Cardiac and Extracardiac Sympathetic Denervation in Parkinson's Disease with Orthostatic Hypotension and in Pure Autonomic Failure

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The uptake of 6-^{18}F-fluorodopamine by cardiac noradrenergic nerves enables visualization of the sympathetic innervation of the left ventricular myocardium by PET. Patients with Parkinson's disease (PD) and orthostatic hypotension (OH) (PD+OH) or with pure autonomic failure (PAF) have markedly decreased myocardial 6-^{18}F-fluorodopamine–derived radioactivity, consistent with cardiac sympathetic denervation, a phenomenon that neurochemical, neuropharmacologic, and, most recently, postmortem neuropathologic studies have confirmed. In this study, we examined whether 6-^{18}F-fluorodopamine can visualize sympathetic innervation in extracardiac organs and, if so, whether patients with PD+OH or PAF have neuroimaging evidence of extracardiac noradrenergic denervation. **Methods:** To validate the method, healthy volunteers underwent 6-^{18}F-fluorodopamine scanning of the head, thorax, and abdomen, with or without treatment with desipramine to block sympathoneural uptake of catecholamines. ^{13}N-Ammonia scanning was used to address possible group differences in 6-^{18}F-fluorodopamine delivery by blood perfusion. **Results:** Desipramine treatment was associated with decreased 6-^{18}F-fluorodopamine–derived radioactivity in the heart, renal cortex, and thyroid gland but not in the liver, spleen, renal pelvis, or salivary glands. Both the PD+OH group and the PAF group had decreased 6-^{18}F-fluorodopamine–derived radioactivity in the heart ($P < 0.0001$) and renal cortex ($P = 0.02$ and $P = 0.005$, respectively). The PD+OH group also had decreased radioactivity in the thyroid gland ($P = 0.01$). Neither group had decreased radioactivity in the other organs, after correction for ^{13}N-ammonia–derived radioactivity. **Conclusion:** 6-^{18}F-Fluorodopamine scanning visualizes sympathetic innervation in the heart, renal cortex, and thyroid gland. Both PD+OH and PAF involve decreased noradrenergic innervation that is most prominent in the heart but is also detectable in extracardiac organs.

Key Words: fluorodopamine; ammonia; pure autonomic failure; Parkinson's disease; PET

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PET after intravenous injection of 6-^{18}F-fluorodopamine enables visualization of cardiac sympathetic innervation (*1*). It was previously reported that patients with Parkinson's disease (PD) and orthostatic hypotension (OH) (PD+OH) have remarkably decreased left ventricular myocardial concentrations of 6-^{18}F-fluorodopamine–derived radioactivity (*2,3*), with values similar to those in patients with pure autonomic failure (PAF). Whether patients with PD+OH have neuroimaging evidence for decreased sympathetic innervation in extracardiac organs has been much less clear. Studies with ^{123}I-metaiodobenzylguanidine have indicated that in patients with PD, sympathetic denervation is confined to the heart (*4,5*). On the other hand, Li et al. obtained preliminary evidence for decreased 6-^{18}F-fluorodopamine–derived radioactivity in the thyroid gland and renal cortex of patients with PD (*6*).

This study had 2 purposes. The first was to assess the validity of 6-^{18}F-fluorodopamine scanning for visualization of sympathetic innervation in organs such as the liver, spleen, salivary glands, thyroid gland, and kidneys. The second was to examine whether patients with PD+OH or PAF have evidence of decreased sympathetic innervation in organs in which 6-^{18}F-fluorodopamine scanning was validated as a means of assessing sympathetic innervation.

To validate sympathetic neuroimaging by 6-^{18}F-fluorodopamine scanning, we tested the effects of oral desipramine treatment on the uptake and subsequent loss of 6-^{18}F-fluorodopamine–derived radioactivity in organs of healthy volunteers. Desipramine, a tricyclic antidepressant, is a classical inhibitor of neuronal uptake of catecholamines via the cell membrane norepinephrine transporter. We reasoned that in organs with sympathetic innervation visualized by 6-^{18}F-fluorodopamine scanning, desipramine would decrease the amount of 6-^{18}F-fluorodopamine–derived radioactivity (*7*). Comparison of data from desipramine-treated volunteers with those from patients with PD+OH then would enable inferences about whether the patients had

decreased sympathetic innervation in those organs. On the other hand, in organs in which desipramine did not decrease the amount of 6-^{18}F-fluorodopamine–derived radioactivity, one would not expect the concentrations of 6-^{18}F-fluorodopamine–derived radioactivity to indicate validly the density of sympathetic innervation, and assessments of that radioactivity in patients with PD+OH or PAF would not address the issue of possible sympathetic denervation in those organs.

