

## SYMPATHETIC CARDIONEUROPATHY IN DYSAUTONOMIAS

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### ABSTRACT

**Background** The classification of dysautonomias has been confusing, and the pathophysiology obscure. We examined sympathetic innervation of the heart in patients with acquired, idiopathic dysautonomias using thoracic positron-emission tomography and assessments of the entry rate of the sympathetic neurotransmitter norepinephrine into the cardiac venous drainage (cardiac norepinephrine spillover). We related the laboratory findings to signs of sympathetic neurocirculatory failure (orthostatic hypotension and abnormal blood-pressure responses associated with the Valsalva maneuver), central neural degeneration, and responsiveness to treatment with levodopa-carbidopa (Sinemet).

**Methods** Cardiac scans were obtained after intravenous administration of 6-[<sup>18</sup>F]fluorodopamine in 26 patients with dysautonomia. Fourteen had sympathetic neurocirculatory failure — three with no signs of central neurodegeneration (pure autonomic failure), two with parkinsonism responsive to treatment with levodopa-carbidopa, and nine with central neurodegeneration unresponsive to treatment with levodopa-carbidopa (the Shy-Drager syndrome). The rates of cardiac norepinephrine spillover were estimated on the basis of concentrations of intravenously infused [<sup>3</sup>H]norepinephrine during catheterization of the right side of the heart.

**Results** Patients with pure autonomic failure or parkinsonism and sympathetic neurocirculatory failure had no myocardial 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity or cardiac norepinephrine spillover, indicating loss of myocardial sympathetic-nerve terminals, whereas patients with the Shy-Drager syndrome had increased levels of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity, indicating intact sympathetic terminals and absent nerve traffic. Patients with dysautonomia who did not have sympathetic neurocirculatory failure had normal levels of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity in myocardium and normal rates of cardiac norepinephrine spillover.

**Conclusions** The results of 6-[<sup>18</sup>F]fluorodopamine positron-emission tomography and neurochemical analyses support a new clinical pathophysiologic classification of dysautonomias, based on the occurrence of sympathetic neurocirculatory failure, signs of central neurodegeneration, and responsiveness to levodopa-carbidopa. (N Engl J Med 1997;336:696-702.)

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DYSAUTONOMIAS, derangements of sympathetic or parasympathetic nervous system function, are seen fairly often in neurology and cardiology. Autonomic hypofunction or failure has received the most attention,<sup>1</sup> and its causes include drugs and disease-associated polyneuropathy (e.g., diabetes and amyloidosis). Less commonly, autonomic failure occurs without an identifiable cause or in association with a disease in which the pathophysiologic basis for dysautonomia remains obscure.

A consensus statement by the American Autonomic Society and the American Academy of Neurology<sup>2</sup> distinguished three forms of primary dysautonomia: pure autonomic failure, defined as a sporadic, idiopathic cause of persistent orthostatic hypotension and other manifestations of autonomic failure that occurs without other neurologic features; Parkinson's disease with autonomic failure; and multiple-system atrophy, a sporadic, progressive disorder of adults characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination. According to the consensus statement, in a patient with multiple-system atrophy, the term "striatonigral degeneration" applies when parkinsonism dominates the clinical picture; the term "olivopontocerebellar atrophy" is used when cerebellar features predominate; and the term "Shy-Drager syndrome" is used when autonomic failure predominates. Patients with parkinsonism in the setting of multiple-system atrophy have a poor or brief response to levodopa therapy (in the United States, a combination of levodopa and carbidopa [Sinemet] is used).

Except for the subjective impression of responsiveness to levodopa-carbidopa, the classification does not distinguish Parkinson's disease with autonomic failure from the striatonigral-degeneration subtype of multiple-system atrophy. The classification also treats all types of autonomic failure identically, despite the fact that sympathetic failure produces orthostatic hypotension and parasympathetic failure produces constipation and urinary retention.

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Moreover, subtypes of multiple-system atrophy defined only on the basis of the relative predominance of clinical manifestations may or may not reflect pathophysiologically distinct entities.

