Significance of Cardiac Sympathetic Nervous System Abnormality for Predicting Origin of Tachyarrhythmia in Patients with a History of Paroxysmal Palpitation

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Abstract: Cardiac sympathetic nervous system abnormality can predict sudden cardiac death due to arrhythmia. However, it is unknown whether the sympathetic nerve abnormality is related to the origin of tachyarrhythmia. We hypothesized that such a relationship exists and tested it by uptake of iodine-123 metaiodobenzylguanidine (123I-MIBG) in 184 patients (mean ± standard deviation, age: 52.7 ± 18.8 years, 106 males) with a history of paroxysmal palpitation. Patients with organic heart disease or left ventricular dysfunction were excluded. Cardiac sympathetic nerve abnormality was assessed from the heart/mediastinum (H/M) later index and washout ratio (WR). Sustained ventricular tachycardia (VT) in 46 patients and sustained supraventricular tachycardia (SVT) in 103 patients were diagnosed by ECG during onset of arrhythmia or by electrophysiologic tests employing programmed cardiac stimulation. The tachyarrhythmia was not proven in 35 patients (control groups). The H/M index was significantly lower and WR significantly higher in tachyarrhythmia groups compared to controls (H/M index: 2.75 ± 0.55 in VT group, 3.01 ± 0.78 in SVT group vs. 3.34 ± 0.48 in control group, p < 0.001 and p < 0.05, WR: 39.6 ± 12.1% in VT group, 38.1 ± 8.5% in SVT group vs. 34.2 ± 6.8% in control group, p < 0.05 in each). The mean H/M index was lower in the VT group than the SVT group (p < 0.05). Cardiac sympathetic nerve abnormality thus predicts the origin of tachyarrhythmia, and we propose 123I-MIBG scintigraphy as an important tool to discriminate the life-threatening tachyarrhythmia from benign episodes in patients with a history of palpitation.

Key words: ventricular tachycardia, supraventricular tachycardia, sympathetic nerve activation, 123I-MIBG scintigraphy

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Introduction

Sudden cardiac death due to arrhythmia remains a major and unresolved public health problem. In most cases, the direct cause of sudden death is ventricular fibrillation, which is usually preceded by ventricular tachycardia (VT). However, the life-threatening tachyarrhythmia is sometimes difficult to detect and treat because the onset and termination of palpitation appear abruptly. Recent studies demonstrated that sympathetic nerve abnormality predicts sudden cardiac death from arrhythmia \(^1\), although whether the sympathetic nerve activity predicts the origin of tachyarrhythmia remains unclear. Heart imaging with an analogue of norepinephrine, iodine-123 metaiodobenzylguanidine (\(1^{23}\)-MIBG), can be used for noninvasive assessment of sympathetic nerve activity \(^2\). \(1^{23}\)-MIBG accumulates in the endings of sympathetic nerves through the uptake-1 mechanism and thereby can delineate cardiac sympathetic nerve distribution and function. We hypothesized that sympathetic nerve abnormality detected using \(1^{23}\)-MIBG scintigraphy could strongly predict arrhythmia in patients with a history of paroxysmal palpitation.

Materials and Methods

Patients

We studied patients with a history of paroxysmal palpitation who underwent \(1^{23}\)-MIBG scintigraphy. Patients with an inadequate image quality (i.e., lung uptake exceeding 30% of heart uptake, or of liver uptake interfered) \(^3\) and patients with a metabolic disorder such as diabetes mellitus or a sympathetic nerve disorder such as Parkinson’s disease were excluded from the study. The conditions of idiopathic VT or supraventricular VT (SVT) were diagnosed based on documented sustained tachycardia in the absence of morphological, functional, and organic heart disease. Patients with coronary artery disease, hypertrophic or dilated cardiomyopathies, and congenital, valvular, or inflammatory heart diseases diagnosed from either two-dimensional echocardiography, left ventriculography, or coronary angiography were also excluded from this study. All patients had sinus rhythm on ECG. A total of 184 patients were recruited for this study (mean age \(\pm\) standard deviation of 53 \(\pm\) 19 years, 71.6% males). VT in 46 patients and SVT in 103 patients were diagnosed by 12-lead ECG or holter monitoring during onset of palpitation, or by electrophysiologic studies employing programmed cardiac stimulation. The patients with SVT included 31 patients with atrioventricular nodal reentrant tachycardia, 29 patients with Wolff-Parkinson-White syndrome and 43 patients with paroxysmal atrial fibrillation. Tachycardia was not apparent in 35 patients (control group).