Because of the well-known contributions of sympathetic innervation of arterioles to resistance to blood flow in body organs, it is possible that sympathetic denervation alters the delivery of the neuroimaging agent by blood perfusion and thereby alters the local concentrations of 6-^{18}F-fluorodopamine–derived radioactivity. In this study, we used ^{13}N-ammonia, a perfusion imaging agent (8–10), to evaluate this possibility. We found that the validity of ^{13}N-ammonia concentrations as a measure of tissue perfusion depended substantially on the particular organ.

PAF is well known to be associated with diffuse loss of sympathetic noradrenergic innervation. Therefore, comparing tissue 6-^{18}F-fluorodopamine–derived radioactivity concentrations in patients with PD+OH and patients with PAF may enable inferences about the more problematic issue of extracardiac sympathetic denervation in patients with PD+OH.

MATERIALS AND METHODS

The study protocol was approved by the Intramural Research Board of the National Institute of Neurologic Disorders and Stroke and the National Institutes of Health (NIH) Radiation Safety Committee. Each subject gave written informed consent.

Subjects

Healthy subjects were screened on the basis of their medical history, physical examination, electrocardiogram, and blood and urine tests (complete blood count, clotting parameters, serum electrolyte concentrations, hepatic and renal function tests, and urinalysis).

Twelve healthy volunteers (age range, 25–70 y; body weight, 50–110 kg) were studied without drug treatment. Of these 12, 5 were also studied 1–2 h after oral desipramine treatment (125 mg/70 kg of body weight).

Patients had PAF ($n = 10$; mean age, 64 y; age range, 60–70 y; mean body mass, 72 kg; body mass range, 40–110 kg) or PD+OH ($n = 26$; mean age, 55 y; age range, 30–70 y; mean body mass, 70 kg; body mass range, 55–130 kg), diagnosed according to previously published clinical criteria (11).

Caffeine-containing beverages, decaffeinated coffee, cigarettes, and alcohol were not allowed for at least 24 h before PET. Patients were allowed to take their usual medications, including levodopa, except for medications known to inhibit neuronal uptake of catecholamines.

PET Scanning

Transmission and emission scans were acquired on a GE Advanced Tomograph (GE Healthcare). Tomographic images were acquired in 35 contiguous transaxial slices and 4.25 mm apart.

Before injection of each radioligand, the subject underwent a 2-min transmission scan for correct positioning and an 8-min transmission scan for attenuation correction. In this study, 185 MBq of ^{13}N-ammonia was injected intravenously over 30 s. Dynamic 3-dimensional (3D) emission scans of the thoracoabdominal region were obtained for 10 min (20 frames for 0.2 min, 1 frame for 0.5 min, and 1 frame for 5 min), and then static 3D emission scans of the head and neck were obtained for 10 min.

6-^{18}F-Fluorodopamine was administered at least 60 min after ^{13}N-ammonia. The radiochemical purity of 6-^{18}F-fluorodopamine was determined to be at least 90%. The specific radioactivity of 6-^{18}F-fluorodopamine at the time of injection averaged 18 MBq/mmol (range, 13–26 MBq/mmol). 6-^{18}F-Fluorodopamine (37 MBq) was injected intravenously over 3 min with a syringe pump (Harvard PhD 2000; Harvard Apparatus). Dynamic 3D emission scans of the thoracoabdominal region were obtained for 30 min (5 frames for 1 min, 3 frames for 5 min, and 1 frame for 10 min), and then static 3D emission scans of the head and neck were obtained for 15 min. Dynamic and static emission scans were obtained for groups of untreated healthy volunteers and groups of desipramine-treated healthy volunteers, patients with PAF, and patients with PD+OH.