Physiologic and neurochemical tests have also failed to separate forms of dysautonomia adequately. For instance, most patients with pure autonomic failure have low antecubital venous plasma levels of norepinephrine, the sympathetic neurotransmitter, but some do not<sup>3</sup>; and patients with multiple-system atrophy have normal norepinephrine levels, regardless of the subtype.<sup>4</sup>

Positron-emission tomographic (PET) scanning after systemic administration of 6-[<sup>18</sup>F]fluorodopamine can be used to visualize sympathetic innervation of tissue.<sup>5,6</sup> One might expect the absence of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity in myocardium in a patient with dysautonomia and diffuse sympathetic denervation. Analyses of trends in myocardial radioactivity over time can provide information about sympathoneural function.<sup>7</sup> For instance, blockade of ganglionic neurotransmission increases 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity in myocardium<sup>6,8</sup> and might be expected in a patient with dysautonomia and functionally intact sympathetic terminals but absent sympathetic-nerve traffic.

Assessments of the rate of entry of norepinephrine into the cardiac venous drainage (cardiac norepinephrine spillover) provide a neurochemical means to examine sympathoneural function.<sup>9</sup> Patients with autonomic failure can have virtually absent cardiac norepinephrine spillover,<sup>10,11</sup> a situation consistent with the loss of functional cardiac sympathoneural terminals.<sup>11</sup>

We examined whether 6-[<sup>18</sup>F]fluorodopamine PET scanning and measurements of cardiac norepinephrine spillover could be used to identify pathophysiologically distinct forms of dysautonomia.

## METHODS

The study protocol was approved by the Clinical Research Subpanel of the National Institute of Neurological Disorders and Stroke. Each patient provided written informed consent.

### Patients

Twenty-six patients referred for dysautonomia underwent testing at the National Institutes of Health Clinical Center. Fourteen had sympathetic neurocirculatory failure, as defined below. Nine had multiple-system atrophy that was unresponsive to levodopa-carbidopa (the Shy-Drager syndrome), two had parkinsonism that was responsive to levodopa-carbidopa and had neurogenic orthostatic hypotension, and three had pure autonomic failure. The remaining 12 patients did not have sympathetic neurocirculatory failure: 4 had multiple-system atrophy with parasympathetic dysfunction (urinary incontinence, urinary retention, and constipation), 2 reflex sympathetic dystrophy, 2 neurocardiogenic syncope, 2 idiopathic orthostatic tachycardia syndrome, 1 adrenal failure, and 1 baroreflex failure.

Sympathetic neurocirculatory failure was diagnosed on the basis of persistent orthostatic hypotension and characteristic blood-pressure abnormalities during and after the performance of the Valsalva

maneuver — a progressive fall in blood pressure during phase II (normally, mean arterial pressure increases from its nadir by the end of phase II) and the lack of an increase in systolic pressure above base line during phase IV.<sup>12</sup> The Shy-Drager syndrome was diagnosed on the basis of sympathetic neurocirculatory failure and progressive central neural degeneration — parkinsonism resistant to levodopa-carbidopa, progressive cerebellar ataxia, or supranuclear or bulbar palsy. Pure autonomic failure was diagnosed on the basis of sympathetic neurocirculatory failure without signs of central neural degeneration. Multiple-system atrophy with parasympathetic autonomic failure was diagnosed by the presence of central neural degeneration and persistent impotence, constipation, urinary incontinence, urinary retention, or decreased sweating, without specific evidence of sympathetic neurocirculatory failure.

### PET Scanning

For PET scanning the patient was positioned in a Posicam body scanner (Positron, Houston) or a General Electric Advance scanner (General Electric, Milwaukee), with his or her thorax in the gantry. Myocardial perfusion was assessed by PET scanning of the thorax for 20 minutes after a 1-minute infusion of 5 mCi of [<sup>13</sup>N]ammonia. 6-[<sup>18</sup>F]Fluorodopamine (specific activity, 0.2 to 1.0 Ci per millimole; dose in most cases, 1.0 mCi)<sup>6</sup> was dissolved in about 10 ml of normal saline and, beginning at least one hour after the administration of [<sup>13</sup>N]ammonia, was infused intravenously at a constant rate for three minutes, with continuous thoracic PET scanning for up to three hours afterward. A brachial arterial cannula was inserted percutaneously for blood-pressure monitoring and blood sampling. For purposes of analysis, the total scanning time was divided into intervals of 5 to 30 minutes, and the tomographic results for each interval were assessed. Data acquisition was independent of the phase of the electrocardiographic cycle.

