with a template derived from MRI and SPECT images from the healthy population, the software automatically determined the following Volume of Interest (VOIs): caudate nucleus, anterior and posterior putamen, striatum and a reference in the occipital posterior region. Striatal binding ratios (SBR) were determined as previously described [9] and compared to the vendor normal database population in the similar age group originating from the PPMI study [8] processed on GE gamma cameras with the same reconstructions parameters. In line with international recommendations, the semi-quantitative analysis was limited to the uptake of both striata [10].

Use of DaTQUANTTM Normal Database with CZT Images

Normal database using CZT images are not yet available. The normal database of DaTQUANTTM is based on PPMI database DaTQUANTTM SPECT coming from various Anger cameras and reconstructed using GE specific parameters (OSEM: two iterations, ten subsets) and post-filtered (Butterworth: 0.6 cut-off, factor 10. This software does not apply correction for the partial volume effect. The attenuation corrected database file use a Chang model (μ=-0.11 cm-1). To validate the use of the normal database of DaTQUANTTM for CZT images, we used an anthropomorphic striatal phantom (RSD, Moedling, Austria), filled with I-123. The 2 striatal compartments were filled with a concentration of 40 kBq/mL and the brain compartment with a concentration of 5 kBq/mL, giving a striatum to background ratio of 8:1. Phantom was acquired on the CZT camera and images were reconstructed using parameters mentioned above. Phantom acquisition was also performed on a camera referred in the ENC-DATPPMI database (Symbia T2, Siemens) using routine clinical parameters: 60 projections of 30s and Flash3DTM software (t, riple energy window 159 keV +/- 87.5%, and two additional scatter energy windows, OSEM 3D) but with. Symbia's images were reconstructed using Siemens SyngoTM software but with the same reconstruction parameters used for the DaTQUANTTM normal database (2 iterations, 10 subsets). SBR values were calculated using DaTQUANTTM for striata, putamens and caudates VOIs. CZT SBR values showed a systematic positive bias compared to the Symbia SBR values (mean bias 0.27, min 0.21, max 0.33), due to the higher spatial resolution of CZT images. However, the amplitude of GE's normal database 95% confidence interval is considerably larger for SBR, around 1.7. We therefore considered that the small difference in SBR between CZT images and Symbia's images validated the use of this normal database for CZT images.

Quantitative Analysis

Quantitative variables are displayed by their mean +/- standard deviation and binary variables by their percentage. Means were compared using Wilcoxon test as no variables assumed a Gaussian distribution. Pearson correlation coefficients and Bland-Altmann plots were generated for each dataset, taking as reference values those obtained for the 30 min series. Relative measurement biases of the SBR were calculated according to either the normal or the pathological condition determined by the expert's interpretation of the 30 min series (CS) and in line with the clinical signs (contralateral to the most affected SBR). Need to define a cut-off for reproducibility (above 5% statistically different SBR)