Data Analysis and Statistics

Tomographic images were reconstructed after correction for attenuation and physical decay. Decay-corrected time–activity curves and static radioactivity are presented in units of becquerel-kilogram/cubic centimeter-megabecquerel (Bq-kg/cm^3-MBq) to normalize for differences in body weight and administered radiotracer doses.

PET images were analyzed with Pixelwise modeling computer software (PMOD 2.61; PMOD Group). The organs of interest were visualized easily on 6-^{18}F-fluorodopamine PET scans. We placed circular regions of interest well within the borders of the organs. In dynamic emission scans of the thoracoabdominal region, circular regions of interest were drawn on transverse tomographic slices of the interventricular septum, left ventricular chamber, liver, spleen, renal cortex, and renal pelvis. For the renal cortex and renal pelvis, we exploited the fact that 6-^{18}F-fluorodopamine–derived radioactivity always appears in the renal cortex before it appears in the renal pelvis. In static emission scans of the head and neck, circular regions of interest were drawn on transverse tomographic slices of the nasopharynx, parotid gland, submandibular gland, and thyroid gland.

The kinetics of uptake, retention, and loss of 6-^{18}F-fluorodopamine–derived radioactivity differ from those of ^{13}N-ammonia–derived radioactivity, in that peak ^{13}N-ammonia–derived radioactivity already has been attained by 2–3 min after injection, whereas peak 6-^{18}F-fluorodopamine–derived radioactivity is attained a few minutes later. When dynamic data acquisition was done (for organs of the chest and abdomen), we divided the peak 6-^{18}F-fluorodopamine–derived radioactivity (usually at about 8 min after initiation of the 3-min injection) by the ^{13}N-ammonia–derived radioactivity (in the 2- to 3-min scanning interval after initiation of the 30-s injection). When static data acquisition was done (for organs of the head and neck), we divided the 6-^{18}F-fluorodopamine–derived radioactivity (midpoint, about 45 min after initiation of the injection) by the ^{13}N-ammonia–derived radioactivity (midpoint, about 12 min after initiation of the injection). 6-^{18}F-Fluorodopamine–derived radioactivity corrected for ^{13}N-ammonia–derived radioactivity previously was used

successfully to identify local sympathetic denervation in several situations in which 6-^{18}F-fluorodopamine–derived radioactivity alone was insufficient (12–14).

Mean ± SEM concentrations of ^{13}N-ammonia–derived radioactivity and 6-^{18}F-fluorodopamine–derived radioactivity in the various organs were compared among the subject groups. Differences between groups in trends over time were assessed by factorial analyses of variance for repeated measures, the between-groups factor being diagnostic group and the repeated measure being time. For healthy volunteers tested without treatment and after desipramine treatment, the factor was treatment and the repeated measure was time. For post hoc testing, the Fisher Protected Least Significant Difference test was used. A *P* value of <0.05 defined statistical significance.

RESULTS

The interventricular septum, left ventricular chamber, liver, spleen, renal cortex, and renal pelvis were visualized clearly after 6-^{18}F-fluorodopamine injection. These regions also were visualized clearly on ^{13}N-ammonia PET images, with the exception of the renal pelvis, which was not seen. With both radiotracers, regions of interest in the nasopharynx, parotid gland, submandibular gland, and thyroid gland were visualized clearly on the static emission scans of the head and neck.

Organs differed greatly in time–activity curves after ^{13}N-ammonia injection (Fig. 1). In particular, ^{13}N-ammonia–derived radioactivity increased progressively in the liver while concurrently decreasing in the spleen. At all time points, the subject groups had similar values for mean ^{13}N-ammonia–derived radioactivity in the interventricular septum, left ventricular chamber, liver, spleen, and renal cortex. Desipramine treatment was associated with decreased ^{13}N-ammonia–derived radioactivity in the nasopharynx ($P = 0.01$).