### Kinetics of Norepinephrine in Cardiac Tissue

Most patients also underwent catheterization of the right side of the heart for the estimation of norepinephrine spillover into coronary-sinus plasma. A tracer amount of [<sup>3</sup>H]norepinephrine (levo-[2,5,6]-[<sup>3</sup>H]norepinephrine, New England Nuclear, Boston) was infused intravenously, with coronary-sinus blood flow measured by thermodilution and arterial and coronary-sinus blood sampled after at least 20 minutes.<sup>10,13</sup>

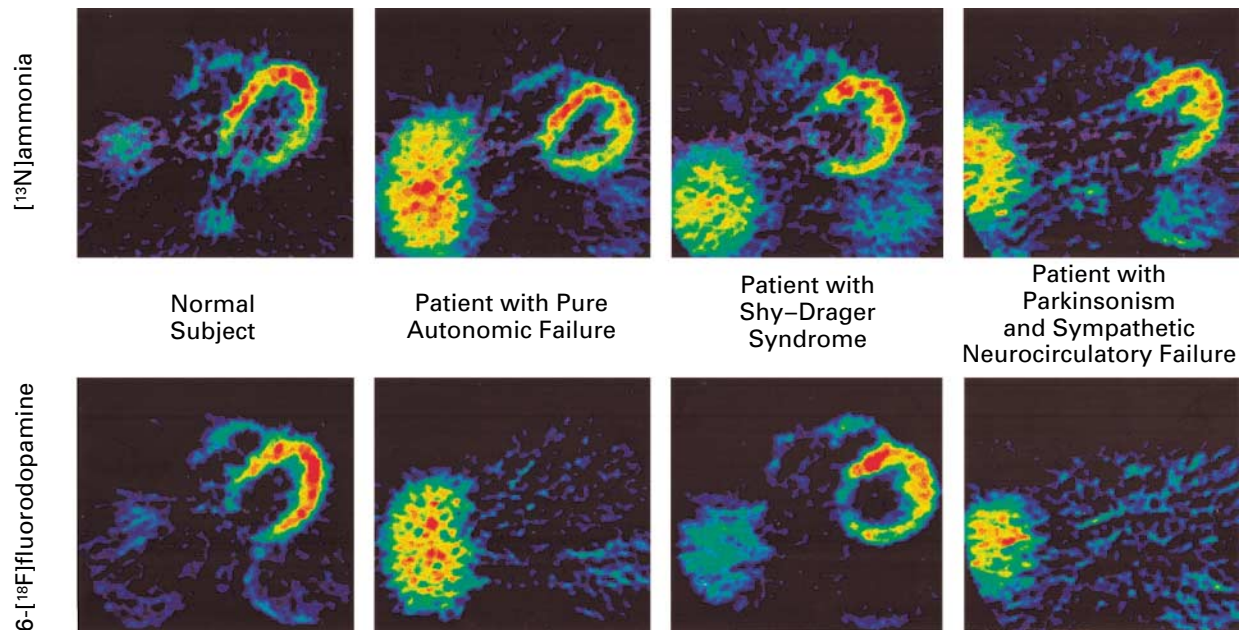
### Blood Samples and Assays

Plasma obtained from arterial blood before and after the administration of 6-[<sup>18</sup>F]fluorodopamine was assayed for this compound and its deaminated metabolite, 6-[<sup>18</sup>F]fluorodihydroxyphenylacetic acid.<sup>6,14</sup> Arterial and coronary-sinus plasma obtained during catheterization of the right side of the heart was assayed for endogenous and [<sup>3</sup>H]-labeled norepinephrine and for 1-dihydroxyphenylalanine (levodopa, the precursor of the catecholamines), dihydroxyphenylglycol (a neuronal metabolite of norepinephrine), and dihydroxyphenylacetic acid (a deaminated metabolite of dopamine).<sup>13</sup> Concentrations corrected for the rate of decay (in nanocuries per milliliter) were adjusted for the dose of radioactive drug (in millicuries) per kilogram of body weight.