Visual analysis

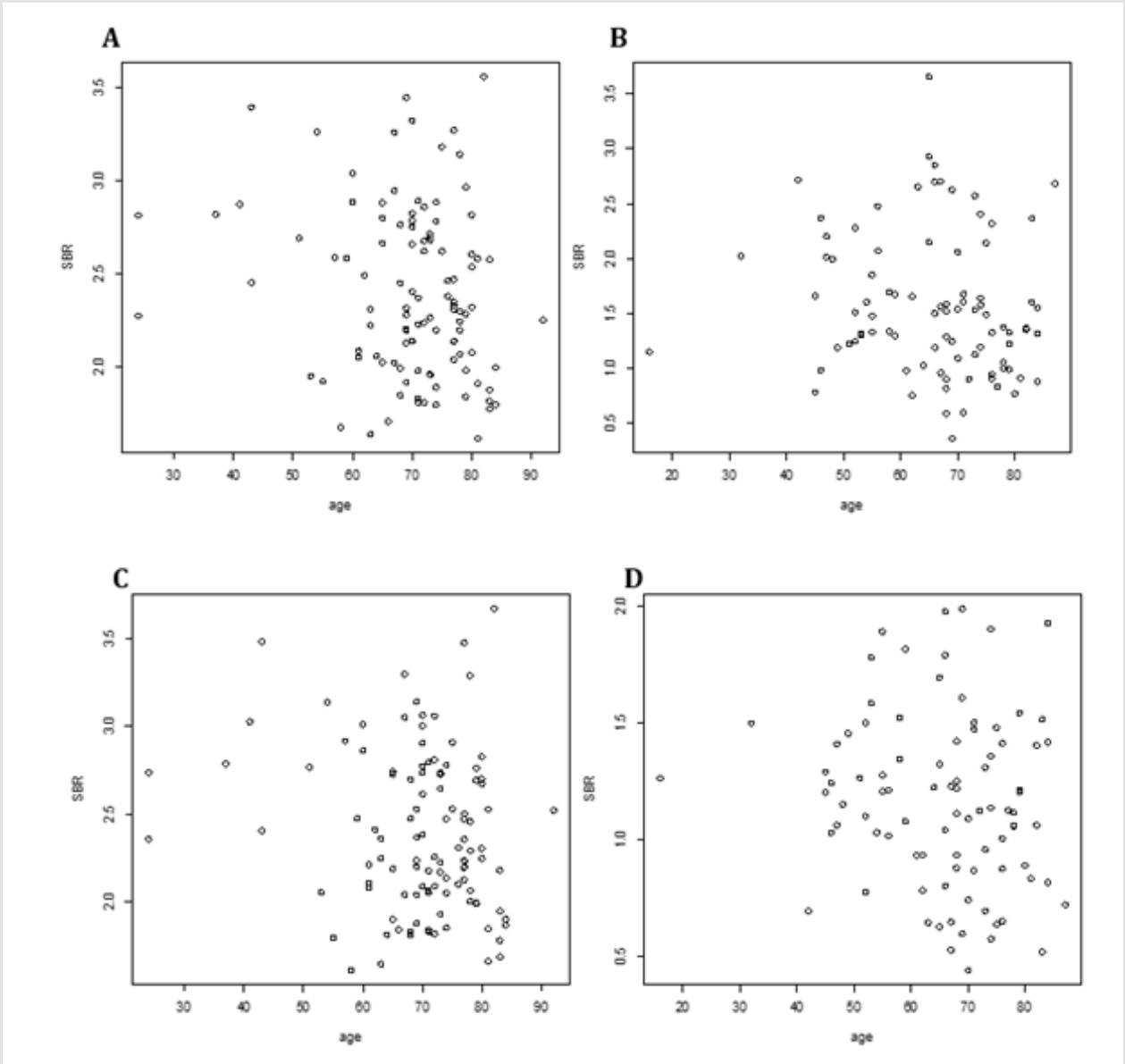
Taking as reference image obtained for the 30 min series, the shortest serie relative to SBR stability was visually compared to after anonymization (by SS), SPECT were classified either as "normal" or "pathologic" through combining a visual analysis performed according to the criteria defined by the Peripheral and Central Nervous Drugs Advisory Committee Meeting to the results of DaTSCANTM by two independent readers (CS, ABS). The two series have been read a month apart in a random order. Both readers were blind of clinical data. Inter and intra-observer reproducibility comparing the 30 and the 15 min series were determined by calculating Kappa coefficients. Statistical significance threshold was set at 5% for all analyses. All statistical analyses were performed using Matlab 7 (The MathWorks, Natick, MA, USA).

Results

199 consecutive patients were retrospectively included. The details of their characteristics can be found in Table 1. Not a single patient was excluded from the analyses. The mean radius of rotation was 13.9 cm (+/- 0.9). Mean numbers of counts for the acquisitions of 30, 24, 18, and 15 and 12 min were respectively 2M (+/- 0.49), 1.63M (+/- 0.42), 1.31M (+/- 0.33), and 1.02M (+/-0.29) and X M (+/- X). Significant statistical differences of mean numbers of counts were not noted between the normal and the pathological 123I-IFP SPECT either at 30 min (p= 0.33) or at 15 min (p= 0.96) what about the 12 min (p=?). The mean radius of rotation was 13.9 cm (+/- 0.9). As for the subjects with normal 123I-IFP SPECT, mean SBR were measured at 2.28 +/- 0.52 at the right and 2.25 +/-0.59 at the left for the reference series. There was no significant statistical difference (p= 0.86) between the two sides. In the pathological subjects, mean SBR were measured at 1.57 +/- 0.64 at the right and at 1.17 +/- 0.38 at the left. Here, the significant statistical difference was noted (p<0.001). The distribution of the reference SBR values from the right and the left striata according to age and 123I-IFP SPECT status as classified by the expert are displayed in the Supplementary Figure 1. Reproducibility analysis of the semi-quantitative results of SBR measured by DATquant is presented in Table 2. For all series, Pearson's correlation coefficients were ≥ 0.97 (p<0.001) For 15-min acquisition time, relative differences

of standard deviations of SBR were 1.42% at the right and 1.44% at the left. For 12-min acquisition time, relative differences of standard deviations of SBR were X % at the right and X % at the left.