6-^{18}F-Fluorodopamine–derived radioactivity was markedly decreased in the interventricular septum in both the PD+OH group and the PAF group ($P < 0.0001$) as well as in healthy volunteers treated with desipramine (Fig. 2A). Desipramine-treated subjects also had lower 6-^{18}F-fluorodopamine–derived radioactivity in the left ventricular chamber than did untreated volunteers or patients with chronic autonomic failure (Fig. 2B). Desipramine-treated subjects had higher ($P = 0.01$) 6-^{18}F-fluorodopamine–derived radioactivity in the liver than did untreated volunteers or patients with PAF or PD+OH (Fig. 2C). 6-^{18}F-Fluorodopamine–derived radioactivity in the spleen did not vary with desipramine treatment or subject group (Fig. 2D). In the renal cortex, peak 6-^{18}F-fluorodopamine–derived radioactivity was lower in desipramine-treated subjects ($P = 0.04$) and in patients with PAF ($P = 0.005$) or PD+OH ($P = 0.02$) than in untreated volunteers (Fig. 2E). 6-^{18}F-Fluorodopamine–derived radioactivity in the renal pelvis was higher in patients with PAF or PD+OH than in healthy volunteers (Fig. 2F).

Among organs of the head and neck, 6-^{18}F-fluorodopamine–derived radioactivity was lower in the nasopharynx ($P = 0.01$) and thyroid gland ($P < 0.001$) in desipramine-treated subjects than in untreated subjects. 6-^{18}F-Fluorodopamine–derived radioactivity corrected for ^{13}N-ammonia–derived radioactivity was decreased significantly in the thyroid gland in desipramine-treated subjects only ($P = 0.04$). 6-^{18}F-Fluorodopamine–derived radioactivity was decreased in the thyroid gland in the PD+OH group ($P = 0.01$) (Fig. 3C) with or without correction for ^{13}N-ammonia–derived radioactivity. The PAF group had normal 6-^{18}F-fluorodopamine–derived radioactivity in the thyroid gland after correction for ^{13}N-ammonia–derived radioactivity (Fig. 3C). Neither the PD+OH group nor the PAF group had decreased 6-^{18}F-fluorodopamine–derived radioactivity in the nasopharynx after correction for ^{13}N-ammonia–derived radioactivity.

DISCUSSION

In this study, the finding that desipramine treatment decreased concentrations of 6-^{18}F-fluorodopamine–derived radioactivity in the interventricular septum, renal cortex, and thyroid gland after intravenous injection of the sympathoneural imaging agent supported the validity of 6-^{18}F-fluorodopamine for assessing sympathetic innervation in these organs.

In contrast, desipramine treatment did not decrease 6-^{18}F-fluorodopamine–derived radioactivity in the liver, salivary glands, spleen, or renal pelvis, despite classical literature indicating that these organs possess sympathetic innervation. In the liver, concentrations of 6-^{18}F-fluorodopamine–derived radioactivity mainly reflect nonneuronal uptake of 6-^{18}F-fluorodopamine by parenchymal cells (15). The increased 6-^{18}F-fluorodopamine–derived radioactivity in the liver in desipramine-treated subjects could have been attributable to displacement of radioactivity from other organs.

The progressive increase in ^{13}N-ammonia–derived radioactivity in the liver could be explained by metabolic "trapping" of ^{13}N-ammonia as part of the urea cycle (16). ^{13}N-Ammonia–derived radioactivity in the spleen decreased progressively from its peak value, suggesting that the radioactivity was delivered to the liver via the portal vein.