### Statistical Analysis

Cardiac images were analyzed as described previously.<sup>6</sup> Circular regions of interest (in which the diameters were about half the width of the ventricular wall) were created with time-averaged (5 to 20 minutes for [<sup>13</sup>N]ammonia and 5 to 180 minutes for 6-[<sup>18</sup>F]fluorodopamine) images of single slices. Radioactivity concentrations in two regions of interest in the left ventricular free wall and two in the septum were averaged.

PET data in patients with dysautonomia were compared with those in 22 healthy, normal subjects (age range, 22 to 82 years) who were studied at the National Institutes of Health.<sup>6</sup> The rates of cardiac norepinephrine spillover in the patients were compared



**Figure 1.** Thoracic PET Scans after the Intravenous Injection of 5 mCi of  $[^{13}\text{N}]\text{ammonia}$  and 1 mCi of  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$  in a Normal Subject, a Patient with Pure Autonomic Failure, a Patient with the Shy-Drager Syndrome, and a Patient with Parkinsonism and Sympathetic Neurocirculatory Failure.

The images represent time-averaged, non-gated data, with the color-scale units adjusted so that red indicated the peak and black the minimal radioactivity concentration. The right side of each picture corresponds to the left side of the subject.

with those in 32 healthy subjects (age range, 18 to 69 years) who were studied at the Baker Medical Research Institute, Prahran, Victoria, Australia, or at Sahlgrenska University Hospital, Goteborg, Sweden.<sup>9</sup> The rates of cardiac norepinephrine spillover and the cardiac arteriovenous increments in plasma levels of catechols (the differences between the venous and arterial concentrations) were assessed by dependent-means t-tests. Analyses of variance for repeated measures were used to assess differences in trends of  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$ -derived radioactivity in myocardium or plasma levels of  $6\text{-}[^{18}\text{F}]\text{fluorodihydroxyphenylacetic acid}$  between patients with the Shy-Drager syndrome and normal subjects. A P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

In healthy subjects, thoracic  $[^{13}\text{N}]\text{ammonia}$  and  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$  PET scans were very similar (Fig. 1).

Among the three patients with pure autonomic failure, one had a low concentration of arterial plasma norepinephrine in the supine position (22 pg per milliliter [0.13 nmol per liter]), whereas the other two had normal concentrations (167 and 133 pg per milliliter [0.99 and 0.79 nmol per liter]). None of the three patients had detectable  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$ -derived radioactivity in myocardium (Fig. 1), cardiac norepinephrine spillover, or cardiac arteriovenous increments in plasma levels of levodopa, dihydroxyphenylglycol, or dihydroxyphenylacetic acid (Table 1).

All nine patients with the Shy-Drager syndrome had clearly visible  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$ -derived ra-

dioactivity in the left ventricle (Fig. 1), and the level of radioactivity was higher than that in patients with multiple-system atrophy without sympathetic neurocirculatory failure and normal subjects (Fig. 2). Patients with the Shy-Drager syndrome had normal rates of cardiac norepinephrine spillover and had higher arterial plasma levels of  $6\text{-}[^{18}\text{F}]\text{fluorodihydroxyphenylacetic acid}$  (Fig. 2) than the normal subjects.

Patients with multiple-system atrophy without sympathetic neurocirculatory failure had normal levels of  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$ -derived radioactivity in myocardium, normal rates of cardiac norepinephrine spillover, and in most cases, normal arteriovenous increments in plasma levels of levodopa, dihydroxyphenylglycol, and dihydroxyphenylacetic acid.