Protocol for MIBG imaging

From 1 day before to 1 day after the study, 1 mg of potassium iodide was given orally to block thyroid uptake of \(1^{23}\)-MIBG. Patients were placed in the supine position, and an intravenous catheter was placed through an antecubital vein. 111 MBq of \(1^{23}\)-MIBG was injected (Dai-ichi Radioisotope Laboratory) and flushed through with saline solution. Myocardial images were acquired using a dual-detection gamma camera equipped with a medium energy, parallel-hole collimator (Prism 2000XP, Phillips, Picker, Ohio USA). A 20% window centered at 159 keV. Anterior view chest planar image was acquired in a 512 \(\times\) 512 matrix, with the first acquisition initiated 15 min after the tracer injection (early
images). Cardiac single photon emission computed tomography (SPECT) was also performed. Data were acquired in a 128 × 128 matrix involving 32 step-and-shoot projections over 180°, at 40 sec per angle, beginning 45° in the right anterior oblique projection. The data from both acquisitions were reconstructed on an Odyssey computer (Phillips, Picker) utilizing a Butterworth filter with a cutoff frequency of 0.35 cycles/pixel. A ramp filter was applied during back projection. The reconstructed transaxial slices were then reoriented into vertical long, horizontal long, and short axes. Identical acquisition was concluded 4 hours after tracer injection (delayed images).

**Analysis of MIBG scintigraphic imaging**

Left ventricular MIBG activity was measured using a manually drawn region of interest (ROI) around the left ventricular myocardium. A 20 × 20 pixel ROI was placed over the upper mediastinal area. Background subtraction was performed using the upper mediastinal ROI. To evaluate the myocardial accumulation of MIBG uptake and spillout as an analogue of norepinephrine, the heart/mediastinal (H/M) activity ratio was calculated from delayed scintigraphic images obtained 4 hours after 123I-MIBG injection. Washout ratio (WR) (%) reflected the increase of MIBG spillover as sympathetic hyperactivity was defined as a percent change in activity from the early and delayed images within the left ventricle. Polar maps using SPECT imaging were constructed by plotting circumferential profiles of sequential maximal counts, ranging from the apex to the base, into successive rings on the polar map. The polar map was divided into anterior, septal, lateral, inferior, and apex areas. An abnormality was considered to be present if there was less than 60% uptake of radioactivity in these areas.

**Statistical analysis**

All statistical analyses were done using Statcel with Excel 2003 Windows Edition (OMS Co. Tokyo Japan). One-way ANOVA was used for continuous variables, H/M ratio, and washout ratio to identify whether group differences were significant. Continuous variables are presented as means ± SD. Two group comparisons were made using the post-hoc test (Fisher exact testing). Patient characteristics among the three groups were analyzed using the Chi-square test to test significance. A P value < 0.05 was considered significant.

**Results**

**Clinical characteristics**

The 46 patients with VT were significantly younger than the 103 patients with SVT or 36 control patients (Table 1). There was no significant difference among these groups in other covariates including gender, hypertension, hyperlipidemia, obesity, left ventricular function (ejection fraction), and the use of beta-blockers and/or calcium channel antagonists. 123I-MIBG scintigraphy on the sinus rhythm, which showed no paroxysmal tachycardia, revealed no significant changes in heart rate or blood pressure (Table 1).

**Case presentation**

ECG and 123I-MIBG images were particularly analyzed in 2 patients with a history of palpitation. One was a 41-year-old male, and VT was triggered by exercise (Fig. 1). 123I-MIBG delayed images were taken when he remained in sinus rhythm, and showed
markedly reduced tracer uptake in the inferior area. The H/M index was low at 2.8, and washout ratio high at 40.8%. The other case was 26 years female, and 12-lead ECG showed Wolff-Parkinson-White syndrome (type B according to the Rosenbaum classification; Fig. 2). SVT was detected by electrophysiological studies, and MIBG images showed moderately reduced tracer uptake in inferior area. The H/M index was low at 2.83, and washout ratio high at 39.1%. One month after successful catheter ablation (a Kent bundle was found in the right lateral ventricular wall), both H/M and washout ratio were recovered to