In the salivary glands, superior cervical ganglionectomy, which abolishes local sympathetic innervation, produces surprisingly small decreases in 6-^{18}F-fluorodopamine–derived radioactivity after adjustment for the volume of perfused tissue, which may be decreased by atrophy (1). A simple explanation for the failure of desipramine to decrease 6-^{18}F-fluorodopamine–derived radioactivity in the liver and salivary glands is that in these organs, metabolites of 6-^{18}F-fluorodopamine–derived radioactivity accumulate and are excreted in the bile and saliva. Because of the binding of 6-^{18}F-fluorodopamine to blood cell membranes (17), one might expect a failure of desipramine to decrease 6-^{18}F-fluorodopamine–derived radioactivity in the spleen. In the nasopharynx, desipramine decreased both 6-^{18}F-fluorodopamine–derived radioactivity and ^{13}N-ammonia–de-
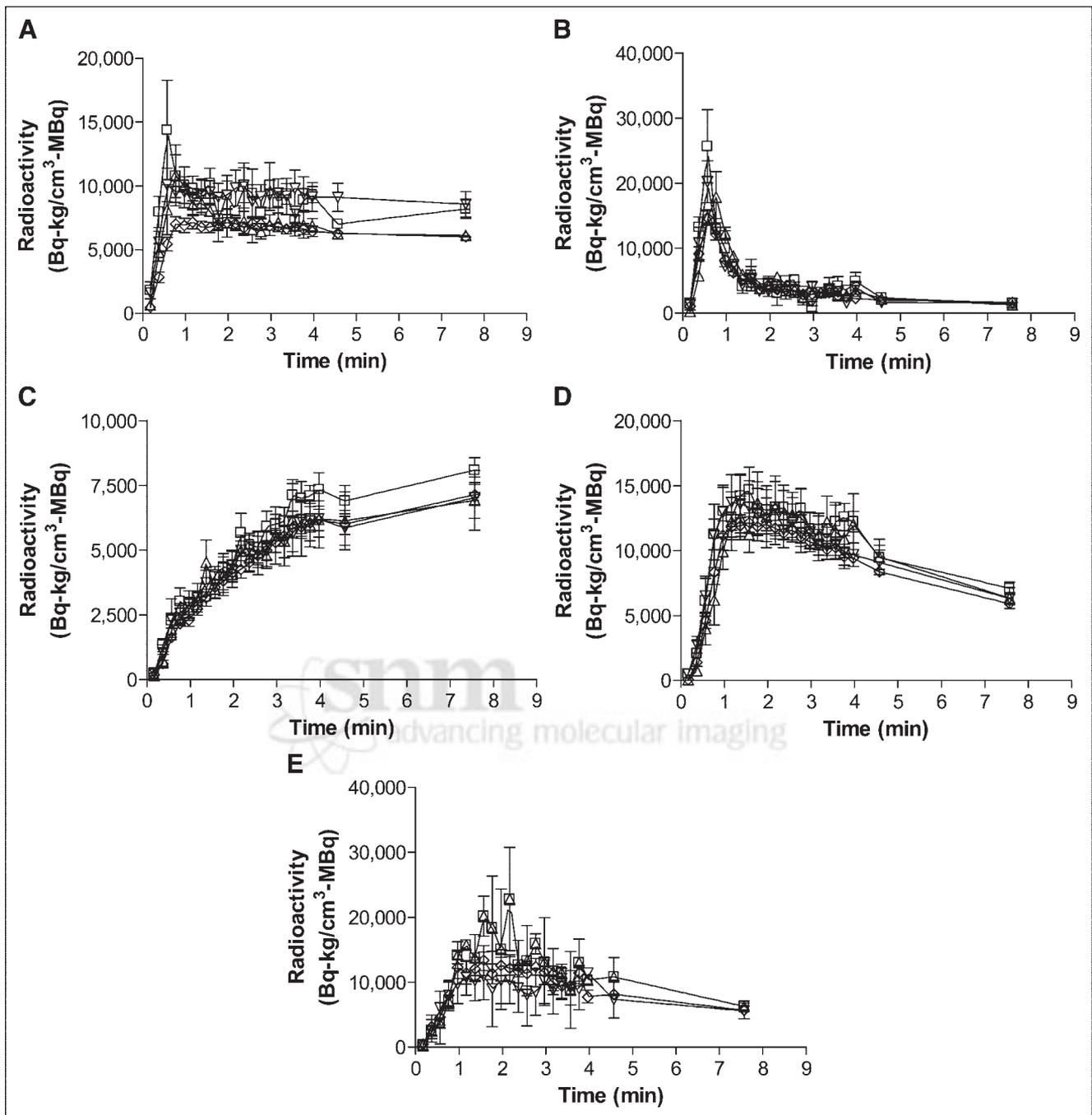
FIGURE 1. Time–activity curves for ^{13}N-ammonia–derived radioactivity (mean $\pm$ SEM) in interventricular septal myocardium (A), left ventricular chamber (B), liver (C), spleen (D), and renal cortex (E) in untreated healthy volunteers ($\square$), desipramine-treated healthy volunteers ($\triangle$), patients with PAF ($\triangledown$), and patients with PD+OH ($\diamond$).

rived radioactivity, so that the ratio did not change significantly.