Both patients with parkinsonism that was responsive to levodopa-carbidopa and sympathetic neurocirculatory failure had undetectable levels of  $6\text{-}[^{18}\text{F}]\text{fluorodopamine}$ -derived radioactivity in myocardium (Fig. 1) and no detectable cardiac norepinephrine spillover or arteriovenous increments in plasma levels of levodopa, dihydroxyphenylglycol, or dihydroxyphenylacetic acid (Table 1).

## DISCUSSION

Our results show that there are different types of deranged cardiac sympathetic neuronal function (sympathetic cardioneuropathy), a finding that supports both the concept that there are pathophysio-

**TABLE 1.** MEAN CORONARY-SINUS BLOOD FLOW AND CONCENTRATIONS OF NOREPINEPHRINE AND OTHER CATECHOLS IN PATIENTS WITH DYSAUTONOMIAS AND NORMAL SUBJECTS.\*

VARIABLE	DIAGNOSIS				NORMAL SUBJECTS
	PURE AUTONOMIC FAILURE	SHY-DRAGER SYNDROME	PARKINSONISM AND SNF	OTHER†	
Coronary-sinus blood flow (ml/min)	142±14	184±18	205±20	144±27	184±15
No. of subjects	3	7	2	8	32
Norepinephrine					
Arterial plasma concentration (pg/ml)	107±44	235±20	732±483	331±57	226±15
No. of subjects	3	9	2	13	32
Percentage extracted by myocardium	6±3	70±4‡	12±4	68±5‡	81±2‡
No. of subjects	3	8	2	9	32
Spillover into coronary-sinus plasma (ng/min)	0±0	21±4‡	4±1	27±12‡	18±2‡
No. of subjects	3	7	2	8	32
Arteriovenous increment in plasma levodopa in patients not treated with levodopa-carbidopa (pg/ml)	7±39	120±33‡	-52±43	155±24‡	236±18‡
No. of subjects	3	8	2	7	32
Arteriovenous increment in plasma dihydroxyphenylglycol (pg/ml)	-17±11	472±106‡	18±2	633±105‡	711±35‡
No. of subjects	3	8	2	9	32
Arteriovenous increment in plasma dihydroxyphenylacetic acid (pg/ml)	91±140	117±26‡	-38±32	152±35‡	331±50‡
No. of subjects	3	8	2	7	32

\*Plus-minus values are means ±SE. SNF denotes sympathetic neurocirculatory failure. To convert the values for norepinephrine, dopamine, dihydroxyphenylglycol, and dihydroxyphenylacetic acid to nanomoles per liter, divide by 169, 197, 170, and 168, respectively.

†Other diagnoses consisted of multiple-system atrophy with parasympathetic dysfunction in four patients, reflex sympathetic dystrophy in two, neurocardiogenic syncope in two, idiopathic orthostatic tachycardia syndrome in two, adrenal failure in one, and baroreflex failure in one.

‡P<0.05 for the comparison with zero.

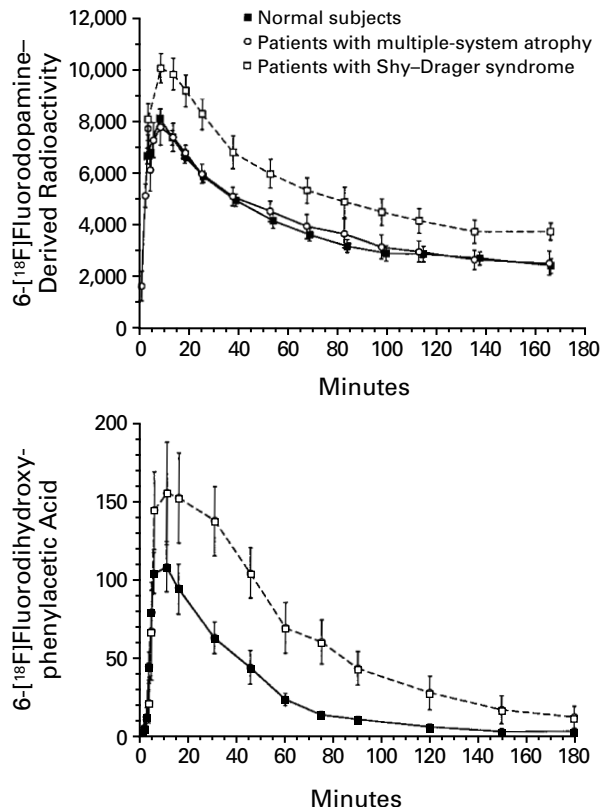
logically distinct dysautonomias and the move to modify the clinical diagnostic classification of autonomic failure in adults.<sup>15,16</sup> The absence of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity in the myocardium of the three patients with pure autonomic failure probably reflected a loss of postganglionic sympathetic terminals in cardiac tissue. Decreased activity of a sympathoneuronal membrane transporter can also produce this result<sup>7</sup>; however, the same patients had strong neurochemical evidence of cardiac sympathetic denervation: virtually no cardiac spillover of norepinephrine<sup>11</sup> and no cardiac production of levodopa,<sup>11</sup> dihydroxyphenylglycol,<sup>13</sup> or dihydroxyphenylacetic acid.<sup>17,18</sup>

