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Functional effects of cardiac sympathetic denervation in neurogenic orthostatic hypotension

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Abstract

Background: Diseases characterized by neurogenic orthostatic hypotension (NOH), such as Parkinson disease (PD) and pure autonomic failure (PAF), are associated with cardiac sympathetic denervation, as reflected by low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity. We studied the impact of such denervation on cardiac chronotropic and inotropic function.
Methods: Cardiac inotropic function was assessed by the pre-ejection period index and the systolic time ratio index in response to the directly acting beta-adrenoceptor agonist, isoproterenol, and to the indirectly acting sympathomimetic amine, tyramine, in patients with PD + NOH or PAF (PD + NOH/PAF group, $N = 13$). We compared the results to those in patients with multiple system atrophy, which usually entails NOH with normal cardiac sympathetic innervation (MSA, $N = 15$), and in normal control subjects ($N = 5$).
Results: The innervated and denervated groups did not differ in baseline mean pre-ejection period index or systolic time ratio index. Tyramine increased cardiac contractility in the MSA patients and controls but not in the PD + NOH/PAF group. For similar heart rate responses, the PD + NOH/PAF group required less isoproterenol ($p < 0.01$) and had lower plasma isoproterenol levels ($p < 0.01$) than did the MSA group.
Conclusions: Among patients with NOH those with cardiac sympathetic denervation have an impaired inotropic response to tyramine and exaggerated responses to isoproterenol. This pattern suggests that cardiac denervation is associated with decreased ability to release endogenous norepinephrine from sympathetic nerves and with supersensitivity of cardiac beta-adrenoreceptors.
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Keywords: Parkinson disease; Pure autonomic failure; Sympathetic denervation; Pre-ejection period

1. Introduction

Sympathetic noradrenergic innervation of the heart constitutes a major effector for central neural control of cardiovascular function. Norepinephrine released from sympathetic nerves occupies adrenoceptors on myocardial cells, exerting a positive inotropic effect. The same neurotransmitter released from sympathetic nerves in the adventitia and media of arteriolar walls evokes vasoconstriction in most vascular beds. Generalized increases in sympathetic noradrenergic outflows augment cardiac output and increase peripheral vascular resistance, thereby increasing blood pressure.

Parkinson disease, pure autonomic failure, and multiple system atrophy are in a class of neurodegenerative disorders called synucleinopathies [1]. All three diseases feature autonomic dysfunction manifested by neurogenic orthostatic hypotension, but with clear differences in the status of the sympathetic innervation of the heart. Over the past decade compelling evidence has accrued for profound cardiac sympathetic denervation in both pure autonomic failure and in Parkinson disease with neurogenic orthostatic hypotension [2–4]. In contrast, most

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patients with multiple system atrophy have intact cardiac and overall sympathetic innervation [3].

The functional effects of cardiac sympathetic denervation in synucleinopathies have been unknown.

In the present study we compared patients with neurogenic orthostatic hypotension and denervated hearts (Parkinson disease and pure autonomic failure) to patients with neurogenic orthostatic hypotension and innervated hearts and to normal controls in terms of hemodynamic and neurochemical responses to tyramine and isoproterenol. We hypothesized that patients with neurogenic orthostatic hypotension and cardiac sympathetic denervation (Parkinson disease with neurogenic orthostatic hypotension or pure autonomic failure) would have attenuated inotropic responses to i.v. administration of the indirectly acting sympathomimetic amine tyramine and intact inotropic and chronotropic responses to the directly acting beta-adrenoceptor agonist, isoproterenol. In contrast, patients with neurogenic orthostatic hypotension and intact cardiac sympathetic innervation (multiple system atrophy) would have normal responses.

2. Methods

2.1. Subjects

The study population consisted of a total of 28 patients with chronic autonomic failure, stratified in two groups. The first group consisted of 13 patients (9 Parkinson disease with neurogenic orthostatic hypotension, 4 pure autonomic failure, aged 67 ± 2 years old (standard error of mean), 7 males) who had neuroimaging evidence for cardiac sympathetic denervation (DEN group). The Hoehn and Yahr stage of the Parkinson disease subjects ranged from 1 to 5. The second group consisted of 15 multiple system atrophy with neurogenic orthostatic hypotension patients who had neuroimaging evidence of intact sympathetic innervation (INN group, 56 ± 3 years old, 12 males). Five additional healthy volunteers (aged 48 ± 9 years old, 4 males) served as a normal control group.

The subjects were studied at the National Institutes of Health Clinical Center after giving informed, written consent to participate in protocols approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke.