The concentrations of 6-^{18}F-fluorodopamine–derived radioactivity in tissues therefore appeared to indicate the density of sympathetic innervation in the heart, renal cortex, and thyroid gland, with less clear validity in nasopharyngeal tissue. In examining the status of local sympathetic innervation in patients with PD+OH or PAF, we focused on these organs. As noted previously (2,3), the PD+OH and

PAF groups had similar, marked decreases in interventricular septal myocardial 6-^{18}F-fluorodopamine–derived radioactivity with or without correction for ^{13}N-ammonia–derived radioactivity. The 2 groups also had significantly decreased 6-^{18}F-fluorodopamine–derived radioactivity in the renal cortex. These abnormalities could not be explained easily by decreased renal perfusion, because both groups had normal concentrations of ^{13}N-ammonia–derived radioactivity and had, if anything, increased concentrations of
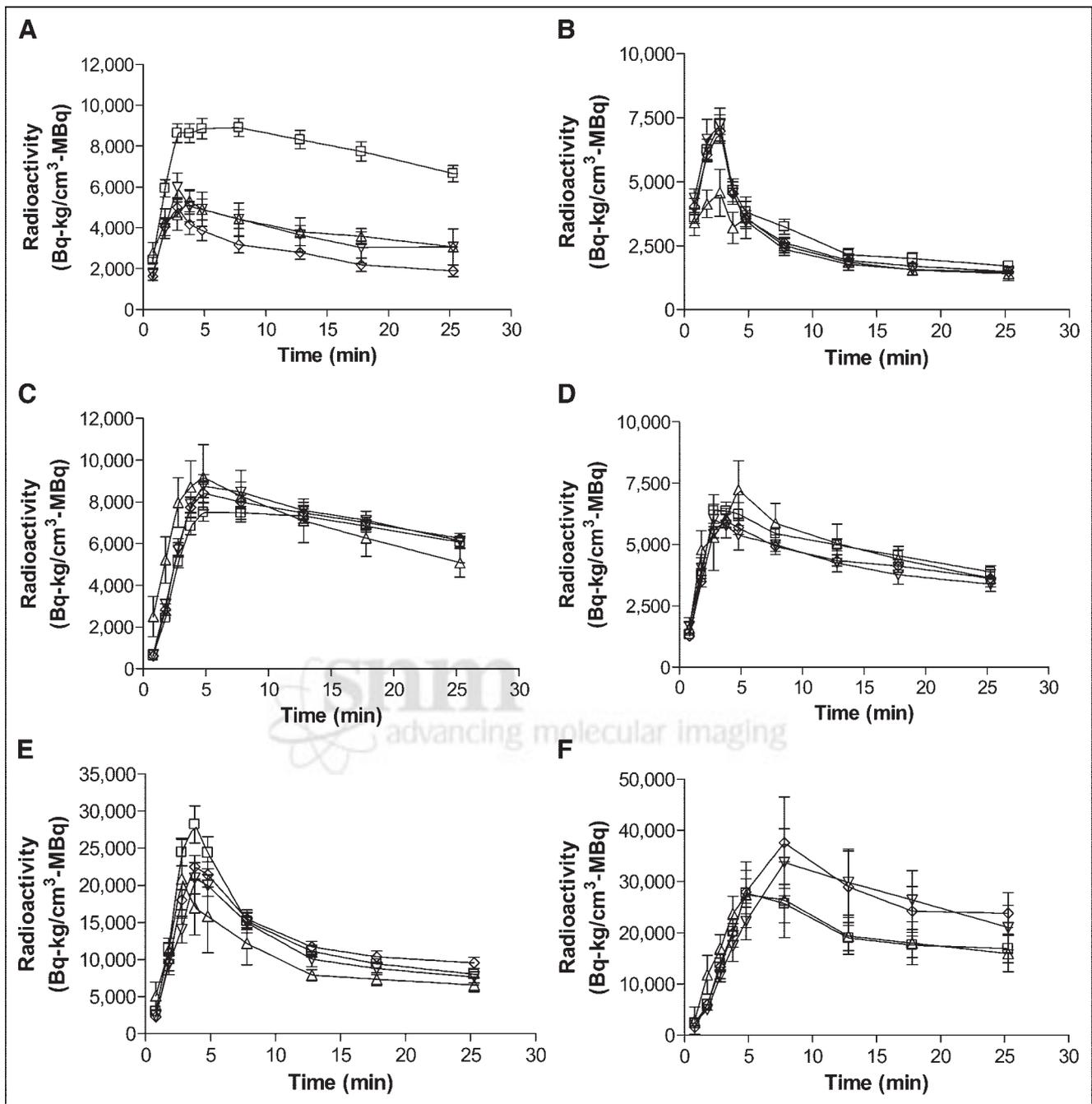
FIGURE 2. Time–activity curves for 6-^{18}F-fluorodopamine–derived radioactivity (mean ± SEM) in interventricular septal myocardium (A), left ventricular chamber (B), liver (C), spleen (D), renal cortex (E), and renal pelvis (F) in untreated healthy volunteers (□), desipramine-treated healthy volunteers (△), patients with PAF (▽), and patients with PD+OH (◇).

