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Positron Emission Tomographic Imaging of Cardiac Sympathetic Innervation Using 6-[^{18}F]Fluorodopamine: Initial Findings in Humans

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Objectives. **This study evaluated the safety, efficacy and validity of 6-[^{18}F]fluorodopamine positron emission tomographic scanning of cardiac sympathetic innervation and function in humans.**

Methods. **Positron emission tomographic (PET) scans, arterial blood and urine were obtained after a 3-min intravenous infusion of 6-[^{18}F]fluorodopamine (1 to 4 mCi, 188 to 809 mCi/mmol) in healthy volunteers, with or without pretreatment with oral desipramine to inhibit neuronal uptake of catecholamines.**

Results. **6-[^{18}F]Fluorodopamine PET scanning visualized the left ventricular myocardium. Blood pressure increased slightly and transiently. The estimated absorbed radiation dose to the main target organ, the wall of the urinary bladder, was 0.8 to 1.0 rad/mCi of injected 6-[^{18}F]fluorodopamine. By 24 h after the injection, the main 6F-compound in urine was 6F-vanillylmandelic acid, a metabolite of 6F-norepinephrine. Desipramine attenuated accumulation of myocardial 6-[^{18}F]fluorodopamine–derived radioactivity and plasma 6F-dihydroxyphenylacetic acid.**

Conclusions. **6-[^{18}F]Fluorodopamine produces negligible hemodynamic effects and acceptable radiation exposure at doses that visualize the left ventricular myocardium. Sympathetic nerves take up 6-[^{18}F]fluorodopamine, which is translocated from the axoplasm into storage vesicles, where is it beta-hydroxylated to the fluorinated analogue of the sympathetic neurotransmitter norepinephrine. Therefore, the basis for visualization of myocardium after 6-[^{18}F]fluorodopamine injection in humans is radiolabeling by 6-[^{18}F]fluorodopamine and 6-[^{18}F]fluoronorepinephrine of vesicles in sympathetic terminals. 6-[^{18}F]Fluorodopamine PET scanning provides a novel means for assessing sympathetic innervation and function noninvasively in the human heart.**

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6-[^{18}F]Fluorodopamine is a positron-emitting analogue of dopamine. We recently reported a method for visualizing cardiac sympathetic innervation in vivo using positron emission tomography (PET) after intravenous injection of 6-[^{18}F]fluorodopamine in dogs (1). The present report summarizes the results of administering 6-[^{18}F]fluorodopamine in humans, focusing on issues of safety, efficacy and validity, not only for visualizing sites of sympathetic innervation but also for assessing aspects of sympathoneural function noninvasively.

The neuronal uptake and intraneuronal disposition of fluorocatecholamines are qualitatively similar to those of endogenous catecholamines (1–5). Preclinical studies using desipramine to block uptake of 6-[^{18}F]fluorodopamine in myocardial sympathetic nerve terminals, reserpine to block transport of 6-[^{18}F]fluorodopamine from the axonal cytoplasm to storage vesicles, and 6-hydroxydopamine to destroy sympathetic nerve terminals have provided pharmacologic evidence that in the heart, 6-[^{18}F]fluorodopamine is taken up rapidly in sympathetic nerve terminals and transported into axoplasmic vesicles, where the 6-[^{18}F]fluorodopamine is converted to 6-[^{18}F]fluoronorepinephrine. The 6-[^{18}F]fluoronorepinephrine is stored in the vesicles, and as blood radioactivity declines, the innervated myocardium is delineated. During sympathetic stimulation, 6F-norepinephrine appears to be released from sympathetic nerve terminals in a manner similar to that of [^{3}H]norepinephrine (5).

The similarity between the disposition of 6-[^{18}F]fluorodopamine and endogenous catecholamines suggests the possibility that assessment of myocardial radioactivity-time curves (time-activity curves) after 6-[^{18}F]fluorodopamine administration may indicate aspects of cardiac sympathoneural function. This would constitute an important advantage over other sympathoneural imaging agents, such as radioiodinated *meta*-iodobenzylguanidine, 6-[^{18}F]fluorometaraminol and [^{11}C]hydroxyephedrine (6–9), which are not substrates for the catecholamine-metabolizing

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enzymes monoamine oxidase and catechol-*O*-methyltransferase.

The present study addressed the following questions: 1) Can 6-[^{18}F]fluorodopamine be used to visualize the sympathetic innervation of the myocardium in humans? 2) At doses required to visualize the myocardial innervation adequately in humans, what are the hemodynamic effects of 6-[^{18}F]fluorodopamine, and what is the estimated radiation dose to the main target organ, the wall of the urinary bladder (10)? 3) What is the fate of circulating 6-[^{18}F]fluorodopamine, and how does this relate to the use of 6-[^{18}F]fluorodopamine as a sympathoneural imaging agent? 4) What are the effects of treatment with desipramine, a drug that blocks neuronal uptake of catecholamines (uptake 1) and decreases sympathetic nerve activity (11) on the PET and neurochemical results after injection of 6-[^{18}F]fluorodopamine?

Methods

Subjects and experimental sequence. Fifteen PET scanning sessions were conducted in 13 healthy male volunteers (age 24 to 69 years, weight 70 to 100 kg) with their written informed consent. Screening medical history, physical examination, electrocardiogram (ECG) and blood and urine tests were normal. The study protocol was approved by the Institute Clinical Research Subpanels of the National Institute of Neurological Disorders and Stroke, National Heart, Lung, and Blood Institute, National Institutes of Health PET Scientific Review and Radiation Safety Committees. 6-[^{18}F]Fluorodopamine was administered to humans under Investigational New Drug Application No. 33,866.

The subjects were studied after having fasted overnight and having refrained from cigarette smoking, caffeinated or decaffeinated coffee and alcohol for at least 12 h. The subjects were allowed to eat a light breakfast (such as toast and orange juice or cereal and skim milk) before arriving in the PET area of the National Institutes of Health Clinical Center at ~10:30 AM.

An antecubital venous catheter was inserted for administration of 6-[^{18}F]fluorodopamine. Electrocardiographic leads were attached. The subject was then positioned in a Posicam body scanner (Positron Corporation), with the subject's thorax in the gantry. The Posicam body scanner produces 21 overlapping planes (12.5-mm thickness, 5.1-mm apart, pixel volume 1.7 mm^3, transverse spatial resolution 6.8 mm). A transmission scan using a rotating pin source was obtained to confirm the location of the heart before administration of 6-[^{18}F]fluorodopamine and to correct the emission scans for photon attenuation.

For continuous monitoring of blood pressure and for drawing blood samples, a brachial or radial artery catheter was inserted percutaneously after anesthesia of the overlying skin using lidocaine. The catheter was flushed occasionally with a dilute heparin solution.

6-[^{18}F]Fluorodopamine passed quality control testing (chemical and radiochemical purity at least 90%) before being administered (12). It was dissolved in ~10 ml of normal saline solution and infused by syringe pump at a constant rate for 3 min (1 min in one subject), at doses of 1 (one study), 1.5 (one study), 2 (two studies), 3 (two studies) and 4 (nine studies) mCi.

Continuous PET scanning began at the beginning of drug administration and ended 2.5 to 3 h later. For purposes of data analysis, scanning intervals ranged from 5 to 30 min. The data acquisition was not gated to the ECG.

Arterial blood was obtained just before drug administration and at 0.25, 0.5, 0.75, 1, 2, 3, 3.5, 4, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after drug administration. The samples at 0.25, 0.5, 0.75, 2 and 3.5 min were 1 ml, the baseline sample was 10 ml and the other samples were 5 ml. The total amount of blood drawn was ~100 ml. In one subject, a Foley catheter was placed for continuous collection of urine during the PET scanning.

Five subjects underwent 6-[^{18}F]fluorodopamine PET scanning beginning ~2 h after taking desipramine, 125 mg orally. At 1.5 to 2 h during the PET scanning, a supplemental 50-mg dose of desipramine was given.

