Denervated Sympathetic Nerve Distributed to Motor Muscle as a Possible Cause of Enhanced BP Response to Exercise in Patients with Heart Disease

Nagaharu Fukuma, Keiko Oikawa, Kazuyo Kato, Yuko Kato, Kyoichi Mizuno, Shinichiro Kumita

We assessed the function of sympathetic nerves distributed to skeletal muscles by measuring the uptake of iodine 123 metaiodobenzylguanidine (MIBG), and examined the relationship to pressor responses during exercise. A total of 24 patients with heart disease performed treadmill exercise, and whole body delayed MIBG imaging was carried out. Based on the leg to brain ratio of MIBG (L/B), subjects were classified into two groups consisting of 10 with low L/B and 14 with preserved L/B. Results: 1) The peak systolic blood pressure (BP) during exercise was higher in the group with low L/B than in the group with preserved L/B. 2) There were no differences in plasma noradrenaline levels between the two groups. Conclusion: These results suggest that denervation supersensitivity may influence the BP response to exercise in patients with heart disease.

KEY WORDS: exercise, blood pressure, sympathetic nerve, denervation, heart disease

I. Introduction

It is well-known that sympathetic denervation induces enhanced sensitivity to catecholamines, a phenomenon known as denervation supersensitivity. Sympathetic terminal dysfunction has also been reported to occur frequently in pathophysiological conditions such as excess oxidative stress in patients with heart failure. Based on these observations, we speculated that denervation supersensitivity could develop in some patients with heart disease, although this phenomenon has not yet been clinically clarified.

Intense exercise stress usually leads to increase in BP, and the mechanism is mainly attributed to sympathetic excitation resulting in increased vascular resistance. The pathway from exercise stress to elevated BP may be influenced by both the excitability of sympathetic nerves, and the sensitivity of resistance vessels. Accordingly, we sought to relate the phenomenon of denervation supersensitivity to enhanced BP responses during exercise.

Measurement of sympathetic nerve denervation in muscles has been carried out by evaluation of muscular sympathetic nervous activity (MSNA), characterized by measurement of burst frequency of neurons innervating skeletal muscle. While this method is thought to provide reliable data and to accurately reflect sympathetic vasomotor tone, the method is invasive and is accompanied by technical difficulties. Furthermore, MSNA is able to directly reflect the only activity of neurons, but not the function of sympathetic terminal function in contact with adrenoreceptors. In our present report we assessed the uptake of iodine 123 metaiodobenzylguanidine (MIBG) to evaluate sympathetic terminal function. Several papers concerning the use of whole body MIBG scintigraphy to examine sympathetic nerve terminal function have been reported. Taki, et al. showed through the investigation of whole-body distribution of MIBG in hypertrophic cardiomyopathy that differences exist between heart and other organs including skeletal muscle. Hirayama, et al. investigated MIBG uptake of femoral skeletal muscle in patients with autonomic failure, and suggested that MIBG uptake in skeletal muscle reflected chiefly the sympathetic function of peripheral vessels supplying skeletal muscles. These reports appear to establish the role of MIBG uptake in the extremities for evaluating sympathetic terminal function of peripheral vessels in skeletal muscle. Furthermore, whole body MIBG scintigraphy is non-invasive and relatively simple to quantify.

On the basis of these findings, we hypothesized that denervation supersensitivity of exercising muscle in patients with heart disease could play an important role in contributing to the enhanced BP response to exercise. Therefore, we investigated the relationship between lower limb MIBG uptake and exercise-induced BP responses.
II. Material and Methods

1. Study population

We studied 24 male patients (mean age 54±12 years) with heart disease without decompensated heart failure and/or exercise-induced myocardial ischemia. All subjects were clinically stable, and none had any significant lung disease or neuropathy including diabetic neuropathy. The group of 24 patients included 15 with angina pectoris, 5 with old minor myocardial infarction and 4 with paroxysmal supraventricular tachycardia after percutaneous transluminal radiofrequency ablation. Among this group there were 20 patients with ischemic heart disease who had a prior coronary intervention procedure. Excluded were patients who had a myocardial infarction within three months prior to the study, those with symptomatic peripheral artery disease of the extremities, and patients who were more than 70 years old or who had secondary hypertension or a resting BP greater than 160/90 mmHg. Subjects were eligible for study if exercise was only limited by symptoms of fatigue or dyspnea, but not if exercise caused angina, syncope or claudication. Also excluded were patients taking α- and β-sympathetic receptor blockers. Informed consent for participation in this study was obtained from all subjects in accordance with the ethics committee of our institution.