SBR Bland-Altman plots can be found in in Figure 1. In comparison to the reference series, the acquisitions reconstructed at 24, 18 and 15 min have a low measurement bias. At 15 min, only 10 patients (5%) (six at the left and four at the right) had a statistically different SBR compared to the reference series (30 min). However, at 12 min, x% patients had statistically different SBR compared to the reference series. Relative measurement bias according to123I-IFP SPECT status as classified by the expert and laterality are shown in Figure 2. In the subjects with normal 123I-IFP SPECT, the maximum measurement bias was -1.5% at the 24 min series for both sides. In the pathological 123I-IFP SPECT, relative measurement biases were measured at the maximum at +1.6% and – 3.9% for the right and the left striatum respectively for the 15 min series. Kappa coefficient of intra-observer reproducibility between the two series; 30 and 15 min, were equal to one for both observers. Kappa coefficient of inter-observer reproducibility was equal to 0.94 for the two series (30 and 15 min). Illustrative images obtained with reduced acquisition time in two subjects with normal and pathological 123I-IFP SPECT are shown in Figure 3.



Supplementary Figure 1: References SBR (30min) of right striata in normal 123I-IFP SPECT (A), pathological 123I-IFP SPECT (B) and of left striata in normal 123I-IFP SPECT (C) and pathological 123I-IFP SPECT as a function of age.

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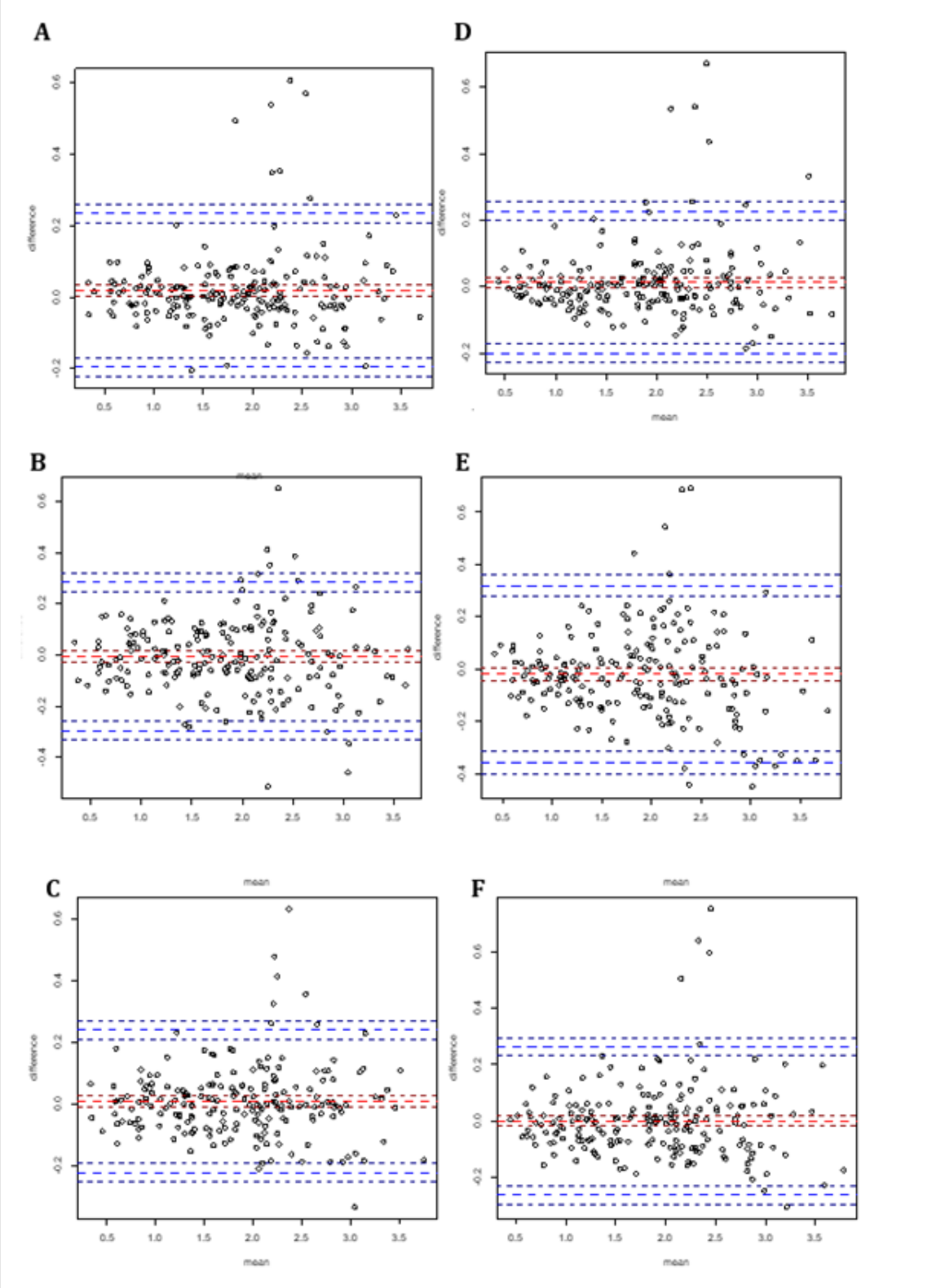