Synthesis of 6-[^{18}F]fluorodopamine. For most studies, 6-[^{18}F]fluorodopamine was synthesized from 6-[^{18}F]fluorodopa by enzymatic decarboxylation using an L-amino acid decarboxylase, as described previously (1,12). To decrease the synthesis time and increase the radiochemical purity, yield and specific activity of 6-[^{18}F]fluorodopamine, a direct synthesis method was devised and used in the last five testing sessions. The specific activities of the 6-[^{18}F]fluorodopamine ranged from 188 to 809 mCi/mmol at the time of injection. In both procedures, <1 in 10^7 molecules of 6F-dopamine carries fluorine-18, the remainder carrying stable fluorine-19.

The direct synthesis used a modification of the high yield radiofluorodemercuration method previously used in the synthesis of 6-[^{18}F]fluorodopa (13). At the end of bombardment, [^{18}F]F_2 (200 μmol) in the target chamber was passed through a KOAc/HOAc column (0.6 × 10 cm, 2.5 g, 50 ml/min). The effluent was directed to a reaction vessel containing *N*-(trifluoroacetyl)-3,4-dimethoxy-6-trifluoroacetoxymercuro-beta-phenethylamine (110 mg, 200 μmol, synthesized in the PET Department, National Institutes of Health) dissolved in 3 ml of acetonitrile and diluted to 11 ml with chloroform. The mixture stood for 5 min before transfer through a silica-packed column (6-mm internal diameter × 110-mm length, 4.44 g). The reaction vessel and column were washed with 10 ml of chloroform. The solvent was evaporated under vacuum, with heat supplied by a thermostatically controlled oil bath (130 ± 10°C). For hydrolysis, hydroiodic acid (47% stabilized with 0.04% hypophosphoric acid, 1.6 ml) was added and refluxed at 130 ± 10°C for 10 min. The hydroiodic acid was then removed under vacuum and heat using the oil bath and the residue dissolved in 2 ml of high performance liquid chromatographic (HPLC) mobile phase (0.1 mol/liter of monosodium phosphate, 0.01% ascorbic acid, pH 3). The solution

was loaded in the 5-ml injection loop of an HPLC apparatus connected to a semipreparative column (YMC AQ-313, reverse phase, 5 μm, 10 × 250 mm, YMC Inc., flow rate 5 ml/min). The fraction eluting from the HPLC column at a retention time corresponding to 6-fluorodopamine was collected and transferred through a 0.22-μm filter to a 20-ml amber sterile vial with a Teflon-faced red rubber stopper and aluminum crimp containing 350 ± 50 μl of sterile 0.1-mol/liter dibasic sodium phosphate buffer, pH 10. Each batch passed quality control testing for pH, chemical and radiochemical purity and levels of mercury immediately at the end of synthesis, before the radiopharmaceutical was dispensed. Using the direct synthesis method, radiochemical purity averaged ~98%, and the specific activity of 6-[^{18}F]fluorodopamine was ~800 mCi/mmol at the time of injection.

Levels of radioactivity, 6-[^{18}F]fluorodopamine and metabolites. Aliquots of whole arterial blood and arterial plasma (obtained after centrifugation at room temperature for 5 min) were assayed directly for concentrations of total radioactivity. Arterial blood samples, for subsequent assays of 6F-compounds after complete radioactive decay, were collected in chilled, evacuated, heparinized glass tubes and placed immediately on ice. At the end of the scanning session, the plasma was separated by refrigerated centrifugation, transferred to plastic cryotubes and stored at −70°C until assayed within 1 month. Arterial plasma concentrations of free and sulfate-conjugated 6F-dopamine and metabolites were assayed by liquid chromatography with electrochemical detection after addition of internal standards (dihydroxybenzylamine or 2-fluorodopamine) and batch alumina extraction (14). For assays of sulfate-conjugated compounds, the internal standard was added to the alumina supernate, and the mixture was incubated with 500 μl of sulfatase (14.5 U/ml, 5 U/mg of protein, Sigma Corp., diluted 1:100 in 1.0 mol/liter of Tris per 20 g/liter of ethylenediaminetetraacetic acid buffer, pH 8.6) at 37°C for 20 min. The alumina extraction step was repeated, and 90 μl of the alumina eluate was injected into the liquid chromatographic apparatus. For assays of plasma levels of *O*-methylated 6F-compounds (n = 3), 80 μl of the alumina supernate was injected into a liquid chromatographic apparatus coupled to a multichannel electrode array detector (ESA) using a gradient (6% to 95% acetonitrile) elution protocol. The detection limits were ~0.5 pmol/ml for catechols and ~50 pmol/ml for *O*-methylated metabolites using the detector.

The first void of urine after the PET scanning session was collected in a preweighed urinal, and the volume and time were recorded. Three 300-μl aliquots were assayed for radioactivity. Another aliquot was acidified with 6N hydrochloric acid and stored at −70°C until assayed for unlabeled fluorinated metabolites of 6F-dopamine and 6F-norepinephrine within ~1 month. Each subsequent void until 24 h after injection of 6-[^{18}F]fluorodopamine was transferred into a separate, plastic, preweighed receptacle containing ~30 ml of 6N hydrochloric acid, and the time was recorded.

For assays of free and sulfate-conjugated catechols in urine, 25 μl of freshly thawed urine was assayed with or without deconjugation as described earlier for plasma. For measurements of free (unconjugated) O-methylated metabolites (including 6F-homovanillic acid, 6F-methoxyhydroxyphenylglycol and 6F-vanillylmandelic acid), freshly thawed urine (n = 4) was diluted ~1:4 (depending on the total volume), and 80 μl was injected directly into a liquid chromatographic apparatus connected to the multichannel electrode array detector, using the same gradient (6% to 95% acetonitrile) elution protocol as for plasma. For assays of sulfate-conjugated O-methylated compounds in urine, 100 μl of urine was added to 400 μl of sulfatase (diluted 1:100 in a 20:80 ratio mixture of 0.04 mol/liter of phosphoric acid and 0.2 mol/liter of acetic acid) and incubated at 37°C for 20 min before injection of 80 μl into the liquid chromatographic system. Concentrations of the compounds of interest were calculated by comparison with directly injected standards. Incubation of free (unconjugated) standards, in aqueous solution or in plasma, with sulfatase did not affect the peak height of the standards.

Data analysis. Cardiac PET images were analyzed as described previously (1). Circular regions of interest with diameters ~one half the width of the ventricular wall were defined using a composite of the images for a single plane in each subject. The radioactivity concentrations for two regions of interest each in the left ventricular free wall and septum were averaged.

For constructing time-activity curves, the logs of the concentrations of radioactivity (adjusted for the dose/kg body weight, i.e., in units of nCi-kg/ml-mCi) in left ventricular myocardium and in arterial blood were expressed as a function of time after injection of the tracer. The specific activity of 6-[^{18}F]fluorodopamine at the time of injection and the assayed plasma concentrations of 6-[^{18}F]fluorodopamine were used for estimating the proportions of the total plasma radioactivity that were due to 6-[^{18}F]fluorodopamine and its metabolites.