6-^{18}F-fluorodopamine–derived radioactivity in the renal pelvis. The extent of the decrease in renal cortical 6-^{18}F-fluorodopamine–derived radioactivity in the PD+OH group was about the same as that in the PAF group. Therefore, in addition to cardiac sympathetic denervation, both PD+OH and PAF seem to involve the loss of renal sympathetic nerves. Because of the well-known importance of renal sympathetic innervation in the regulation of sodium balance, extracellular fluid volume, and blood pressure, renal

sympathetic denervation may in turn contribute to dysregulation of circulatory homeostasis in both diseases (18,19).

Patients with PD+OH also had decreased 6-^{18}F-fluorodopamine–derived radioactivity in the thyroid gland with or without correction for ^{13}N-ammonia–derived radioactivity. The finding of decreased thyroid gland radioactivity confirmed the previous observation of decreased 6-^{18}F-fluorodopamine–derived radioactivity in PD overall (20). Relatively little is known about the functional role of such
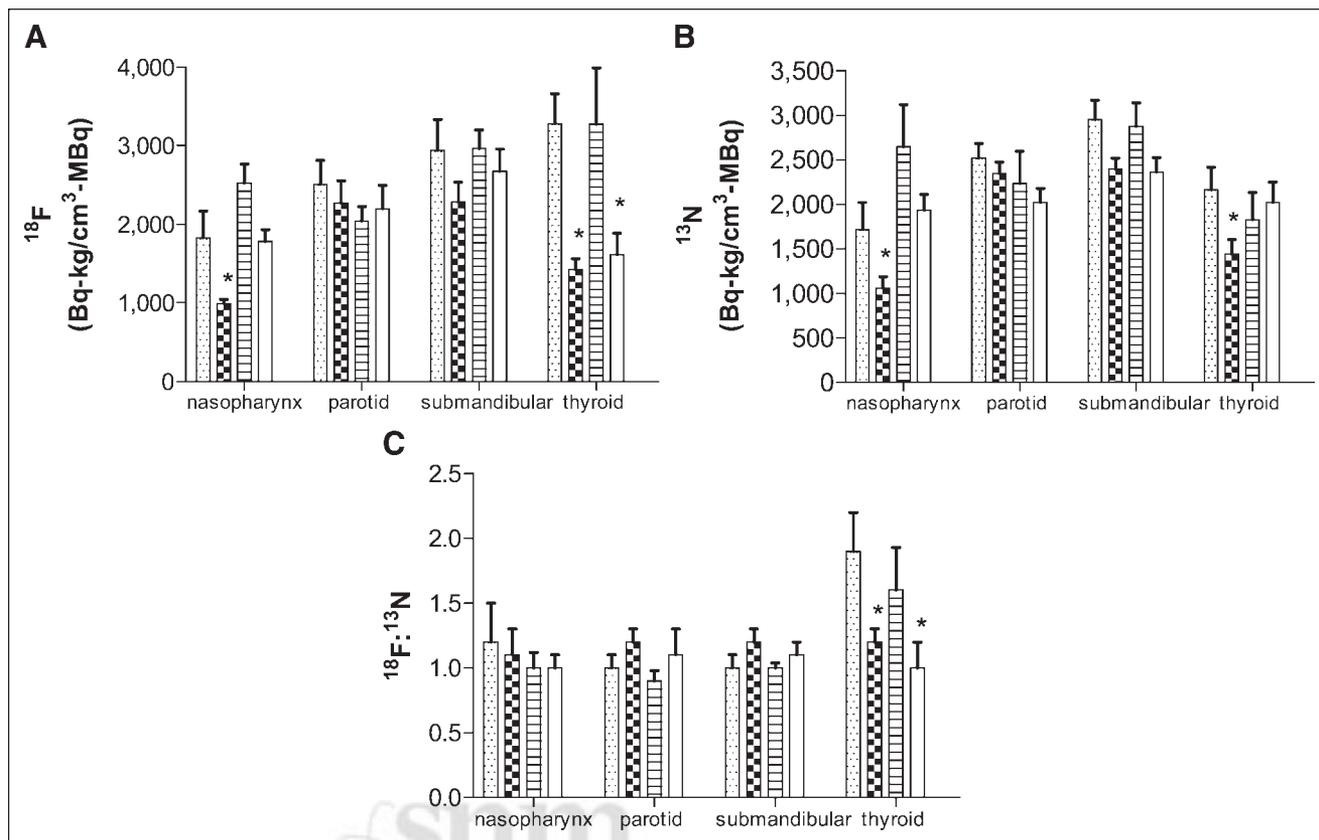
FIGURE 3. 6-^{18}F-Fluorodopamine–derived radioactivity (A), ^{13}N-ammonia–derived radioactivity (B), and ratios of 6-^{18}F-fluorodopamine–derived radioactivity to ^{13}N-ammonia–derived radioactivity (C) (mean ± SEM) in nasopharynx, parotid gland, submandibular gland, and thyroid gland in healthy volunteers (▨), desipramine-treated healthy volunteers (▩), patients with PAF (▤), and patients with PD+OH (□). *$P < 0.05$ (compared with healthy volunteers).

