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Clinical Research Paper

Dobutamine stress test unmasks cardiac sympathetic denervation in Parkinson's disease

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Abstract

Objective: Cardiac uptake of [^{123}I]metaiodobenzyl guanidine (MIBG) is reduced in patients with Parkinson's disease (PD). However, the cardiac sympathetic abnormality associated with this reduction is unclear. To unmask this abnormality in PD patients we examined the functional consequences of cardiac beta-receptor activation.
Methods: Cardiovascular responses to stepwise administration of the beta1-receptor agonist, dobutamine (DOB), were assessed in 25 PD patients and 12 age-matched controls. Changes in blood pressure were compared to determine the optimal dose at which to detect denervation supersensitivity, and cardiac contractility was measured by DOB echocardiography, based on peak aortic flow velocity. The relations of these cardiovascular responses to the ratio of MIBG uptake into the heart vs. that into the mediastinum (H/M ratio) were analyzed.
Results: At 4 μg/kg/min DOB, systolic blood pressure increased more in PD patients than in controls (PD, 17.5±12.3 mm Hg; control, 7.2±6.2 mm Hg, $p<0.01$), suggesting the presence of denervation supersensitivity. At this DOB dose cardiac contractility also increased more in PD than in controls (PD, 39.0±15.7%; control, 23.5±5.2%, $p<0.005$) and this hyperdynamic response was significantly correlated with reduced H/M ratios (early: $r=-0.63$, $p<0.01$, delayed: $r=-0.66$, $p<0.01$).
Conclusion: Low-dose DOB unmasks cardiac sympathetic denervation in PD patients, and decreased MIBG uptake indicates the presence of denervation supersensitivity within the heart, resulting in hyperdynamic cardiac contractility in response to a beta 1-stress condition.

Keywords: Parkinson's disease; Dobutamine; Denervation supersensitivity; Cardiac sympathetic denervation; Dobutamine echocardiography; MIBG; Cardiac contractility

1. Introduction

Since Hakusui first demonstrated cardiac sympathetic nerve damage in patients with Parkinson's disease (PD) by decreased cardiac [^{123}I]metaiodobenzyl guanidine (MIBG) uptake [1], a large number of studies have documented this phenomenon [2–4]. Uptake of MIBG reflects myocardial sympathetic nerve function [5]. Histological assessment of the sympathetic nerve axon population innervating cardiac muscle is also markedly decreased in PD patients and is considered to account for the decrease in MIBG uptake [6,7]. Severe abnormal MIBG findings in peripheral vessels were also found in PD with autonomic failure [8]. However, the cardiac sympathetic abnormality correlated to reduced MIBG uptake in PD patients has not been clarified. Echocardiography has demonstrated normal ventricular systolic function under resting conditions in PD patients [9].

Cardiovascular responses to sympathomimetic agents have been anecdotally described to be exaggerated in PD patients [10,11] but it is unclear whether these responses are due to impaired cardiac sympathetic nerve function or other

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peripheral/central autonomic system abnormalities. Dobutamine (DOB) is a synthetic sympathomimetic amine that directly stimulates beta-adrenergic receptors, especially beta1-receptors [12,13]. In normal subjects, infusion of DOB in doses up to 10 μg/kg/min increases cardiac output and heart rate (HR) but has little effect on blood pressure (BP) [13,14]. DOB is commonly used in the stress test to diagnose ischemic heart disease [15,16]. Specifically, low-dose DOB has been used, because it is safe and convenient to administer, to identify viable myocardial impairment [17,18].

In PD patients, various degrees of primary chronic autonomic failure are seen and some patients with orthostatic hypotension display evidence of cardiac sympathetic denervation [19]. Thus, it is clinically important to clarify how this cardiac denervation correlates with the decreased MIBG uptake that is commonly seen in PD patients. The purpose of this study was to assess the cardiovascular response of beta1-adrenergic receptors using low-dose DOB to detect cardiac denervation supersensitivity and unmask the cardiac abnormality associated with decreased MIBG uptake in patients with PD. Echocardiography was performed to evaluate the cardiac response to DOB and verify the association between this response and the degree of cardiac MIBG uptake.

2. Subjects and methods

2.1. Subjects

We included 25 patients with PD (10 men, 15 women) who were referred to the Nagoya University Hospital. PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria [20]. All patients underwent precise neurological examinations and brain MRIs to exclude diagnoses other than PD. In all cases, no obvious heart disease, including experience of anginal pain, or diabetes mellitus was detected and electrocardiographs were all normal. The mean patient age was 65.5 ± 8.1 and the mean duration since the onset of symptoms was 4.8 ± 3.7 years (range: 1 to 12 years; Table 1). The control subjects were normal healthy volunteers (5 men, 7 women, 61.1 ± 14.0 years old) with no history of heart disease, diabetes mellitus, or intracranial disease and no obvious abnormalities observed on physical examination. Orthostatic hypotension was absent during head-up tilt testing in the control group. Informed consent was obtained from all participants and the protocol of the study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

2.2. DOB infusion test

Patients abstained from eating and the use of anti-parkinsonian drugs on the morning of testing. No patient took other drugs that might influence BP responses, such as midodorine or droxidopa. The subjects were tested in the supine position. After resting for at least 5 min, DOB (2 μg/kg/min; 0.5 ml/min) was administered by continuous intravenous infusion via a brachial venous cannula using a constant infusion pump. After 5 min the infusion was increased to 4 μg/kg/min and continued for another 5 min until: (1) the systolic BP (SBP) was > 170 mm Hg or the SBP increase was > 40 mm Hg, or (2) the HR > 100/min, or (3) there was an increase in the frequency of arrhythmias, or (4) the development of untoward side effects. BP and HR were recorded every minute with an automated sphygmomanometer (BP-508, Nippon Colin, Tokyo, Japan), designed for autonomic studies, placed on the upper arm opposite to that used for the DOB infusion. The electrocardiogram was monitored continuously throughout the procedure.

Table 1
Clinical characteristics

	PD (n=25)	Control (n=12)	p value
Age (years)	65.5 (8.1)	61.1 (14.0)	N.S.
Gender (M/F)	10/15	5/7	N.S.
Disease duration (years)	4.8 (3.7)		
Hoehn and Yahr stages	I:3; II:6; III:8; IV:8		
Levodopa (mg/day)	254.8 (190.4)		

Values are expressed as mean (±SD). PD = Parkinson's disease; N.S. = not significant.

2.3. Echocardiographic examination

DOB echocardiography of Doppler examinations were performed using a Hewlett Packard Sonos 1500 ultrasound system (Andover, MA) with 1.9 MHz (Pedoff) transducers. The entire exam was performed by a single investigator who did not know the results of the MIBG scintigraphy. The aortic flow velocity (AFV) waveform was acquired by continuous-wave Doppler from the supraclavicular fossa and angled toward the ascending aorta. Peak AFV was used to evaluate changes in cardiac contractility [21]. Monitoring of the aortic flow wave using echocardiography was performed 3 min after each incremental DOB infusion. When sharp, well-defined velocity waveforms were seen on the monitor and maximal pitch was heard through the integral loudspeaker, a 5-s recording was "frozen" on-screen and measurements were made directly from the monitor using a built-in light pen system with dedicated software.

2.4. MIBG scintigraphy

MIBG (111 mBq) was injected intravenously into each subject. The early image of cardiac uptake was obtained 15 min later and the delayed image was obtained after 3 or 4 h. Regions of interest included the whole heart and mediastinum in the anterior projection. The ratio of MIBG uptake by the heart to that in the mediastinum (H/M ratio)