Monoexponential, biexponential and triexponential curve fitting was used to describe the empiric relations between radioactivity concentrations (in myocardium, blood and plasma) and time, using a "peeling" approach as follows. The monoexponential line of best fit (CricketGraph, Cricket Software) was determined for the averaged data during the late phase between 60 and 180 min after injection of 6-[^{18}F]fluorodopamine. From the y intercept value and slope, estimated values were obtained for the period between the peak concentration after the 6-[^{18}F]fluorodopamine injection (at 7.5 min for myocardium and 3 min for blood and plasma) and ~40 min later. The difference between the estimated and empiric values was graphed, and the monoexponential line of best fit for this early phase was determined. From the equations for the two lines, biexponential curves were generated and compared visually with the empiric data. For myocardial radioactivity, biexponential curve fitting described the empiric results very well. For blood and plasma, however, a third

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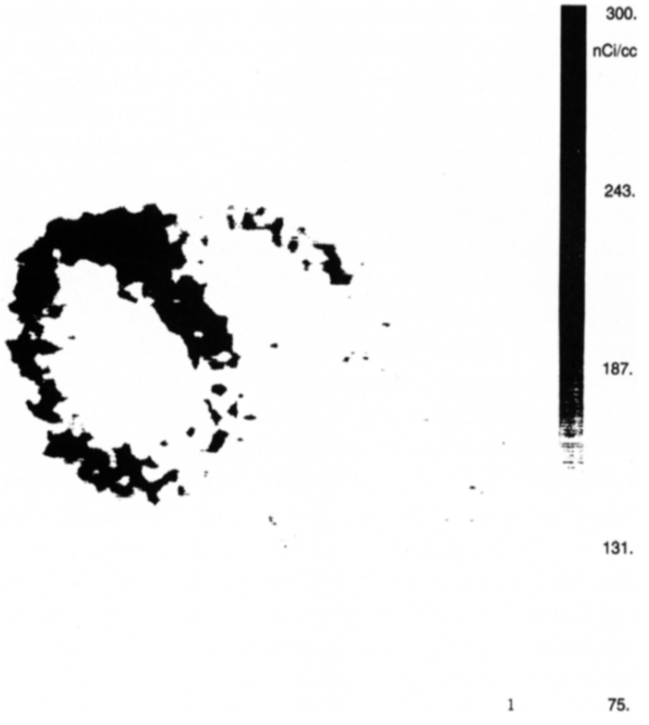

Figure 1. Thoracic positron emission tomographic scan after 6-[^{18}F]fluorodopamine administration in a human subject. Shown is a time-averaged composite image for the interval from 5 to 180 min after intravenous injection of 4.0 mCi of the tracer. The numbers at right have been retouched.

term (triexponential curve of best fit) was required for the period between 10 and 45 min after initation of the 6-[^{18}F]fluorodopamine injection, and the monoexponential line of best fit for this period was determined as previously described.

Data are expressed as mean value ± SEM. For statistical comparisons between untreated and desipramine-treated groups, for each subject biexponential curve fitting was conducted on the myocardial PET data. The y intercepts and slopes of the lines of best fit in the two groups were compared by independent means *t* tests. Tissue radioactivity–drug dose relations were evaluated by calculating linear correlation coefficients. For all statistical tests, a p value < 0.05 defined statistical significance.

Results

Myocardial positron emission tomographic scans. Within a few minutes after injection of 6-[^{18}F]fluorodopamine, the left ventricular myocardium was visualized in all subjects (Fig. 1). The interventricular septum, right ventricular wall and left and right ventricular chambers were delineated. At the 1-, 1.5- and 2-mCi doses, total thoracic radioactivity was sufficient to visualize the left ventricular myocardium for only ~2.5 h after 6-[^{18}F]fluorodopamine administration. The pattern of 6-[^{18}F]fluorodopamine–derived radioactivity was generally homogeneous in the myocardium; however, in a few subjects, the radioactivity concentration in the anterior portion of the interventricular septum was slightly higher than in other regions. The atrial walls were delineated poorly.

Hemodynamic effects of 6-[^{18}F]fluorodopamine. During and after the 3-min infusion of 6-[^{18}F]fluorodopamine at doses of 1 to 2 mCi (0.5 to 1.2 mg), there were no changes in blood pressure, heart rate or cardiac rhythm. In the subjects who received the 3- or 4-mCi (1.9- to 3.6-mg) doses, small, transient increases in mean arterial pressure were noted, with the peak increases near the end of the infusion (mean increase of 6.3 mm Hg from baseline to 3 min during infusion, *t* statistic = 3.19, $p < 0.02$). Heart rate was unchanged. By ~5 min after the end of the infusion, arterial pressure was similar to the baseline value in all subjects.

One subject, who received 1.9 mg of 6-[^{18}F]fluorodopamine for 1 rather than 3 min, reported sensations of flushing and tingling for several seconds after the injection ended. In another subject, who received 3.1 mg of 6-[^{18}F]fluorodopamine for 3 min, four asymptomatic, unifocal premature ventricular contractions were noted for ~15 s beginning just after the infusion ended. Except for these findings, 6-[^{18}F]fluorodopamine administration produced no symptoms or changes in cardiac rhythm.

Myocardial time-activity curves. When myocardial radioactivity (in nCi/ml) was adjusted for the dose of 6-[^{18}F]fluorodopamine (in mCi/kg), the resultant time-activity curves were similar in all subjects (Fig. 2). In the first scanning interval (5-min duration, midpoint 2.5 min after initiation of the infusion of 6-[^{18}F]fluorodopamine), the mean concentration of radioactivity in the left ventricular myocardium was similar to that in the arterial blood and higher than that in arterial plasma (Fig. 2, bottom).

After the infusion ended, myocardial radioactivity continued to increase briefly, peaking in the scanning interval with midpoint 7.5 min after initiation of the 6-[^{18}F]fluorodopamine infusion. Thereafter, the decline in myocardial radioactivity appeared to be biexponential. The equation for the curve of best fit in myocardium was $y = 4{,}551e^{-0.0473t} + 4{,}697e^{-0.00767t}$, yielding half-life values of 14.7 min in the early phase and 90 min in the late phase (after 60 min).

The peak myocardial radioactivity concentration (in nCi/ml) was positively and linearly ($r = 0.90$, $p < 0.01$) related to the 6-[^{18}F]fluorodopamine dose. When expressed as nCi-kg/ml-mCi, the peak myocardial radioactivity concentration was also positively and linearly ($r = 0.72$, $p < 0.05$) related to the peak arterial 6F-dopamine concentration.

Circulating concentrations of total radioactivity, 6-[^{18}F]fluorodopamine and 6F-metabolites. Plasma and whole blood total radioactivity concentrations reached plateau levels within a few minutes after initiation of the infusion of 6-[^{18}F]fluorodopamine and then decreased rapidly beginning after the end of the infusion. Whereas a biexponential curve fit the empiric data well for myocardial 6-[^{18}F]fluorodopamine–derived radioactivity, a triexponential curve was required to fit

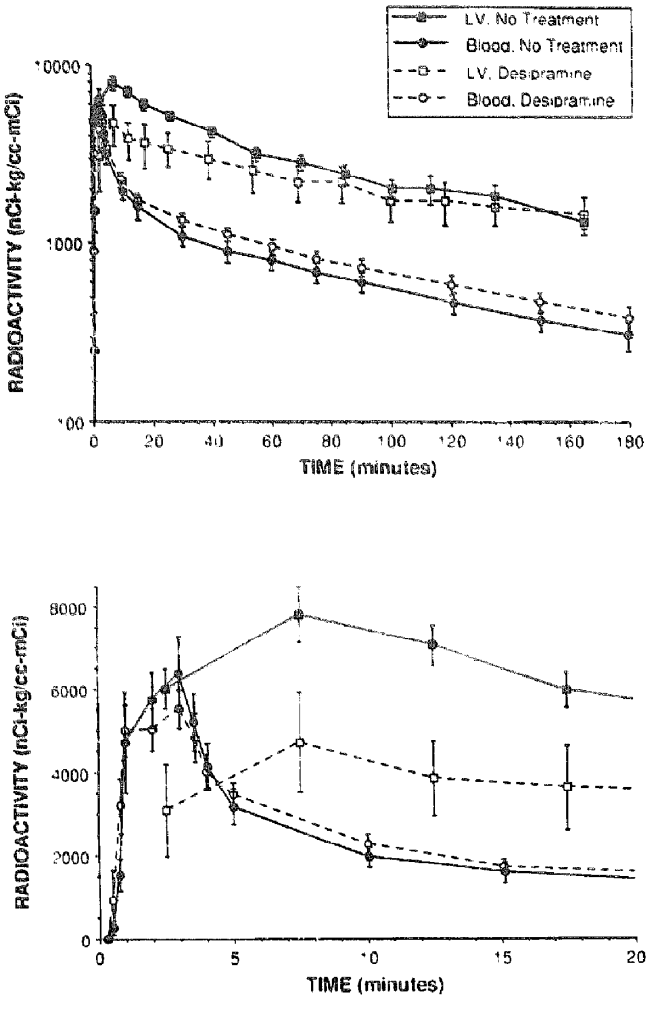

Figure 2. Left ventricular (LV) myocardial and arterial blood mean (±SEM) radioactivity concentrations as a function of time after intravenous injection of 6-[^{18}F]fluorodopamine in healthy humans, with or without desipramine treatment (125 mg orally). **Top,** Across the entire positron emission tomographic scanning interval; **Bottom,** During the 1st 20 min of scanning.