In contrast, patients with the Shy-Drager syndrome (multiple-system atrophy with sympathetic neurocirculatory failure) clearly had 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity in myocardium, normal rates of cardiac spillover of norepinephrine, and substantial cardiac production of levodopa, dihydroxyphenylglycol, and dihydroxyphenylacetic acid, confirming the presence of functionally intact cardiac sympathetic terminals. In fact, these patients had higher myocardial concentrations of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity than normal subjects or patients with multiple-system atrophy and

no sympathetic neurocirculatory failure. The increased radioactivity did not result from increases in either coronary blood flow or plasma concentrations of 6-[<sup>18</sup>F]fluorodopamine. Since the rates of loss of 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity depend partly on ongoing sympathoneural traffic,<sup>7</sup> decreased or absent sympathetic outflow to the heart can explain the increased myocardial radioactivity in patients with the Shy-Drager syndrome.

Plasma levels of 6-[<sup>18</sup>F]fluorodihydroxyphenylacetic acid reflect the metabolism of 6-[<sup>18</sup>F]fluorodopamine in sympathetic nerves.<sup>6,8</sup> The elevated 6-[<sup>18</sup>F]fluorodihydroxyphenylacetic acid levels in patients with the Shy-Drager syndrome therefore probably reflected generalized increases in neuronal concentrations of 6-[<sup>18</sup>F]fluorodopamine, as would be expected if 6-[<sup>18</sup>F]fluorodopamine built up in the axoplasm as a result of a generalized absence of sympathetic-nerve traffic.<sup>7</sup>

When patients with multiple-system atrophy were stratified according to the occurrence of sympathetic neurocirculatory failure (persistent orthostatic hypotension, a progressive decline in blood pressure during performance of the Valsalva maneuver, and the lack of a phase IV increase in systolic blood pressure above base line after the maneuver), the find-



**Figure 2.** Mean ( $\pm$ SE) Concentrations of 6-[ $^{18}$ F]Fluorodopamine-Derived Radioactivity in Myocardium and of Arterial Plasma 6-[ $^{18}$ F]Fluorodihydroxyphenylacetic Acid as a Function of Time after the Infusion of 6-[ $^{18}$ F]Fluorodopamine in Patients with the Shy-Drager Syndrome, Patients with Multiple-System Atrophy without Sympathetic Neurocirculatory Failure, and Normal Subjects.

Concentrations corrected for the rate of decay (in nanocuries per milliliter) were adjusted for the dose of radioactive drug (in millicuries) per kilogram of body weight.

ings on 6-[ $^{18}$ F]fluorodopamine PET scanning and the neurochemical results clearly distinguished the two groups. The patients with sympathetic neurocirculatory failure (the Shy-Drager syndrome) had increased 6-[ $^{18}$ F]fluorodopamine-derived radioactivity, and the patients without sympathetic neurocirculatory failure did not. These results suggest that the Shy-Drager syndrome differs pathophysiologically from multiple-system atrophy without sympathetic neurocirculatory failure, in that only the former is associated with decreased or absent sympathetic-nerve traffic.