Note: SBR Bland-Altman plots for the right striatum at 24 min (A), 18 min (B), 15 min(C) 12min(D) and for the left striatum at 24min (E), 18min (F), 15min(G), 12min(H)

Figure 1: SBR Bland-Altman plots.

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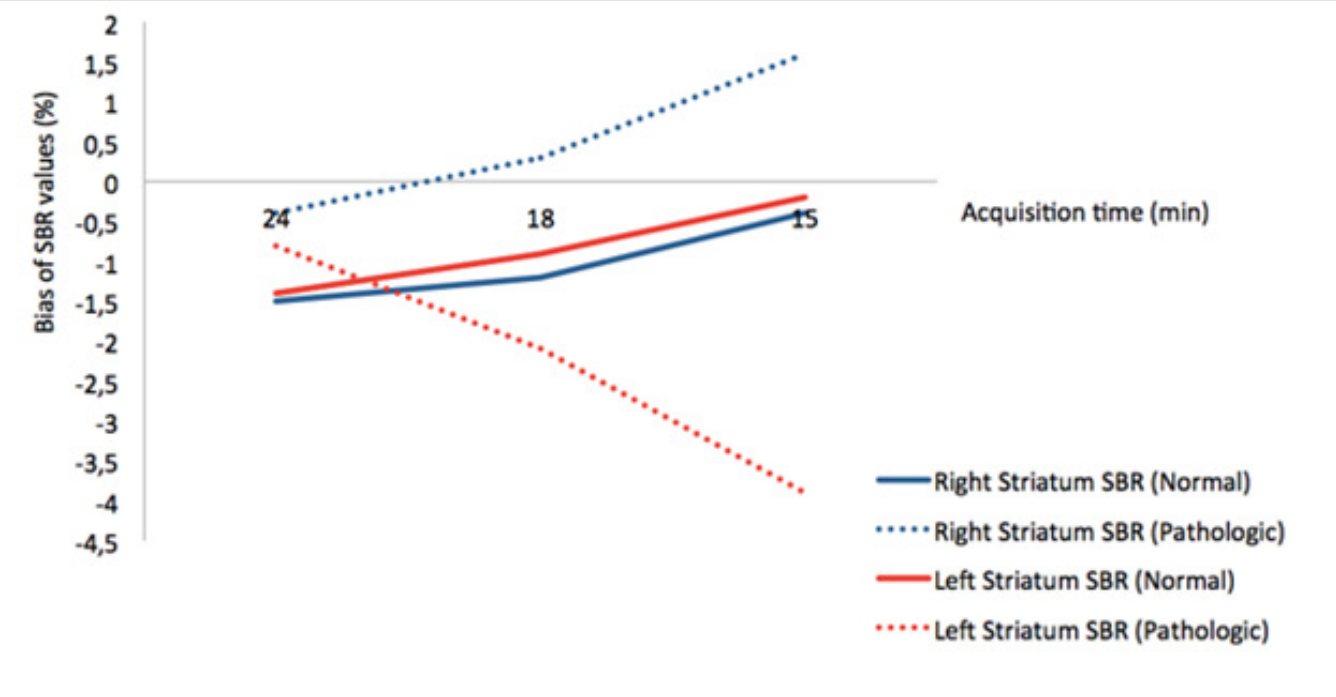