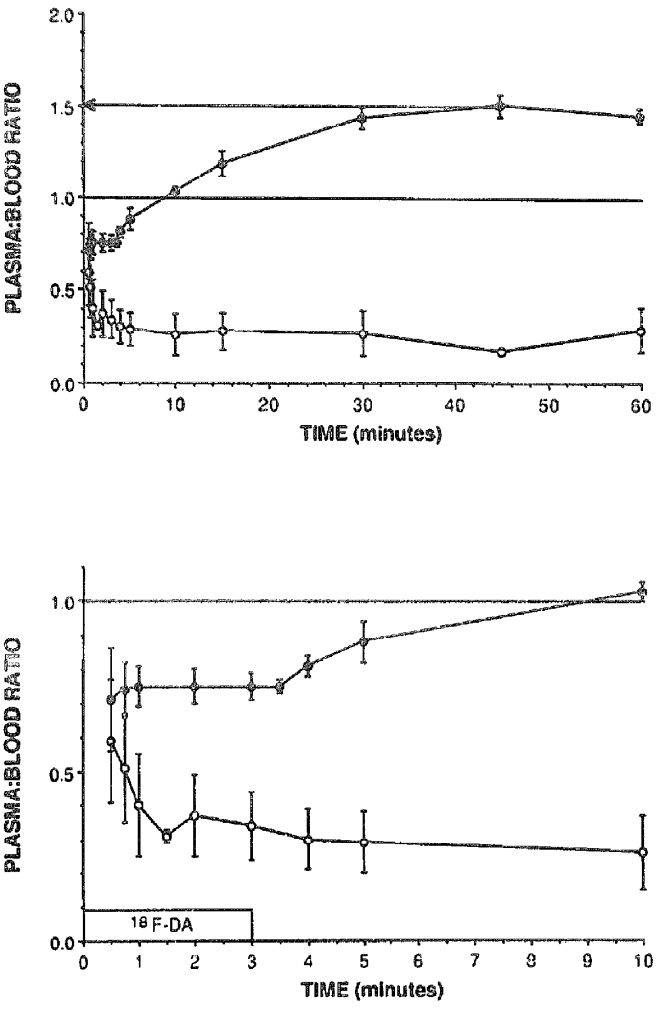

Figure 3. Arterial plasma/arterial blood radioactivity concentration ratio as a function of time after a 3-min infusion of 6-[^{18}F]fluorodopamine (n = 8, solid circles) or addition of 6-[^{18}F]fluorodopamine to blood incubated at 37°C (n = 5, open circles). **Top,** Across the entire positron emission tomographic scanning interval. **Bottom,** During the 1st 10 min of scanning or incubation. The plateau ratio was 1.50 (arrow).

the empiric data for 6-[^{18}F]fluorodopamine–derived radioactivity in blood and plasma. The equations for the curves of best fit were (for blood) $y = 21{,}921e^{-0.7779t} + 1{,}921e^{-0.0989t} + 1{,}249e^{-0.00792t}$ and (for plasma) $y = 18{,}355e^{-0.5427t} + 581e^{-0.0447t} + 1{,}933e^{-0.00798t}$. In blood and plasma, the half-life values were therefore 1.4 and 1.3 min for the rapid early component, 7 and 16 min for the middle component and 88 and 87 min for the slow late component. Similar triexponential curves for radioactivity in blood and plasma were obtained in desipramine-treated subjects.

The time-activity curve for plasma differed from that for blood. During and for a few minutes after the infusion of 6-[^{18}F]fluorodopamine, the plasma total radioactivity concentration was less than the whole-blood radioactivity concentration in all subjects. The fluorine-18 concentration in whole blood subsequently declined more rapidly than did the plasma radioactivity concentration in all subjects, so that the two time-activity curves crossed at ~10 min. Thereafter, the plasma radioactivity exceeded the blood radioactivity by ~50%. Thus, beginning at ~1 min during the injection of 6-[^{18}F]fluorodopamine and for a few minutes afterward, the plasma/blood radioactivity ratio was <1 (Fig. 3), and the ratio then progressively increased, to a plateau value averaging 1.5. In contrast with these in vivo findings, when 6-[^{18}F]fluorodopamine was added to blood in vitro and incubated at 37°C, the plasma/blood radioactivity ratio was much less than 1 throughout the period of incubation (Fig. 3).

Plasma concentrations of radioactivity due to 6-[^{18}F]fluorodopamine at each time point were calculated from the product of the 6F-dopamine concentration (after complete radioactive decay) and the specific activity of the tracer at the time of injection. Arterial plasma 6-[^{18}F]fluorodopamine concentrations began to decrease immediately after the end of the infusion (Fig. 4). By 7 min

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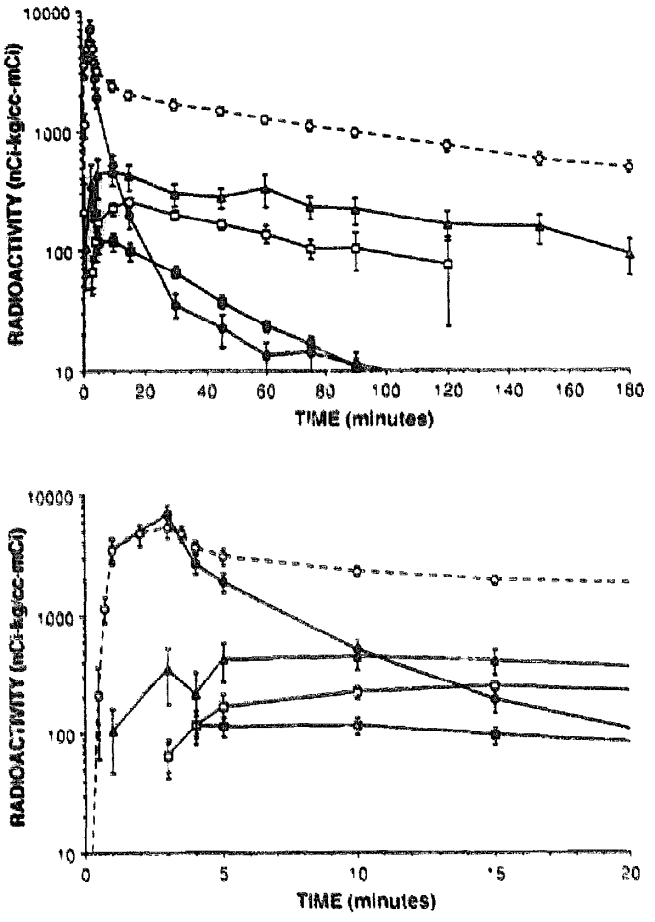

Figure 4. Total arterial plasma radioactivity and estimated plasma concentrations of 6-[^{18}F]fluorodopamine (6F-DA, n = 10, **solid circles**) and metabolites as a function of time after intravenous injection of 6-[^{18}F]fluorodopamine in humans. 6F-DOPAC = 6-[^{18}F]fluorodihydroxyphenylacetic acid (n = 10, **solid squares**); 6F-DA sulfate = 6-[^{18}F]fluorodopamine sulfate (n = 9, **triangles**); 6F-HVA = 6-[^{18}F]fluorohomovanillic acid (n = 3, **open squares**); **open circles** = plasma.