The Shy-Drager syndrome has been thought to involve a central neural derangement of baroreflex function,<sup>19</sup> because the patients have normal plasma norepinephrine levels while supine<sup>4,20</sup> but deficient norepinephrine responses while standing.<sup>20</sup> This explanation predicts that while supine, the patients should have normal sympathetic outflows; however,

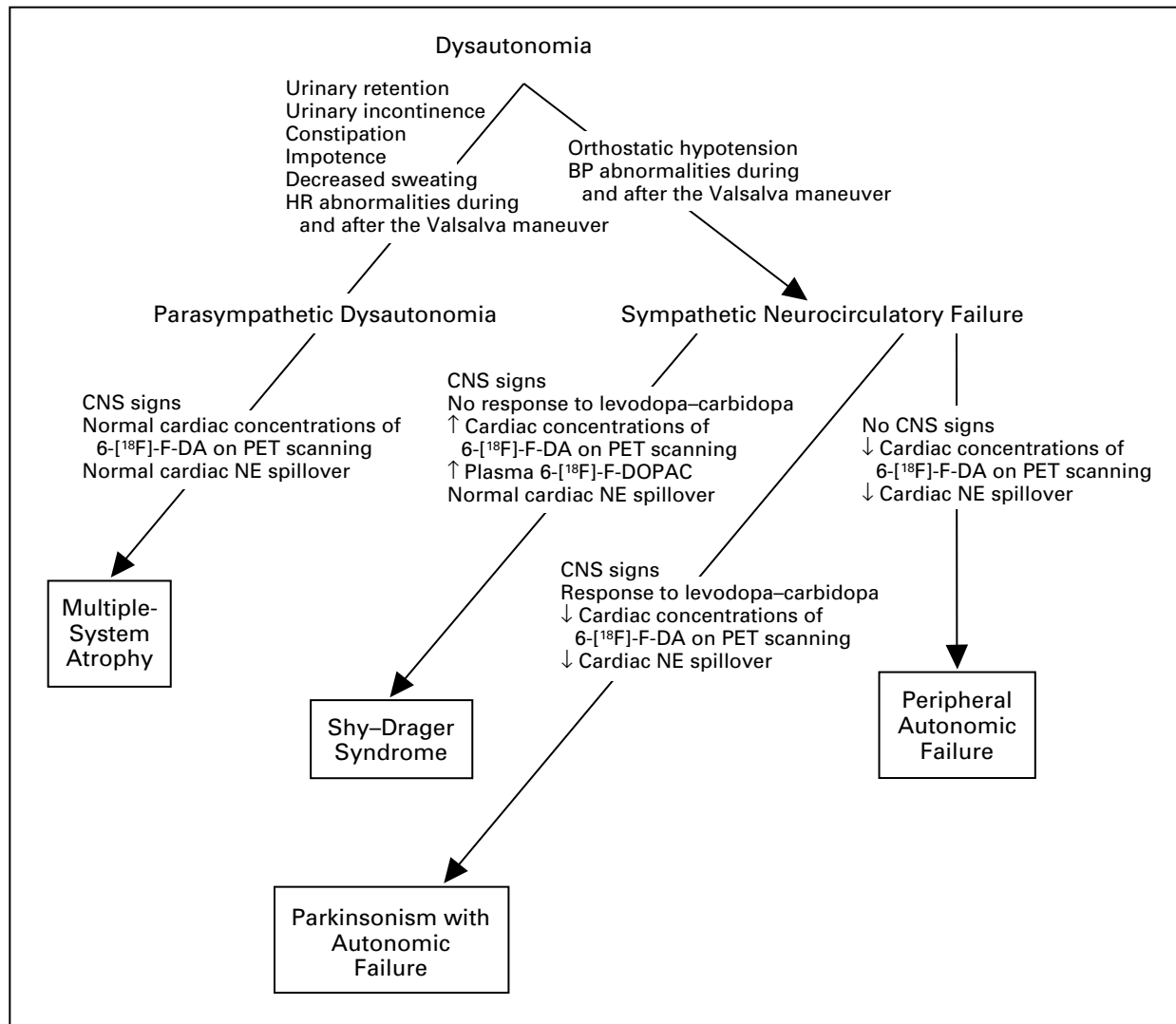
pathological reports concerning these patients have noted central nervous system lesions, such as in the intermediolateral columns of the spinal cord,<sup>21-24</sup> that would decrease or abolish sympathetic-nerve traffic. Attempts to quantify sympathetic-nerve traffic directly by microneurography in patients with the Shy-Drager syndrome have failed.<sup>25-27</sup>