Figure 2: Relative measurement biases as function of the acquisition time according to 123I-IFP SPECT status as classified by the expert and laterality.

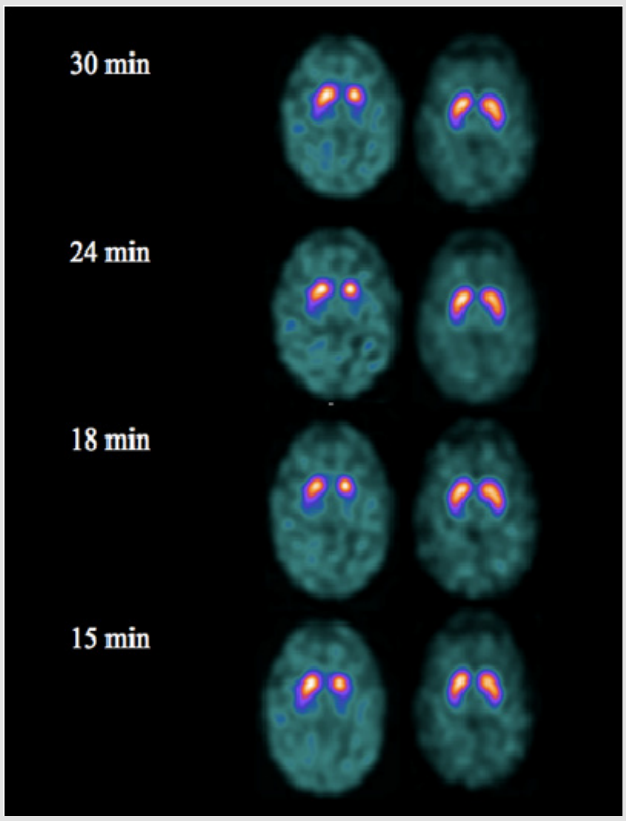

Figure 3: Examples of 123I-IFP obtained with the reduction of acquisition time in a pathological subject (left) and in a normal subject (right).

Table 1.

Population characteristics	
Age (years)	67.9 (+/- 12.2)*
Sex	
Female	79 (39.7)†
Male	120 (60.3)†
Indication	
Essential Tremor versus Parkinson disease	105 (52.8%)†
Drug induced tremor versus Parkinson disease	39 (19.6%)†
Lewy body disease versus Alzheimer's disease	34 (17%)†
Other	21 (10.6%)†

Note: *+/- standard deviation, † % of entier population

Table 2: Reproducibility of SBR.

SBR†		Pearson's correlation coefficient	Absolute difference of standard-deviations*	Relative difference of standard-deviations (%)**
Right striatum				
30 min	1.85 +/- 0.75	Reference	Reference	Reference
24 min	1.85 +/- 0.74	0.98	1.06	1.41
18 min	1.86 +/- 0.75	0.98	1.06	1.41
15 min	1.86 +/- 0.76	0.98	1.07	1.42
12 min				
Left striatum				
30 min	1.87 +/-0.75	Reference	Reference	Reference
24 min	1.88 +/- 0.74	0.98	1.05	1.40
18 min	1.87 +/- 0.75	0.98	1.06	1.41
15 min	1.89 +/- 0.77	0.97	1.07	1.44
12 min				

Note: *Difference of standard-deviations in absolute value, ** Difference of standard-deviations in relative value (%) † Striatal Binding ratio (mean +/- standard-deviation)