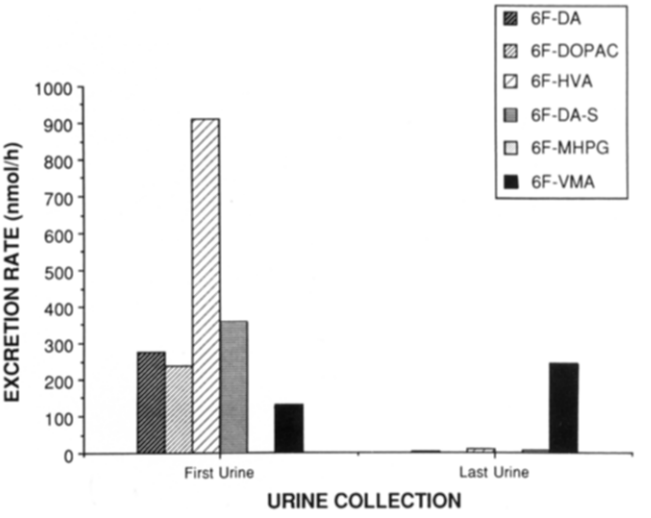

Figure 5. Urinary excretion rates of 6-fluorodopamine and metabolites in the first and last collection of voided urine between the end of the Scanning session and 24 h after 6-[^{18}F]fluorodopamine administration: n = 6 for 6-[^{18}F]fluorodopamine (6F-DA) and 6-[^{18}F]fluorodihydroxyphenylacetic acid (6F-DOPAC); n = 5 for 6-[^{18}F]fluorodopamine sulfate (6F-DA-S); and n = 3 for 6-[^{18}F]fluorohomovanillic acid (6F-HVA), 6-[^{18}F]fluoromethoxyhydroxyphenylglycol (6F-MHPG) and 6-[^{18}F]fluorovanillylmandelic acid (6F-VMA).

later, the mean arterial plasma level of 6-[^{18}F]fluorodopamine had decreased by 94% and, during the interval from 1 to 7 min after cessation of the infusion, plasma 6-[^{18}F]fluorodopamine levels decreased with a half-life of 2.4 min. Thereafter, low but detectable levels of 6-[^{18}F]fluorodopamine were present for the remainder of the scanning session.

During and immediately after injection, 6-[^{18}F]fluorodopamine accounted for all the plasma radioactivity (Fig. 4, bottom). The proportion of the total plasma radioactivity that was due to 6-[^{18}F]fluorodopamine declined rapidly after cessation of the infusion. The difference between the total radioactivity concentration and the concentration of 6-[^{18}F]fluorodopamine was attributed to metabolites of the amine. 6-[^{18}F]Fluorodihydroxyphenylacetic acid, 6-[^{18}F]fluorohomovanillic acid and 6-[^{18}F]fluorodopamine sulfate accumulated rapidly in plasma after injection of 6-[^{18}F]fluorodopamine. 6-[^{18}F]Fluoromethoxytyrosine, 6-[^{18}F]fluoronorepinephrine and metabolites of 6-[^{18}F]fluoronorepinephrine were not detected in plasma.

Urinary radioactivity excretion. Each subject voided at the end of the scanning, at a mean of 3.31 h after initiation of the injection of 6-[^{18}F]fluorodopamine. After decay correction, 59.2 ± 6.5% of the injected radioactive agent was in the voided urine at this time. These results were used to estimate radiation doses to the wall of the urinary bladder.

In the first void after the scanning session, 6F-homovanillic acid was the main metabolite of 6F-dopamine in urine (Fig. 5). In the last void at the end of the 24-h collection period, 6F-vanillylmandelic acid was the main metabolite. In the subject with an indwelling Foley catheter during the scanning session, excretion of 6F-compounds occurred in three phases, with 6F-dopamine the main 6F-compound in the first several minutes, 6F-homovanillic acid the main compound in subsequent samples during the scanning session and 6F-vanillylmandelic acid the main compound in the remainder of the 24-h urine collection. In the four subjects with measured excretion rates of catechols and O-methylated metabolites, 94 ± 26% of the injected compound was excreted as 6F-dopamine or metabolites of 6F-dopamine or 6F-norepinephrine during the 24 h after injection of 6-[^{18}F]fluorodopamine.

Effects of desipramine pretreatment. Pretreatment with oral desipramine markedly affected the PET and neurochemical results. In desipramine-treated subjects, visualization of the left ventricular myocardium was invariably poor. During and just after 6-[^{18}F]fluorodopamine administration, myocar-

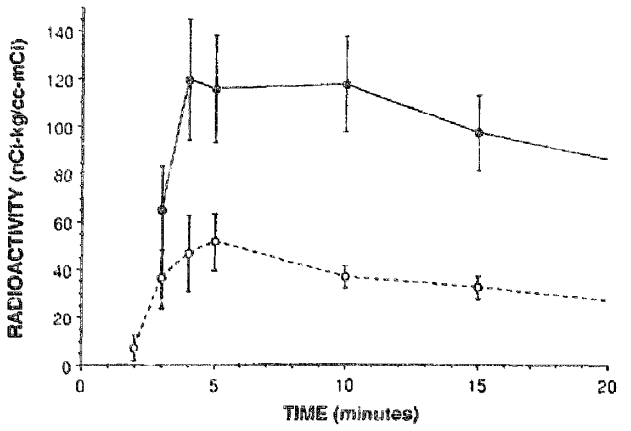

Figure 6. Plasma levels of 6-[^{18}F]fluorodihydroxyphenylacetic acid (6F-DOPAC) after 6-[^{18}F]fluorodopamine administration in humans with (n = 5, open circles) or without (n = 10, solid circles) desipramine treatment.

dial radioactivity in desipramine-treated subjects averaged ~50% of that in untreated subjects (Fig. 2). From the averaged data, the half-life value for the early phase was 18.5 min, and the y-intercept value was 1,912 nCi-kg/ml-mCi in desipramine-treated subjects, in contrast to 14.7 min and 4,551 nCi-kg/ml-mCi in untreated subjects. The latter difference was statistically significant and indicated a decline of 58% in the y intercept value for the early phase. Analogously, the half-life value for the late phase (after 60 min) was 152 min, and the y intercept value was 3,012 nCi-kg/ml-mCi in desipramine-treated subjects, in contrast to 90 min and 4,697 nCi-kg/ml-mCi in untreated subjects. The group differences in both the half-life and y intercept values were statistically significant and indicated a 69% decrease in the rate of decline of 6-[^{18}F]fluorodopamine–derived myocardial radioactivity and a 36% decline in the y intercept value in the late phase. Desipramine treatment also attenuated by ~50% to 70% the accumulation of 6-[^{18}F]fluorodihydroxyphenylacetic acid in arterial plasma (Fig. 6).

Discussion

Visualization of cardiac sympathetic innervation using 6-[^{18}F]fluorodopamine in humans. 6-[^{18}F]Fluorodopamine is a novel PET imaging agent that has been used successfully to visualize cardiac sympathetic innervation in dogs (1). The present results show that after intravenous injection of 6-[^{18}F]fluorodopamine in humans, the myocardium is delineated similarly, with visualization of the left ventricular free wall, septum and chamber.

The percent of injected 6-[^{18}F]fluorodopamine taken up by the left ventricular myocardium can be estimated, assuming a normal left ventricular mass of 175 g in a 70-kg adult (15) and a tissue density of 1.1 g/ml (16). For a dose of 0.05 mCi/kg, the peak left ventricular myocardial radioactivity concentration was 426 nCi/ml, or 968 nCi/kg, corresponding to ~2% of the administered dose. Considering that only ~4% of the cardiac output is distributed to the entire human heart (17), the results suggest that in humans the innervated myocardium removes most of 6-[^{18}F]fluorodopamine in the local arterial inflow. In anesthetized dogs, it has been estimated that ~4% of the administered dose of 6-[^{18}F]fluorodopamine is removed by the entire heart (10).