2. Exercise test and transthoracic echocardiography

All subjects performed symptom-limited treadmill exercise testing according to the standard Bruce protocol.11) Exercise was stopped by symptoms of fatigue or dyspnea, or when patients reached a rating of 17 on the Borg perceived exertion scale.12) Heart rate (beats/min) and 12-lead electrocardiogram were monitored continuously during exercise using the Case 15 Stress System (Marquette Electronics, Inc., Milwaukee, WI, USA). BP (mmHg) was measured every minute with an automatic sphygmomanometer (STBD-780B, Nihon Collin Co., Ltd., Aichi, Japan). A metabolic equivalent at peak exercise (METs ml/kg/min) was estimated using the formula described by the American College of Sports Medicine.13) Transthoracic echocardiography (Sonos 5500, Hewlett-Packard, Palo Alto, CA, USA) was performed at rest, and the left ventricular ejection fraction was calculated.

3. Whole body 123I-MIBG imaging

We performed whole body MIBG imaging, as described in past reports.9, 10) An anterior view of whole-body scintigraphy was obtained 4 hours (delayed image) after intravenous injection of MIBG (MyoMIBG-I123, Daiichi Radioisotope Laboratories, Tokyo, Japan) at a dose of 111 MBq using a γ-camera (Vertex, ADAC, Milpitas, CA, USA). To assess the function of sympathetic nerve endings distributed to skeletal muscle, we set the region of interest on the lower limb, and measured the uptake of MIBG in delayed images. Results were compared with delayed images obtained over the brain, which was selected as a reference because MIBG does not pass through the blood brain barrier and there is little muscle on the skull. We considered the ratio of limb (L) to brain (B) uptake, or L/B, to reflect the function of sympathetic nerve endings in femoral muscle.

Present investigation did not examine the early image of MIBG which was obtained 15 minutes after MIBG injection and washout rate from early to delayed MIBG uptake. The reason is that the early image and washout rate are insufficient to reflect the sympathetic denervation. Previous investigation reported that early image of MIBG is not determined only by uptake 1 but also by uptake 2 as passive diffusion. And washout rate of MIBG is calculated by parameters including the early uptake. Therefore, these two parameters of MIBG in limb are thought to be impossible to indicate precisely sympathetic denervation.

4. Plasma noradrenaline concentration

For measurement of noradrenaline, we collected blood samples into a tube containing EDTA from the antecubital vein when the patient was at rest and during peak exercise. Blood samples were centrifuged at 3,000 rpm for 10 min, and plasma was extracted. The plasma concentration of noradrenaline was measured with high performance liquid chromatography.

5. Statistical analysis

All values are expressed as mean±SD. Comparisons of variables between groups were performed using the unpaired Student’s t-test and chi-square analysis. Differences with p values less than 0.05 were considered statistically significant.

III. Results

The study population was classified into two groups based on the value of MIBG uptake near the average (mean L/B ratio=1.127), and included 10 subjects with a value less than 1.1 in the low L/B ratio group and 14 subjects with a value of 1.1 or more in the preserved L/B ratio group. In comparing the clinical characteristics of these two groups, we found no differences in age, prevalence of hypertension and diabetes mellitus, or left ventricular ejection fraction (Table 1). The exercise test findings are indicated in Table 2. There were no significant differences in work load, symptoms of shortness of breath or leg fatigue at endpoint, or resting and peak heart rate between the two groups.

Fig. 1 shows plasma noradrenaline concentrations in the
low and preserved L/B ratio groups. Both at rest and at peak exercise noradrenaline levels were not significantly different between the two groups, although there was a trend toward a lower value in the low L/B group vs the preserved L/B group at peak exercise (994 ± 449 vs 1134 ± 467 pg/ml, p=ns). Fig. 2 shows the relationship between MIBG uptake and systolic BP responses to exercise. The low L/B ratio group had an enhanced BP response compared to the preserved L/B ratio group (196±22 vs 172±31 mmHg, p<0.05), but resting systolic BP did not differ in the two groups (139±16 vs 130±19 mmHg, p=ns).

**Table 1 Clinical characteristics in low and preserved L/B groups**

<table>
<thead>
<tr>
<th></th>
<th>Low L/B (L/B &lt;1.1, n=10)</th>
<th>Preserved L/B (L/B ≥1.1, n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53±14</td>
<td>54±11</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2/10 (20%)</td>
<td>5/14 (36%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5/10 (50%)</td>
<td>4/14 (29%)</td>
<td>ns</td>
</tr>
<tr>
<td>EF (%)</td>
<td>58±8</td>
<td>54±5</td>
<td>ns</td>
</tr>
</tbody>
</table>

Clinical characteristics were not significantly different between low and preserved L/B groups. L/B, Leg to brain MIBG uptake ratio; EF, Left ventricular ejection fraction; ns, not statistically significant. Statistical analysis was performed in comparison between low and preserved L/B groups.

