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EDITORIAL

[18F]FDOPA positron emission tomography for cardiac innervation imaging: a new way or a dead-end street?

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A brief introduction to [18F]FDOPA PET and its clinical use

L-tyrosine is an amino acid converted to dihydroxyphenylalanine (L-DOPA) and then to dopamine (synthesized within nerve cells) in a two-step process. The first step is catalyzed by tyrosine hydroxylase whereas the second step is catalyzed by L-DOPA decarboxylase. In dopaminergic neurons that release dopamine as a neurotransmitter, dopamine is stored in presynaptic nerve terminals vesicles through the vesicular monoamine transporter while the dopamine reuptake transporter (DAT) mediates dopamine reuptake from the synapse [1].

6-[18F]Fluoro-L-DOPA ([18F]FDOPA) is a radiolabeled analog of L-DOPA used to evaluate the central dopaminergic function of presynaptic neurons through positron emission tomography (PET) [1, 2]. [18F]FDOPA uptake on PET reflects L-DOPA transport into the neurons, L-DOPA decarboxylation, and dopamine storage capacity [1]. This radiopharmaceutical is converted to 6-[18F]fluorodopamine ([18F]FDA) by L-DOPA decarboxylase and retained in the striatum. [18F]FDA can be O-methylated by catechol-O-methyltransferase (COMT) to 3-O-methyl-6-[18F]fluoro-L-DOPA (3-OMFD), which is uniformly distributed throughout the brain. [18F]FDA is also metabolized via monoamine oxidase to yield [18F]6-fluoro-3,4-dihydroxyphenylacetic acid (FDOPAC) and subsequently by COMT to yield [18F]6-fluorochomovanillic acid (FHVA). L-DOPA decarboxylase and COMT are also present in peripheral tissues [1].

Beyond the striatum, variable [18F]FDOPA uptake can be seen in the pancreas, adrenal glands, and liver. No significant or only mild [18F]FDOPA uptake is usually noted in the bowel. The gallbladder and biliary tract, kidneys, and urinary bladder are visualized by [18F]DOPA PET as excretion organs [2].

In clinical studies, L-DOPA decarboxylase is commonly inhibited with carbidopa. Carbidopa pretreatment improves imaging of the striatum by preventing early decarboxylation of [18F]FDOPA to [18F]FDA outside the brain. This strategy increases striatal [18F]FDOPA uptake by increasing [18F]FDOPA plasma levels and decreasing its renal excretion [1].

Loss of dopaminergic nigrostriatal neurons causes parkinsonism. Brain [18F]FDOPA PET can diagnose presynaptic dopaminergic deficits in early phases of nigrostriatal degeneration, characterized by reduced radiopharmaceutical uptake in the striatum, with excellent sensitivity and specificity [3].

Beyond the early diagnosis of nigrostriatal degeneration, [18F]FDOPA PET is also used in clinical practice as a whole-body imaging method to evaluate neuroendocrine tumors (NETs) characterized by increased uptake, decarboxylation, and storage of amine precursors, with good diagnostic performance for depicting intestinal NETs, paragangliomas, neuroblastoma and medullary thyroid carcinoma [4]. [18F]FDOPA PET has also high sensitivity and specificity in differentiating between the focal and diffuse form of

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congenital hyperinsulinism and in localizing the focal form of congenital hyperinsulinism [5]. Lastly, brain [^{18}F]FDOPA PET has also been proposed as a useful method for imaging brain tumors because [^{18}F]FDOPA is transported across the blood–brain barrier by amino acid transporters that are overexpressed in brain tumors [6, 7].

[^{18}F]FDOPA PET for cardiac innervation imaging

Several nuclear medicine imaging modalities have been used to evaluate cardiac sympathetic function using single-photon emission computed tomography (SPECT) or PET [8, 9]. PET offers several advantages over SPECT including a better spatial resolution, a smaller amount of injected radioactivity, and the possibility of measuring radioactivity in tissues in absolute terms and through time-activity curves [8, 9]. Injected cardiac sympathetic neuroimaging agents exit the bloodstream almost instantly and are rapidly taken up by sympathetic nerves allowing the evaluation of cardiac sympathetic function through the measurement of myocardial tracer uptake [8, 9].