Fate of 6-[^{18}F]fluorodopamine–derived radioactivity in the human heart. After correction for physical decay of the tracer, the myocardial concentration of radioactivity decreased progressively during the 2.5 to 3 h of PET scanning in all subjects, with a mean half-life of ~1.5 h. This value is similar to that in dogs (1) but more rapid than that in rats (3).

Clinical results using cardiac PET scanning after administration of positron-emitting sympathomimetic amines, such as [^{11}C]hydroxyephedrine and 6-[^{18}F]fluorometaraminol, show little if any decline in myocardial radioactivity during a similar time period (6–9). These differences from the present findings probably reflect differences in the metabolic fates of the tracers, because neither [^{11}C]hydroxyephedrine nor 6-[^{18}F]fluorometaraminol is a substrate for the catecholamine-metabolizing enzymes monoamine oxidase and catechol-*O*-methyltransferase. On the basis of our preclinical findings and the desipramine data discussed later, it is likely that the decline in myocardial radioactivity after 6-[^{18}F]fluorodopamine administration reflects turnover of 6-[^{18}F]fluorodopamine and 6-[^{18}F]fluoronorepinephrine in the storage vesicles in the sympathetic nerve terminals.

Even during the first scanning interval, from 0 to 5 min after initiation of 6-[^{18}F]fluorodopamine administration, the myocardial radioactivity concentration exceeded the arterial plasma radioactivity concentration. Because the blood and interstitium in the myocardial wall constitute only a small fraction of the myocardial volume, 6-[^{18}F]fluorodopamine must exit the bloodstream and enter the myocardium extremely rapidly. Similarly, in rats, by 5 min after intravenous injection of [^{3}H]fluorodopamine, the left ventricular myocardial radioactivity concentration exceeds the blood concentration by eight-fold (3). In mice, within 15 s after intracardiac injection of [^{3}H]d,*l*-norepinephrine, radioautographs reveal distribution of the radioactivity in myocardial cells (18).

In the isolated, perfused rat heart, k_m and V_{max} values (concentration at ½ the maximal rate and to the maximal reaction rate, respectively) for removal of 7-[^{3}H]dopamine by neuronal uptake (uptake 1) are 0.69×10^{-6} mol/liter and 1.45×10^{-9} mol/g, whereas k_m and V_{max} values for removal by nonneuronal uptake (uptake 2) are 5.9×10^{-4} mol/liter and 0.14×10^{-6} mol/g (19), indicating that in the heart, the efficiency of uptake 1 (defined by V_{max}/k_m) for [^{3}H]dopamine removal exceeds that of uptake 2 by ~ten-fold. Assuming similar kinetic values for cardiac uptake of 6-[^{18}F]fluorodopamine in the present study, the peak arterial plasma 6F-dopamine concentration, 1.6×10^{-6} mol/liter at 3 min of infusion of 6-[^{18}F]fluorodopamine, would correspond approximately to the k_m value for the uptake-1 carrier

and to <1% of the k_m value for the uptake-2 carrier. Thus, only a small proportion of the uptake of 6-[^{18}F]fluorodopamine–derived radioactivity in the myocardium would be expected to be by nonneuronal cells. Because there was a positive linear relation between the peak myocardial radioactivity concentration (in nCi/ml) and the dose of 6-[^{18}F]fluorodopamine (in mCi/kg), and because the peak myocardial radioactivity concentration (nCi/ml adjusted for the dose in mCi/kg) failed to decline at high plasma 6F-dopamine concentrations, myocardial uptake and retention mechanisms probably were not saturated at the doses used.

6-[^{18}F]Fluorodopamine–derived radioactivity persisted in the myocardium as blood radioactivity decreased. In animals pretreated with reserpine (which blocks vesicular translocation of amines), with 6-hydroxydopamine (which destroys sympathetic nerve terminals) or with desipramine (which blocks uptake 1), the myocardium fails to retain 6-[^{18}F]fluorodopamine–derived radioactivity (1,4). These results suggest that rapid neuronal uptake and vesicular translocation of interstitial 6-[^{18}F]fluorodopamine explain the myocardial retention of 6-[^{18}F]fluorodopamine–derived radioactivity.

Fate of circulating 6-[^{18}F]fluorodopamine. Immediately after injection of 6-[^{18}F]fluorodopamine, virtually all the radioactivity in plasma was due to the injected compound. Because the arterial plasma concentration of free 6-[^{18}F]fluorodopamine subsequently declined very rapidly, whereas plasma and whole blood radioactivity decreased much more slowly, by a few minutes after the injection most of the radioactivity in the blood and plasma was due not to 6-[^{18}F]fluorodopamine but to metabolites of the administered compound. Approximately one-half of the total radioactivity in plasma was accounted for by metabolites of 6-[^{18}F]fluorodopamine, especially 6-[^{18}F]fluorodopamine sulfate and 6-[^{18}F]fluorohomovanillic acid.

Because the plasma/blood radioactivity ratio was <1 during, and for a few minutes after, injection of 6-[^{18}F]fluorodopamine, some of the 6-[^{18}F]fluorodopamine seems to bind to cellular elements, such as red blood cell membranes. Clinical studies of other tracer-labeled catecholamines have indicated similarly rapid cellular binding (20). Because the plasma/blood radioactivity ratio subsequently increased progressively to a plateau value averaging ~1.5, metabolites of 6-[^{18}F]fluorodopamine appear to be excluded partially from blood cells. If this exclusion were complete, then for a hematocrit of 0.4, the plasma/blood ratio would be expected to stay level at a value of 1.67 (i.e., 1/[1 − hematocrit]). When 6-[^{18}F]fluorodopamine was incubated in blood in vitro, the plasma/blood ratio failed to increase over time, indicating that the increase depends on in vivo cellular uptake and metabolism of the tracer outside the bloodstream.

The red blood cell concentration of radioactivity was quantified from a formula derived in Appendix A. It was estimated that the concentration of radioactivity in the cellular elements was ~17% of that in the plasma. If this proportion applied similarly to the relation between the radioactivity in myocardial cells and that in the interstitial fluid, then cellular retention or binding of metabolites of 6-[^{18}F]fluorodopamine would account for only a small fraction of the myocardial radioactivity.

The temporal pattern of urinary excretion of 6F-compounds after 6-[^{18}F]fluorodopamine administration provides strong support for the view that in humans, 6-[^{18}F]fluorodopamine is translocated into vesicles and beta-hydroxylated in sympathetic nerves. In the subject with an indwelling Foley catheter during the scanning, urinary excretion of 6F-vanillylmandelic acid, a metabolite of 6F-norepinephrine, increased progressively as excretion of 6F-homovanillic acid declined. Similar findings were obtained in the two other subjects whose concentrations of *O*-methylated 6F-compounds in urine were measured. Because dopamine-beta-hydroxylase, the enzyme catalyzing the conversion of dopamine to norepinephrine and of 6-[^{18}F]fluorodopamine to 6-[^{18}F]fluoronorepinephrine, is localized to vesicles in sympathetic nerves, excretion of 6F-vanillylmandelic acid after 6-[^{18}F]fluorodopamine injection indicates that the tracer is translocated into vesicles and converted to the fluorinated analogue of norepinephrine. The results also indicate that 6-[^{18}F]fluoronorepinephrine is a substrate for the catecholamine-metabolizing enzymes monoamine oxidase and catechol-*O*-methyltransferase, because 6-[^{18}F]fluorovanillymandelic acid production reflects the combined actions of these enzymes.