innervation. Unexpectedly, patients with PAF did not have evidence of decreased thyroid gland innervation, as indicated by 6-^{18}F-fluorodopamine–derived radioactivity.

Neither the PD+OH group nor the PAF group had evidence of denervation of the nasopharyngeal mucosa, as assessed by 6-^{18}F-fluorodopamine–derived radioactivity, even after correction for ^{13}N-ammonia–derived radioactivity. On the basis of the dense sympathetic innervation of this tissue, PD+OH and PAF may involve a more severe loss of sympathetic innervation in cardiac than in extracardiac vascular tissue.

Patients with PD+OH often have urinary frequency, urgency, and incontinence, like patients with PD in general (*21*). The findings of decreased 6-^{18}F-fluorodopamine–derived radioactivity in the renal cortex and increased 6-^{18}F-fluorodopamine–derived radioactivity in the renal pelvis in patients with PD+OH led us to speculate that renal sympathetic denervation may contribute to urinary frequency in PD+OH.

Valid application of a model-based approach would require sufficient empiric data about organ perfusion, arterial concentrations of 6-^{18}F-fluorodopamine–derived radioactivity, and cellular/plasma partitioning of 6-^{18}F-fluorodopamine–derived radioactivity in arterial blood. Goldstein et al. published such a model for the fate of 6-^{18}F-fluorodopamine in the human heart (*17*). The model has not been extended yet to other organs. On the basis of the complexities of interpreting ^{13}N-ammonia–derived radioactivity in terms of tissue perfusion in extracardiac organs, such as the liver, a model-based approach would require validation of means for quantifying tissue perfusion, a key determinant of the input function in the model. Because of major gaps in the empiric data, in the present study we did not feel confident in this approach and therefore used semiquantitative methodology. The neuropharmacologic method for identifying specific uptake and retention of 6-^{18}F-fluorodopamine–derived radioactivity by sympathetic nerves did seem to succeed, enabling us to infer that decreased radioactivity in patients with autonomic failure could not be explained by decreased 6-^{18}F-fluorodopamine delivery.

CONCLUSION

6-^{18}F-Fluorodopamine scanning visualized sympathetic innervation in the heart, renal cortex, and thyroid gland. Patients with PD+OH had evidence of decreased sympathetic innervation in all 3 organs. The denervation seemed to be profound in the heart but also could be detected in extracardiac organs by 6-^{18}F-fluorodopamine scanning.

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