Table 1. Patient's characteristics

<table>
<thead>
<tr>
<th></th>
<th>VT group (n = 46)</th>
<th>SVT group (n = 103)</th>
<th>Control group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 21</td>
<td>54 ± 18</td>
<td>57 ± 18</td>
</tr>
<tr>
<td>male</td>
<td>29 (63.0%)</td>
<td>58 (56.3%)</td>
<td>19 (52.8%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>58.5 ± 9.2</td>
<td>67.8 ± 11.7</td>
<td>65.8 ± 5.6</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>3 (6.5%)</td>
<td>5 (4.9%)</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>1 (2.2%)</td>
<td>2 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>21.2 ± 3.4</td>
<td>22.9 ± 4.2</td>
<td>23.5 ± 2.7</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30)</td>
<td>1 (2.2%)</td>
<td>2 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Use of beta-blocker</td>
<td>3 (6.5%)</td>
<td>7 (6.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Use of Ca-antagonist</td>
<td>1 (2.2%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>120.3 ± 19.1</td>
<td>128.0 ± 16.5</td>
<td>131.8 ± 22.2</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>69.0 ± 14.4</td>
<td>77.0 ± 12.3</td>
<td>79.1 ± 11.8</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>65.8 ± 12.4</td>
<td>76.2 ± 23.8</td>
<td>65.8 ± 12.1</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. control group  †p < 0.05 vs. SVT group.  ‡ Ejection fraction was measured by two-dimensional echocardiography using Simpson method within 1 month of 123I-MIBG study.

Fig. 1. Figure shows resting 12-lead ECG (A), ECG with exercise-induced VT (B), and 123I-MIBG delayed imaging (C). 123I-MIBG uptake was markedly reduced particularly in the inferior area.
Sympathetic Nervous Abnormality and Tachyarrhythmia

Fig. 2. Figure shows resting 12-lead ECG (A) and ¹²³I-MIBG delayed imaging (C). ECG showed Wolff-Parkinson-White syndrome (type B of Rosenbaum classification). SVT was provoked on electrophysiological study. ¹²³I-MIBG uptake was moderately reduced, particularly in the inferior area.

3.39 and 33.8%, respectively.

MIBG scintigraphic findings

H/M indices were lower and washout ratio was higher in the tachycardia groups compared to control patients (H/M index: 2.75 ± 0.55 in VT group, 3.01 ± 0.78 in SVT group vs. 3.34 ± 0.48 in control group, p < 0.001 and p < 0.05, washout rate: 39.6 ± 12.1% in VT group, 38.0 ± 8.5% in SVT group vs 34.1 ± 6.8% in control group, p < 0.05 in each) (Fig. 3). The H/M index was much lower in VT group than SVT group (p < 0.05). For regional analysis, MIBG uptake was reduced in the inferior area on all groups of VT, SVT and control (Table 2).

Discussion

The patients in this study with proven tachycardia exhibited severe sympathetic nerve abnormality, low H/M ratios, and high WR compared to the control patients with a history of palpitation but not proven tachyarrhythmia. Further, the incidence of sympathetic nerve abnormality was more severe in VT patients than in those with SVT. The sympathetic nerve abnormality thus could predict the origin of tachycardia despite the sympathetic nerve activation being measured when the patients remained in sinus rhythm, without paroxysmal tachycardia.

Previous myocardial infarction is often identified in sudden cardiac death due to tachyar- rhythmia. The interaction between VT (the trigger) and the diseased myocardium (the
Fig. 3. H/M index and washout ratio on 123I-MIBG delayed imaging in patients with VT, SVT, and control group. H/M index was lower and washout ratio was higher in tachycardia groups than in the control group, and was lower in VT group than in SVT group. VT: the patients with ventricular tachycardia, SVT: the patients with supraventricular tachycardia, Control: the patients of control group.

Table 2. Regional analysis on 123I-MIBG SPECT imaging

<table>
<thead>
<tr>
<th>Left ventricular areas of reduced tracer uptakes</th>
<th>VT group (n = 46)</th>
<th>SVT group (n = 103)</th>
<th>Control group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>6 (13.0%)</td>
<td>17 (16.5%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Anterior</td>
<td>10 (21.7%)</td>
<td>22 (21.4%)</td>
<td>6 (16.7%)</td>
</tr>
<tr>
<td>Septal</td>
<td>10 (21.7%)</td>
<td>18 (17.5%)</td>
<td>4 (11.1%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>9 (19.6%)</td>
<td>18 (17.3%)</td>
<td>6 (16.7%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>28 (60.9%)</td>
<td>66 (58.3%)</td>
<td>19 (52.8%)</td>
</tr>
<tr>
<td>Normal tracer uptake in all areas</td>
<td>10 (21.7%)</td>
<td>24 (23.3%)</td>
<td>15 (41.7%)</td>
</tr>
</tbody>
</table>