Effects of desipramine. Desipramine treatment produces two main effects on sympathoneural function: blockade of neuronal uptake of catecholamines and inhibition of sympathoneural activity (11,21,22). Desipramine treatment attenuated by ~50% the myocardial uptake of 6-[^{18}F]fluorodopamine–derived radioactivity. Because the treatment also attenuated the accumulation of plasma 6-[^{18}F]fluorodihydroxyphenylacetic acid by ~50%, and because plasma levels of this metabolite probably mainly reflect neuronal metabolism of 6-[^{18}F]fluorodopamine (4), the findings in the heart seem to have paralleled those in sympathetic nerves elsewhere in the body. In humans, intravenous desipramine (0.5 mg/kg) decreases cardiac uptake of [^{3}H]*l*-norepinephrine by ~69% (23). In rats, intravenous desipramine (4 mg/kg) decreases uptake of [^{3}H]*l*-norepinephrine into left ventricular myocardium by 94% and decreases concentrations of 2-fluorodopamine by 67% after intravenous injection of these compounds (2), and intravenous desipramine (2 mg/kg) decreases myocardial concentrations of 6F-[^{3}H]*l*-fluoroncrepinephrine by 84% and 6F-[^{3}H]fluorodopamine by 93% after injection of 6-[^{3}H]fluorodopamine (3). In the present study, partial blockade of uptake 1 after oral desipramine (125 mg) can explain the attenuation of accumulation of 6-[^{18}F]fluorodopamine–derived radioactivity in the myocardium and of 6-[^{18}F]fluorodihydroxyphenylacetic acid in arterial plasma.

The myocardial radioactivity concentration measured by PET scanning during or immediately after administration of 6-[^{18}F]fluorodopamine, or the extent of change in that con-

centration after desipramine treatment, may therefore provide a noninvasive means to examine myocardial uptake-1 activity in humans. In particular, if uptake-1 activity were absent in a given myocardial region, owing to a drug or a pathophysiologic process, then the regional myocardial concentration of 6-[^{18}F]fluorodopamine–derived radioactivity would be low, and desipramine treatment would decrease the radioactivity concentration less in the affected region than in the region with normal uptake-1 activity. The ability to assess the activity of the neuronal uptake carrier is potentially important clinically because uptake 1 is the main means for terminating the actions of catecholamines in the human heart (23).

Desipramine treatment also prolonged the loss of myocardial 6-[^{18}F]fluorodopamine–derived radioactivity. Thus, the half-life value for the late phase was 90 min in untreated subjects and 152 min in subjects pretreated with desipramine. Desipramine administration markedly decreases directly recorded skeletal muscle sympathoneural activity in humans (11) and decreases norepinephrine release into the cardiac interstitial space (21,22) in dogs. The rate of decline of myocardial 6-[^{18}F]fluorodopamine–derived radioactivity may therefore reflect the turnover sympathoneural vesicle contents in humans and changes in turnover during stress, in response to drugs, or in various cardiologic pathologic states. This application, however, requires further validation by direct comparison of 6-[^{18}F]fluorodopamine kinetics with myocardial norepinephrine turnover.

Safety issues. *Cardiovascular effects of 6-[^{18}F]fluorodopamine.* Effects of 6-[^{18}F]fluorodopamine on heart rate and mean arterial pressure, although small and transient, were detected in all subjects receiving the 3- to 4-mCi (1.9- to 3.6-mg) doses. Because these doses would correspond to approximately a 10-μg/kg per min infusion of dopamine for 3 min, the known pharmacology of dopamine would predict these hemodynamic changes (24). In one subject, a 15-s interval containing several asymptomatic, unifocal premature ventricular contractions was noted at the end of the 6-[^{18}F]fluorodopamine infusion.

Avoiding these effects would probably require a higher specific activity of 6-[^{18}F]fluorodopamine than that used in most subjects in the present studies. As noted earlier, during the course of the present studies, a method for direct synthesis of 6-[^{18}F]fluorodopamine was devised, increasing the specific activity by ~fourfold at the time of injection. In the subject receiving 6-[^{18}F]fluorodopamine at the highest specific activity in the series (4 mCi at specific activity 809 mCi/mmol), no hemodynamic effects of 6-[^{18}F]fluorodopamine were detected during or after the injection.

Radiation exposures to the wall of the urinary bladder. After systemic administration of tracer-labeled catecholamines, most of the radioactivity is excreted in the urine. In the present study, by ~3.3 h after administration of 6-[^{18}F]fluorodopamine, ~60% of the injected compound was excreted into the urine. Thus, in humans, as in dogs (10), the main target organ for radiation exposure due to 6-[^{18}F]fluorodopamine administration is the wall of the urinary bladder.

Dosimetric calculations based on the empiric data (Appendix B) indicate that the radioactivity exposure to the wall of the bladder is ~0.8 to 1.0 rem per mCi injected, depending on the voiding frequency after the scanning session.

Despite the depiction of the left ventricular myocardium by thoracic PET scanning after 6-[^{18}F]fluorodopamine administration, the radiation dose to the heart wall is very small because of the small percent of the injected 6-[^{18}F]fluorodopamine taken up by the left ventricular myocardium.

Conclusions. The present results indicate that after systemic administration of 6-[^{18}F]fluorodopamine, PET scanning can visualize the myocardium in humans. No important clinical effects of the drug are noted. Estimates of radiation doses to the wall of the urinary bladder seem acceptable. The neuropharmacologic and neurochemical data indicate that 6-[^{18}F]fluorodopamine exits the circulation extremely rapidly and is taken up extensively into sympathetic nerves, where it is translocated into vesicles and converted to the fluorinated analogue of norepinephrine, the sympathetic neurotransmitter. From the desipramine data it appears that kinetic analyses of the accumulation and decline of myocardial 6-[^{18}F]fluorodopamine–derived radioactivity can provide information about the neuronal uptake of catecholamines and the turnover of vesicular amines in the human heart. Thus, thoracic PET scanning after 6-[^{18}F]fluorodopamine injection has the potential to provide clinically relevant information not only about cardiac sympathetic innervation but also about cardiac sympathetic function noninvasively in humans.

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Appendix A

Estimate of the Cellular Concentration of Radioactivity Due to Metabolites of 6-[^{18}F]fluorodopamine

The volume of blood is the volume of plasma plus the volume of cells:

$$V_b = V_p + V_c. \quad [A1]$$

The hematocrit Hct is the red cell volume divided by the total blood volume:

$$Hct = V_c/V_b. \quad [A2]$$

The amount of radioactivity in the blood *b is the sum of the amount of radioactivity in the cells *c and the amount of radioactivity in the plasma *p:

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$$*b = *c + *p. \quad [A3]$$

From the equations A1 to A3,

$$V_b(*b/V_b) = V_c(*c/V_c) + V_p(*p/V_p). \quad [A4]$$

Dividing by V_b and using the definition of the hematocrit,

$$(*b/V_b) = Hct(*c/V_c) + (1 - Hct)(*p/V_p).$$

For Hct = 0.4 and a plasma/blood radioactivity concentration ratio of 1.5, that is, $(*p/V_p)/(*b/V_b)=1.5$,

$$(1/1.5)(*p/V_p) = 0.4(*c/V_c) + 0.6(*p/V_p). \quad [A5]$$

Solving for the cellular radioactivity concentration $*c/V_c$ gives

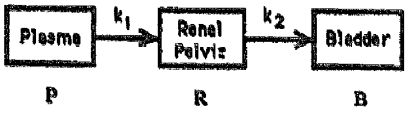
$$*c/V_c = 0.17\cdot(*p/V_p). \quad [A6]$$

Thus, the cellular radioactivity concentration is 17% of the plasma radioactivity concentration.

Appendix B

Estimates of Radiation Doses to the Wall of the Urinary Bladder After Injection of 6-[^{18}F]Fluorodopamine In Humans

The bases for the estimates of radiation doses to the wall of the urinary bladder were the empiric data from the present study and a model for the kinetics of 6-[^{18}F]fluorodopamine–derived radioactivity in the plasma, renal pelvises and urinary bladder:



The model assumes that 6-[^{18}F]fluorodopamine is administered as a bolus at time t = 0 min and that hepatobiliary excretion contributes negligibly to the loss of 6-[^{18}F]fluorodopamine–derived radioactivity from the body (10).