Our results further highlight the apparent paradox of normal entry of norepinephrine into the bloodstream in the setting of apparently decreased or absent postganglionic sympathetic-nerve traffic in patients with the Shy-Drager syndrome. “Constitutive neurosecretion” — spontaneous release of norepinephrine independent of sympathetic-nerve traffic — may explain this phenomenon. Studies of subjects with trimethaphan-induced abolition of postganglionic sympathoneural traffic<sup>28</sup> and studies of laboratory animals<sup>29,31</sup> support the existence of constitutive neurosecretion. The mechanisms of constitutive neurosecretion, if it occurs, in patients with the Shy-Drager syndrome are unknown.

Distinguishing between the Shy-Drager syndrome and parkinsonism with autonomic failure has proved particularly challenging diagnostically, since both entities feature progressive central neural degeneration, neurogenic orthostatic hypotension, and a failure of plasma norepinephrine levels to increase when patients are standing. From the consensus statement on the definition of these disorders,<sup>2</sup> clinical responsiveness to levodopa treatment constitutes the only factor differentiating nigrostriatal degeneration from Parkinson’s disease with autonomic failure. In our study, two patients with parkinsonism and sympathetic neurocirculatory failure had no 6-[ $^{18}$ F]fluorodopamine-derived radioactivity in myocardium, in contrast with the patients with the Shy-Drager syndrome, who had increased radioactivity. This difference provides a clear distinction between these entities and supports the separate classification of Parkinson’s disease with autonomic failure.

The frequency of orthostatic hypotension among patients with Parkinson’s disease remains unknown. Clinicians may ascribe orthostatic hypotension in this setting to treatment with levodopa-carbidopa. The present findings in a small subgroup of patients do not warrant generalization to the overall population of patients with Parkinson’s disease; however, they do demonstrate that orthostatic hypotension in patients with parkinsonism can reflect sympathetic denervation.

We propose a pathophysiologic classification of dysautonomias (Fig. 3) in which sympathetic neurocirculatory failure results from peripheral sympathetic denervation or decreased or absent sympathoneural traffic, with or without signs of central neural degeneration, and in which both parkinsonism with sympathetic neurocirculatory failure and multiple-system atrophy without sympathetic neurocirculatory failure



**Figure 3.** Pathophysiologic Classification of Dysautonomias Based on Clinical Physiologic and Laboratory Findings Indicating Sympathetic Neurocirculatory Failure, the Occurrence of Signs of Central Neurodegeneration, and Clinical Responsiveness to Levodopa-Carbidopa.

HR denotes heart rate, BP blood pressure, CNS central nervous system, 6-[<sup>18</sup>F]-F-DA 6-[<sup>18</sup>F]fluorodopamine-derived radioactivity, 6-[<sup>18</sup>F]-F-DOPAC 6-[<sup>18</sup>F]fluorodihydroxyphenylacetic acid, NE norepinephrine, ↑ an increase, and ↓ a decrease.

differ from the Shy-Drager syndrome. The PET scanning and neurochemical results and the clinical distinctions based on the occurrence of sympathetic neurocirculatory failure, signs of central neurodegeneration, and responsiveness to levodopa-carbidopa support this classification scheme, which differs in some respects from that in the consensus statement.<sup>2</sup>

Refined clinical laboratory means to identify pathophysiologic mechanisms of dysautonomias should allow the development of more effective means to diagnose the type of dysautonomia in individual patients, establish a prognosis, and predict responses to therapy.

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