To date, most cardiac sympathetic neuroimaging studies in research and clinical routine were performed using [^{123}I] metaiodobenzylguanidine ([^{123}I]MIBG), a norepinephrine analog, for SPECT [8, 10, 11]. Cardiac PET is conducted only in research settings to evaluate sympathetic innervation [9]. [^{18}F]FDA, a catecholamine that is avidly taken up by sympathetic nerves via the cell membrane norepinephrine transporter, is an in vivo biomarker able to identify and quantify myocardial noradrenergic deficiency through PET imaging [8]. Impaired cardiac sympathetic innervation by SPECT or PET is an established biomarker in Lewy body diseases and several cardiac diseases characterized by cardiac sympathetic abnormalities [8, 9].

Since [^{18}F]FDOPA is converted to [^{18}F]FDA by L-DOPA decarboxylase which is expressed in cardiac sympathetic nerves, some authors have suggested using [^{18}F]FDOPA PET imaging to evaluate cardiac sympathetic innervation [12–14]. The main findings of these studies are briefly described in Table 1.

In this issue of *Clinical Autonomic Research,* Goldstein and Holmes performed an intra-individual comparison of cardiac innervation imaging through cardiac [^{18}F]FDOPA PET and [^{18}F]FDA PET in 20 subjects (including individuals with neurogenic orthostatic hypotension or parkinsonism and control subjects) [15]. This is the first study comparing cardiac [^{18}F]FDOPA PET with a validated cardiac sympathetic innervation imaging method ([^{18}F]FDA PET) in the same subjects. The main finding of the study by Goldstein et al. was that cardiac [^{18}F]FDOPA-derived radioactivity was unrelated to [^{18}F]FDA-derived radioactivity [15]. There

Table 1 Published studies about [^{18}F]FDOPA PET as cardiac sympathetic neuroimaging method.

Authors	Year	Imaging comparison for [^{18}F]FDOPA PET	Subjects evaluated	Number of patients	Main findings
Burger et al. [12]	2018	None	Patients with known or suspected neuroendocrine tumor	133	Cardiac [^{18}F]FDOPA uptake was significantly higher in women as compared to men. This sex-difference was most pronounced in the apical region of the left ventricle and in individuals > 55 years of age. No age-dependent changes of cardiac [^{18}F]FDOPA uptake were observed in men or in the right ventricular region
Kuten et al. [13]	2020	None	Patients with suspicious Parkinson's disease	76	Quantification of cardiac [^{18}F]FDOPA uptake may be able to differentiate between patients with and without Parkinson's disease
Goyal et al. [14]	2022	None	Patients with autonomic dysfunction and control subjects	50	Significantly reduced [^{18}F]FDOPA uptake is seen in the myocardium of Parkinson's disease patients with sympathetic dysfunction
Goldstein and Holmes [15]	2022	[^{18}F]FDA PET	Patients with neurogenic orthostatic hypotension or parkinsonism or control subjects	20	Compared to a validated cardiac sympathetic neuroimaging method ([^{18}F]FDA PET), [^{18}F]FDOPA PET does not seem to be a valid method to assess cardiac sympathetic function

was substantial [^{18}F]FDOPA-derived radioactivity in the left ventricular chamber and descending aorta (even at a delayed acquisition time of PET) creating difficulty in distinguishing [^{18}F]FDOPA-derived radioactivity in the myocardium from that in the chamber in contrast to [^{18}F]FDA PET [15]. The relatively high concentration of [^{18}F]FDOPA compared to [^{18}F]FDA in the left ventricular chamber may have been the result of uptake and retention of [^{18}]FDOPA in non-neuronal cells. Furthermore, the [^{18}F]FDOPA uptake in other organs beyond the striatum suggests a substantial non-neuronal uptake and metabolism of [^{18}F]FDOPA [15]. In parkinsonian patients, striatal [^{18}F]FDOPA PET did not correlate with cardiac [^{18}F]FDOPA or [^{18}F]FDA PET findings. This finding is in line with previous studies demonstrating independence between nigrostriatal neuronal loss and cardiac sympathetic abnormalities across individuals with Lewy body diseases [15].

The sample size in the study by Goldstein and Holmes was relatively small compared to previous studies [13, 14]. Thus we cannot exclude that a low statistical power may have contributed to the results. Nevertheless, the present study demonstrates that [^{18}F]FDA is better than [^{18}F]FDOPA for evaluating cardiac sympathetic innervation through PET imaging. Despite encouraging results from preliminary feasibility studies using cardiac [^{18}F]FDOPA PET [13, 14], the possible usefulness of [^{18}F]FDOPA PET to assess cardiac sympathetic innervation is not validated. Research should focus on PET tracers other than [^{18}F]FDOPA for cardiac sympathetic imaging [9].

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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