Estimates of Values for k_1 and k_2

In this model, k_1 is the empiric value for the decline of the plasma level of radioactivity (after correction for decay). In the present study, k_1 was 0.479 h^{-1}.

The value for k_2, the rate constant for urinary flow through the collecting tubules and renal pelvises into the ureter, was based on the following: The total effective volume of the renal pelvis was taken to be the volume of urine in the collecting tubules of the renal pyramids plus the volume of the renal pelvis. The latter was estimated to be ~15 ml in a normal human kidney. Each kidney was assumed to weigh 150 g, with 10% from the collecting tubules and urine. Thus, the total effective volume of each renal pelvis was assumed to be 30 ml, or 60 ml for both kidneys. The value for k_2 was calculated from the observed mean value for urinary flow, 72 ml·h^{-1} (excluding any brief diuresis) divided by the estimated effective renal pelvic volume. Therefore, k_2 was 1.20 h^{-1}.

Estimates for Other Variables

There were two components to the excretion of the radioactive compound during PET scanning: an initial "flush," I_0, which was estimated to be ≤4% of the administered dose (10), and a slower component, P_0, derived from the portion of the remainder of the dose that was available for excretion and not sequestered in storage sites. As will be seen, the effective P_0 value was less than the injected amount A_0.

The value of I_0 was calculated from the empiric data as follows. In the subject with an indwelling Foley catheter, after administration of 2.0 mCi of 6-[^{18}F]fluorodopamine, the total amount of radioactivity (corrected for decay) in urine during the 1st 3 h was 0.481 mCi, and 0.025 mCi was excreted in the 1st 8 min. The initial flush I_0 was assumed to be delivered to the renal pelvis with a delay of 1 min. The urinary flow rate during the initial flush was assumed to be that during the initial 8-min diuresis (370 ml·h^{-1}), and the delivery of urine from the renal pelvis to the bladder was assumed to contribute another delay of 1 min. The amount of radiolabeled compound in the bladder B_t at time t is:

$$B_t = I_0[1 - e^{-k'_2(t-2)}], \quad [B1]$$

where k'_2 is the diuretic flow during the initial flush, divided by the estimated effective renal pelvic volume, 60 ml, or 0.103 min^{-1} (6.166 h^{-1}). Ignoring the small contribution of P_0 at this time, rearrangement of equation B1 leads to a value for I_0 of $0.027A_0$, or 2.7% of the administered dose. Thus, at 8 min, ~1.4% of the initial flush remained in the urinary collecting system.

Given this value for I_0, the value for P_0 was calculated. By 3.31 h after administration of 6-[^{18}F]fluorodopamine, 59.2% of the dose (corrected for decay) had been excreted. Because 2.7% of this was I_0, the remainder, 56.5%, was excreted after the initial flush. R_p, the amount of the labeled compound from P_0, corrected for decay, that is in compartment R at time t is

$$R_p = [(k_1P_0)/(k_2 - k_1)](e^{-k_1t} - e^{-k_2t}). \quad [B2]$$

Because $dB_p/dt = k_2R_p$, substituting R_p from equation B2 and solving for B_p gives the total compound from P_0 (corrected for decay) excreted by 3.31 h:

$$B_p = [k_1k_2P_0/(k_2 - k_1)][((1 - e^{-k_1t})/k_1) - ((1 - e^{-k_2t})/k_2))] = 0.691P_0. \quad [B3]$$

Because $B_p = 0.565A_0$ at 3.31 h, $0.565A_0 = 0.672P_0$, and, therefore, $P_0 = 0.841A_0$.

Radiation Exposure to the Bladder

To quantify the total radiation dose to the wall of the urinary bladder, owing to the radioactive urine contents, the contributions from the two components P_0 and I_0 were considered separately. For P_0 the delay in transfer from plasma via the kidneys and ureters to the bladder can be ignored.

A_{B_p}, the amount of radioactivity in the bladder from P_0 at any time, t is

$$A_{B_p} = B_pe^{-k_Dt} = [(k_1k_2P_0)/(k_2 - k_1)][((1 - e^{-k_1t})/(k_1)) - ((1 - e^{-k_2t})/(k_2))]\cdot e^{-k_Dt}, \quad [B4]$$

where k_D is the physical decay constant 0.381/h. Integrating this activity over the time to voiding, 3.31 h, to obtain the cumulative activity $\tilde{A}_{B_p}$ (in mCi-h/mCi injected),

$$\tilde{A}_{B_p} = [(k_1k_2P_0)/(k_2 - k_1)]\{[((1 - e^{-k_Dt})/(k_1k_D)) - ((1 - e^{-(k_1 + k_D)t})/(k_1 + k_D))]$$

$$- [((1 - e^{-k_Dt})/(k_2k_D)) - ((1 - e^{-(k_2 + k_D)t})/(k_2(k_2 + k_D)))]\} = 0.476P_0$$

$$= 0.400 \text{ mCi-h/mCi injected}. \quad [B5]$$

For calculating $\tilde{A}_{B_I}$, the cumulative activity due to I_0 by 3.31 h it could be assumed that all the drug from the initial flush was excreted in the urine by 3.31 h. That is, from equation B1, $B_I = I_0 = 0.027A_0$. The amount of radioactivity due to the drug from the initial flush is

$$A_{B_t} = 0.027A_0e^{-k_Dt}. \quad [B6]$$

Integrating from time t = 0 to 3.31 h, $\bar{A}_{B_t}$ = 0.051 mCi-h/mCi injected. The total cumulative activity at 3.31 h therefore is 0.400 + 0.051 = 0.451 mCi-h per mCi injected. Given that the S factor for radiation exposure to the wall of the urinary bladder is 1.80 rem/mCi-h for fluorine-18, the cumulative radiation dose to the bladder wall during the 3.31 h of PET scanning is 0.81 rem/mCi of injected 6-[^{18}F]fluorodopamine. This ignores the negligibly small contributions from sources other than the radioactive urine contents (10). A 4.0-mCi dose of 6-[^{18}F]fluorodopamine would therefore be expected to lead to ~3.2 rem of bladder radiation exposure during the period of PET scanning.

In the subject never voided, then equation B5 would be reduced to

$$\bar{A}_{B_p} = [(k_1k_2P_0)/(k_2 - k_1)][[1/k_1k_D] - [1/k_1(k_1 + k_D)] - [(1/k_2k_D] - [1/k_2(k_2 + k_D)]]. \quad [B7]$$

The total cumulative radioactivity exposure to the wall of the bladder would be 0.933 + 0.051 = 0.984 mCi-h per mCi injected.

If the subject voided at 3.31 h but never again, then radiation exposure to the bladder wall would be reduced by the cumulative radioactivity exposure that would have resulted if the radioactive urine in the bladder were not excreted at 3.31 h. If 59.2% of the radioactivity due to administration of 6-[^{18}F]fluorodopamine were voided at 3.31 h, the amount of radioactivity in the bladder at that time would be $0.592A_0e^{-3.31k_D}$, or $0.168A_0$. Integrating from t = 0 to t = infinity, the cumulative radioactivity in the bladder if the subject did not void at 3.31 h would be $0.168A_0/k_D$, or 0.440 mCi-h per mCi injected.

Thus, assuming that the subject voids at 3.31 h but never again, the integrated radioactivity exposure to the bladder wall would be 0.984 − 0.440 = 0.544 mCi-h. If the subject voided continuously beginning at the end of the scanning session, the radiation exposure to the bladder wall would be limited to that occurring during the 3.31 h of scanning (i.e., 0.451 mCi-h per mCi injected). Therefore, the actual radioactivity exposure to the bladder wall would be between 0.451 and 0.544 mCi-h per mCi injected, or between 1.80 and 2.18 mCi-h for a 4-mCi dose, depending on the frequency of voiding after the scanning session. For an S factor of 1.8 rem/mCi-h, this would correspond to a radiation dose of 3.2 to 3.9 rem.

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