For each patient, a medical history and physical examination were taken, with emphasis on symptoms and signs of central neurodegeneration and autonomic failure. Drugs known to affect sympathetic neuroeffector function, such as tricyclic antidepressants and sympatholytic agents, were discontinued a week before the study. Other antiparkinsonian drugs including carbidopa/levodopa (9 patients), pramipexole (3 patients), trihexyphenidyl (1 patient), amantadine (2 patients) were discontinued 5 or more days before the study.

2.2. Cardiac sympathetic neuroimaging

All subjects had cardiac sympathetic neuroimaging before the study. Each subject was positioned supine, feet-first in a GE Advance™ scanner (General Electric, Milwaukee, WI), with the thorax in the gantry. After transmission scanning for attenuation correction, 6-[^{18}F] fluorodopamine (usual dose 0.037 MBq, specific activity 7.4–37 MBq/mmol, in about 10 mL of normal saline) was infused i.v. at a constant rate for 3 min. Dynamic scanning data were obtained for thoracic radioactivity, with the midpoint of the scanning interval at 7.5 min after injection of the tracer (data collection interval between 5 and 10 min). Cardiac sympathetic denervation was defined by low concentrations of 6-[^{18}F] fluorodopamine-derived radioactivity in the interventricular septum (less than 5000 Bq/mL per MBq/kg) and left ventricular free wall (less than 4000 Bq/mL per MBq/kg), corresponding to 2 standard deviations below the normal means.

2.3. Study protocol

In most subjects, a brachial arterial catheter was inserted for pressure monitoring and drawing blood samples, and an antecubital venous catheter was used to infuse test drugs. Each patient also had electrocardiographic and impedance cardiographic monitoring (BioZ, Cardiodynamics, San Diego, CA, USA). Continuous vital signs data were digitized and recorded using a PowerLab (AD Instruments Ltd., Castle Hill, Australia) data acquisition system.

2.4. Tyramine infusion

On the day of infusion, tyramine was dissolved in 5% dextrose and infused i.v. at a rate of 1 mg/min for 10 min. Subjects were supine, except that in those with severe supine hypertension (systolic pressure more than 200 mmHg; 4 patients), tyramine was infused during head-up tilting (15–30 degrees), to decrease baseline pressure. Blood samples were drawn after the patient was at rest and then at 10 min during the infusion, transferred to heparinized sample tubes, and placed immediately on ice. The plasma was separated by refrigerated centrifugation. A sample of the tyramine infusate was also taken. The plasma and infusate samples were stored at −70 °C or colder until assayed for catechol contents in our laboratory by batch alumina extraction followed by liquid chromatography with electrochemical detection [5].

2.5. Isoproterenol infusion

On a separate day from that for tyramine infusion, isoproterenol was infused in 10 patients in the DEN group and 14 in the INN group. The setup and data acquisition for the isoproterenol infusion test were similar to those for tyramine infusion, except that a brachial arterial catheter was not used. A catheter was inserted in a vein in each arm, one catheter for blood sampling and the other for isoproterenol infusion. Beat-to-beat blood pressure was monitored non-invasively using a Finometer™ device (Finapres Medical Systems, Amsterdam, Netherlands). After baseline samples were obtained, isoproterenol freshly diluted in normal saline was infused at four incremental doses (3.5, 7, 14, and 35 ng/kg per min, each step for about 10 min), until heart rate increased by about 25 bpm from the baseline value. Blood samples for plasma catechols and isoproterenol plasma levels were processed together with an aliquot of the isoproterenol and stored and assayed as described above.

2.6. Cardiac evaluation

Stroke volume, cardiac output, velocity index, acceleration index, preejection period (PEP), left ventricular ejection time (LVET) and electromechanical systole were measured non-invasively using the BioZ impedance cardiographic device, before and during the tyramine and isoproterenol infusions. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output. Heart rate-corrected indices including LVET index (LVETI) and PEP index (PEPI) were calculated according to Weissler's equations[6] as follows: LVETI = 1.7 × heart rate + LVET and PEPI = 0.4 × heart rate + PEP. Systolic time ratio and systolic time ratio index were calculated as follows: systolic time ratio = PEP/LVET and systolic time ratio index = PEPI/LVETI.

PEP, the interval between the electrocardiographic Q wave and aortic valve opening, corresponds to the isovolumetric ventricular contraction time. PEP and PEPI have been regarded as inverse measures of cardiac contractility [6–11]. A pattern of prolongation of the PEP and shortening of the LVET characterizes acute myocardial infarction, angina pectoris, and heart failure [11–13]. The ratio of PEP to LVET (PEP/LVET) has also been regarded as an inverse measure of left ventricular systolic performance. PEP reduction reflects a positive inotropic effect of the cardiac sympathetic nerves on the myocardium [14].

2.7. Baroreflex evaluation

The Valsalva maneuver was performed as described previously [15]. Baroreflex-cardiovagal gain was calculated from the slope of the relationship