**Table 2 Exercise test findings in low and preserved L/B groups**

<table>
<thead>
<tr>
<th></th>
<th>Low L/B (L/B &lt;1.1, n=10)</th>
<th>Preserved L/B (L/B ≥1.1, n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work load (METs)</td>
<td>6.3±1.4</td>
<td>5.6±1.9</td>
<td>ns</td>
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<tr>
<td>End point SOB</td>
<td>3/10 (30%)</td>
<td>8/14 (57%)</td>
<td>ns</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>7/10 (70%)</td>
<td>10/14 (71%)</td>
<td>ns</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>72±14</td>
<td>77±11</td>
<td>ns</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>138±15</td>
<td>131±21</td>
<td>ns</td>
</tr>
</tbody>
</table>

Exercise test findings were not significantly different between low and preserved L/B groups. L/B, Leg to brain MIBG uptake ratio; SOB, shortness of breath; ns, not statistically significant. Statistical analysis was performed in comparison between low and preserved L/B groups.

**IV. Discussion**

Canon first reported denervation supersensitivity.1, 2) This phenomenon is observed following injury of sympathetic or parasympathetic nerves, which causes the denervated organ to become more sensitive to noradrenaline or acetylcholine administration. Although the cause of denervation supersensitivity is not fully clarified, sympathetic mechanisms are thought to include failure of neuronal reuptake,10) loss of intra-neuronal binding sites for noradrenaline,15) post-junctional changes involving adenylyl cyclase activity,10) and an
increase in number of β-adrenergic receptors. Clinical manifestations of denervation supersensitivity have been previously reported. For example, patients with postganglionic denervation accompanied by up-regulation of α-receptors may have an exaggerated pressor response to the intravenously administered α-sympathetic stimulant phenylephrine, as observed for example in diabetic neuropathy.

Sympathetic terminal function distributed to heart muscle has been clinically examined using MIBG. There have been reports which show that sympathetically denervated myocardium displays irritability and development of arrhythmias with catecholamine stimulation. Ventricular tachycardia may occur with regional denervation even in the absence of coronary artery disease. In the current study, however, we used whole body MIBG uptake as a functional index of sympathetic terminal innervation of skeletal muscle. Previous reports showed that MIBG uptake of skeletal muscle, in reflecting peripheral vascular sympathetic function, may have a different clinical significance from alterations that occur in cardiac MIBG. Therefore, studies of the periphery are thought to have relevance to our understanding of the pathophysiologic role played by skeletal muscle sympathetic dysfunction in heart disease.

We investigated the influence of sympathetic denervation supersensitivity of skeletal muscle on the BP response to exercise. Past reports have shown that the main mechanism of exercise-induced hypertension is a failure to reduce total peripheral vascular resistance during exercise. Impairment of vasodilator capacity in exercising skeletal muscle in hypertensive patients has been previously reported. Bond, et al. reported that the minimum lower leg vascular resistance during exercise was higher in the subjects with a positive family history of hypertension than in the subjects with a negative history. Although peripheral vascular tone during exercise is regulated by a number of different factors, sympathetic tone is reported to play an important role in this control, providing a valid rationale for our studies. Our results indicated that low values for the L/B ratio were related to enhanced BP responses to exercise, although plasma noradrenaline level did not differ between the low and preserved L/B ratio groups. We interpret these findings as indicating that denervation supersensitivity occurred in skeletal and altered the BP response to circulating noradrenaline, a mechanism which could apply even though the noradrenaline levels did not differ significantly between the two groups.

The response of blood pressure in preserved L/B group had a tendency of wide distribution in comparison with that in low L/B group. These phenomenon are able to be explained by following possible mechanism; blood pressure response is enhanced in case with one or more pressor factors including denervation supersensitivity. Therefore, we thought that most of patients with denervation supersensitivity have the enhancement of blood pressure response, but the patients with preserved sympathetic function do not always have the pressor factors and result in the various degree of blood pressure response.

Although our study may have some limitations, including small population study and the inferences derived by comparing the measurements of resting MIBG with pressor responses during exercise, it does represent the first report suggesting the possible role of denervation supersensitivity in altering BP responses to exercise. In future, we should further investigations to confirm the each relationship of denervation and blood pressure response in various heart diseases and examine dynamic MIBG imaging. Past published reports indicate that subjects with normal resting pressure but with excess response of systolic BP during exercise, who is similar to the subjects with low L/H, have an increased risk of developing clinically significant...
These findings indicated that the present study may have pathophysiologic meaning, and provide useful knowledge in clinical settings. Further studies in the future may have relevance to our understanding of hypertension and its treatment.

Conflict of interest
Present article has no conflict of interest.

References
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