substrate) results in the transition of VT to VF and subsequent sudden cardiac death, and sympathetic nerve dysfunction after MI provokes VT\(^7\). Further, recent studies demonstrated that idiopathic ventricular tachycardia is also accompanied by sympathetic nerve dysfunction with 123I-MIBG scintigraphy\(^1,8\). A direct effect of sympathetic nerve activation was also been confirmed in patients with SVT or AF\(^9,10\). Study involving upright posture, treadmill exercise, and isoproterenol or atropine infusion also demonstrated significantly shortened antegrade and retrograde accessory pathway effective refractory periods, AH and VA intervals, as well as the shortest pre-excited RR interval during atrial fibrillation or rapid atrial pacing\(^11-13\). Differences in sympathetic nerve abnormality have been shown, however, between SVT and VT. We first found that patients with VT showed more severe cardiac sympathetic nerve dysfunction than patients with SVT, followed by those without proven tachyarrhythmia. Herweg et al demonstrated that the shorter cycle length of SVT led to higher sympathetic nerve activity\(^10\). Recent studies of HR response during exercise, HR viability, and baroreflex sensitivity demonstrated that sympathetic nerve abnormality
predicts sudden cardiac death, and the severe damage of sympathetic nerve activation is closely associated with life-threatening tachyarrhythmia. A shorter cycle length of tachycardia and more severe risks in patients with VT, compared to the patients with SVT, may explain our results.

We examined sympathetic nerve activation of the patients with a history of paroxysmal palpitation in the absence of organic or functional abnormalities other than paroxysmal tachyarrhythmia. This was done because cardiac sympathetic nerve dysfunction has been described for several heart diseases associated with primary or secondary cardiomyopathy, such as myocardial ischemia and infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy, and heart failure with left ventricular dysfunction or left ventricular enlargement caused by permanent AF. Furthermore, sympathetic nerve activation was measured using ¹²³I-MIBG scintigraphy when the patient remained in the condition of sinus rhythm, not having paroxysmal tachyarrhythmia. It would therefore be important in patients with a history of palpitation and transient tachyarrhythmia to discriminate the origin of tachyarrhythmia using sympathetic nerve activation.

Cardiac electrophysiological studies employing programmed cardiac stimulation have been widely used to discriminate life-threatening arrhythmic events from benign episodes in patients with previous paroxysmal palpitation and with organic heart disease such as ischemic heart disease. However, in patients with unexplained palpitation and no other problem, invasive electrophysiological tests may not be recommended, and might be indicated therefore to detect the sustained VT or VF. Invasive cardiac electrophysiological studies might be indicated therefore to detect sympathetic nerve abnormality in patients with a history of paroxysmal palpitation, but with no structural heart disease.

¹²³I-MIBG is a radiotracer that shares many cellular transport properties with norepinephrine. In the present study, imaging from 4 hours after injection of radiotracer assessed MIBG uptake. This does not allow speculation about the dynamics of MIBG uptake and release. The finding of reduced tracer activity could result from either a reduced re-uptake (uptake-1) of MIBG/catecholamines, an increased release of MIBG/catecholamines into the synaptic cleft, or a combination the two. All mechanisms would lead to an enhanced catecholamine concentration in the synaptic cleft with subsequent downregulation of postsynaptic beta-adrenoreceptor density. Therefore, ¹²³I-MIBG scintigraphy was used to study global myocardial adrenergic nerve activity in the present study. For regional analysis of MIBG, the tracer uptake was reduced in the inferior myocardial segment in all groups. This finding is common across all cardiac diseases and seems to reflect a global sympathetic nerve dysfunction rather than a regional abnormality.

Limitations

The uptake of ¹²³I-MIBG correlates well with the activity of the norepinephrine carrier. Nevertheless, structural differences might induce MIBG scintigraphy to over- or underestimate the changes in norepinephrine carrier activity in the patients. In addition, the commercially available MIBG used in the study contains significant amounts of cold MIBG, which leads to competition of both substances at the carrier site. It is not clear whether or not this competition influences the MIBG results.
References


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