Discussion

Taking a 185 MBq administered dose as reference and for both the number of mean counts is hereby reduced until 33% in comparison to international recommendations (SNMMI). On the other hand, as for the normal and or pathological 123I-IFP SPECT studies, we have demonstrated that 15 min the acquisition time is the fastest scan clinical protocol using our experimental parameters of 15 min is sufficient necessary but for 123I-IFP SPECT in clinical practice. The relative measurement bias of SBR was significantly low, with the maximum of -3.9% at the left striatum for the pathological scans contrary to acquisition time of 12 min where relative measurement bias of SBR was not negligeable (XX) This reduction of the acquisition time while keeping the visual diagnostic power of the results could be explained by the optimization of acquisition and reconstruction parameters permitting to take advantage of higher quality of contrast resolution spatial and energy resolution of the imaging system. When contrast spatial resolution is improved, the total number of counts can be decreased without alteration of the signal-to-noise ratio [11] The optimization of spatial resolution of the system allowed us to maintain a sufficient contrast, thus allowing stable semi-quantification results. Spatial resolution of the imaging system was optimized by limiting an average radius of rotation as low as possible and by using a collimator of equivalent performance to the latest generation high-resolution collimator of the conventional gamma-camera. on account of the smaller frame of the heads of detection allowing closer proximity to the patient head and an automatic body contouring system, the mean radius was limited to 13.9cm and stable.

We selected a window of energy [153-163keV], narrower than the window recommended by the SNMMI [143-175keV], for the conventional gamma-cameras. This allowed the better discrimination of contributing photons to the image thus leading

to improved contrast signal-to-noise ratio [12,13]. The upper energy window width was restricted to 4 keV in order to limit the influence of the high-energy scattered photons of 123iodine. Indeed, the high-energy scattered photons have high detection efficiency making their relative contribution to the detected signal critical when using low-energy high-resolution collimator [14]. The energy window was enlarged to 6 keV towards the low energies to avoid the exclusion of incompletely collected primary photons. Indeed, spectra of CZT detectors exhibit a low energy "tailing". During the interaction of the primary photons with the CZT crystal, there is a non-zero recombination of the charge carriers leading to the trapping of some charges and resulting in an incomplete charge collection [15]. Moreover, the "tailing" of CZT spectrum induces an overestimation of the scattered when conventional methods of the double or the triple energy window are used [16,17]. In the present study, scattered and attenuation corrections were performed using a low-dose CT [18] This study has certain limitations. The patients with pathological 123I-IFP SPECT exhibit higher relative measurement biases than the patients with normal 123I-IFP SPECT. Some of them correspond to the outliers of the Bland-Altmann plots. The patients displayed decreased striatal uptake related to their severe dopaminergic deficit. In addition, the patients with pathological 123I-IFP SPECT have a higher SBR variability of measurement on the left than on the right. Six patients on the left and four patients on the right have exhibited significantly different measurements of SBR for the 15 min series. Of the selected population, the pathological patients had a significantly lower SBR on the left striatum than on the right striatum. This low signal-to-noise ratio may have led to greater fluctuations in ROI placement, particularly for the left striata. However, this did not lead to clinical consequences. The reduction of acquisition time to 15 min did not change the final diagnosis of a single patient [12].

The interpretation of 123I-IFP SPECT at 30 and 15 min only comprised a binary classification: either normal or pathological. As no other analysis criterion was included, this may have overestimated the inter-observer reproducibility. In order to avoid memory bias, the two series have been read separately a month apart. The minimal acceptable number of counts has not been studied. We only assessed the influence of acquisition time reduction through the simulation of three series (24, 18 and 15 min). Further studies need to be conducted to determine the minimal acceptable number of counts for CZT cameras. Although its impact is yet not fully known, involuntary head movements during 123I-IFP SPECT acquisition [19] are frequent among these patients. The reduction of the acquisition time down to 15 mins could contribute to reducing this problem and may improve the comfort of the patients, in elderly patients. For young patients, an activity reduction may be more appropriate than duration reduction, to limit the exposure to ionizing radiation. Our results cannot be extrapolated to conventional gamma-cameras. Further studies assessing the impact of counts reduction would be necessary for these cameras.

Conclusion

For patients with parkinsonian syndromes, a 123I-IFP-SPECT performed after administration of 185 MBq of 123I-IFP using a large field CZT camera, permits the reduction of the acquisition time down to 15 min, with a mean number of counts of 1M without modification of the visual nor the semi-quantitative analysis. This is a significant advantage when faced with specific clinical conditions such as agitated patients or young adults (dose reduction).

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