Abnormality of Left Ventricular Sympathetic Nervous Function Assessed by $^{123}$I-Metaiodobenzylguanidine Imaging in Patients With COPD*

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Background: Cardiac and systemic autonomic nervous function may be impaired in patients with COPD. Few reports, however, have described sympathetic nervous function of the left ventricle (LV) in COPD patients.

Study objective: To assess the LV sympathetic nervous function in patients with COPD using $^{123}$I-metaiodobenzylguanidine (MIBG) imaging of the heart.

Design: Prospective comparison of $^{123}$I-MIBG imaging results in COPD patients and normal subjects.

Participants: Twenty-eight patients with COPD without manifest right ventricular overload and 7 volunteers without cardiopulmonary disease (control subjects).

Measurements: $^{123}$I-MIBG imaging results and plasma norepinephrine concentration were compared between the COPD and control groups. In the COPD group, pulmonary function tests were performed and all subjects were interviewed about their symptoms.

Results: $^{123}$I-MIBG uptake, assessed as the cardiac to mediastinal activity ratio in the delayed image, was significantly lower in the COPD group than in the control group ($p < 0.05$). $^{123}$I-MIBG turnover, expressed as the washout rate (WR) of $^{123}$I-MIBG from 15 to 240 min, was significantly higher in the COPD group than in the control group ($p < 0.01$). In the COPD group, patients with dyspnea showed lower cardiac to mediastinal activity ratios and higher WRs compared with patients who had mild dyspnea. The WR correlated negatively with the vital capacity/predicted value ratio, correlated negatively with the maximal voluntary ventilation volume/predicted value ratio, and correlated positively with the residual volume/total lung capacity ratio in the COPD group. The plasma norepinephrine concentration in COPD patients was higher than that in the control subjects.

Conclusion: Patients with COPD have significant sympathetic nervous impairment of the LV myocardium as a result of generalized sympathetic overactivity.

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Key words: COPD; $^{123}$I-metaiodobenzylguanidine; sympathetic nervous system

Abbreviations: ANS = autonomic nervous system; He/Me = cardiac to mediastinal activity ratio calculated for the early image; H/M = cardiac to mediastinal activity ratio calculated for the delayed image; IVS = interventricular septum; LV = left ventricle, ventricular; MIBG = metaiodobenzylguanidine; MVV = maximal voluntary ventilation; NE = norepinephrine; RV = right ventricle, ventricular; SPECT = single photon emission CT; WR = washout rate

Patients with COPD have increased airway resistance, which correlates with a change of airway tone. Human airway tone is modulated by the parasympathetic cholinergic nervous system\(^1\)–\(^3\) and the sympathetic adrenergic nervous system,\(^3\) as well as by humoral factors, such as substance P.\(^4\) Thus, autonomic nervous system (ANS) dysfunction may be associated with chronic airway obstruction and the pathogenesis of COPD. It has been reported that ANS function, assessed mainly by heart rate variability, is disturbed in patients with COPD.\(^5\)–\(^7\)

The function of efferent cardiac sympathetic nerves may be impaired in patients with COPD for several reasons. Otsuka et al\(^8\) discussed the mecha-
nism by which patients with obstructive sleep apnea syndrome also had associated impaired function of efferent cardiac sympathetic nerves. In COPD patients, similarly, the activity of cardiac sympathetic nerves may be affected by recurrent hypoxemia, hypercapnia, change of airway tone, increased intrathoracic pressure due to airway obstruction, and highly fluctuating heart rate and BP due to increased respiratory effort. However, it remains unclear whether this ANS abnormality contributes to the pathophysiology of COPD or correlates with the severity of COPD. Furthermore, it is controversial whether patients with COPD have left ventricular (LV) alterations as well as latent right ventricular (RV) alterations.9,10 The sympathetic stresses in COPD could cause down-regulation and reduced density of β-adrenoceptors in the LV.11 Assessment of LV sympathetic nervous impairment may be useful for the early detection of LV alterations in patients with COPD.

Metaiodobenzylguanidine (MIBG), an analog of guanethidine, shows a similar metabolism to norepinephrine (NE) with regard to its neuronal transport and storage in systemic nerve endings.12 123I-MIBG imaging of the heart can assess adrenergic neuronal efferents to the heart and the resulting integrity of the heart.13,14 Abnormal 123I-MIBG uptake has been shown in ischemic heart disease,15 aortic stenosis,16 dilated cardiomyopathy,17,18 and transplanted hearts.19 The definitive mechanisms of the decreased cardiac to mediastinal activity ratio of 123I-MIBG and the increased washout rate (WR) in 123I-MIBG remain to be elucidated.14,18 An insufficient cardiac sympathetic nerve supply to the myocardium and increased activity of the sympathetic nervous system with increased NE turnover in the terminals of systemic nerves are considered to be the main mechanisms, according to animal experimental studies and clinical investigations.12–20

We evaluated whether LV sympathetic function, which can be detected by 123I-MIBG imaging, is impaired in patients with COPD and whether there may be latent LV disturbance in patients with COPD by comparing the sympathetic function in COPD patients with that in healthy control subjects and by assessing the correlation between the abnormality of 123I-MIBG imaging findings and the severity of COPD.

Materials and Methods

Patients

Twenty-eight patients (24 men and 4 women; [mean ± SD] age, 71 ± 8 years [range, 55 to 85 years]) with COPD were studied. All patients, except for one woman, had a history of cigarette smoking. Patients with COPD consisted of those having symptoms of chronic bronchitis and those with spirometric abnormalities. Six patients were defined as having symptoms of chronic bronchitis because of persistent cough and production of phlegm for at least 3 consecutive months for ≥ 2 years. Twenty-two subjects received a diagnosis of COPD based on the results of spirometry. The diagnostic measurement was defined as the percentage of measured FEV1 divided by the FVC × 100 ≤ 70%, and which improved < 15% after inhalation of a β-stimulant as compared with the value before inhalation. The duration from the diagnosis to the 123I-MIBG imaging test was 7.7 ± 5.5 years (range, 1 to 20 years). The results of pulmonary function tests are shown in Table 1.

No patients received any α1-blockers. Nine patients received inhaled anticholinergic agents, 17 received oral β-stimulants, and 7 received both. No patients suffered from hypertension, diabetes mellitus, pheochromocytoma, or Shy-Drager syndrome. Exercise electrocardiography by cycle ergometer and echocardiography were performed for all COPD patients. No ST- or T-wave abnormalities were noted on ECG either at rest or during peak exercise. There was no evidence of segmental or diffuse hypokinesis of LV or RV chamber dilatation or hypertrophy, and no atrial enlargement by visual interpretation on echocardiography. From the subcostal images, the size and respiratory dynamics of the inferior vena cava appeared normal, suggesting normal right atrial pressure. Right heart catheterization, coronary angiography, and left ventriculography were performed in eight patients in the COPD group. Significant stenosis of a coronary artery, focal or diffuse hypokinesis of the LV, and RV dysfunction, defined as mean right atrial pressure < 5 mm Hg, RV diastolic pressure < 5 mm Hg, and mean pulmonary arterial pressure < 20 mm Hg, were not found in any patients a result of cardiac catheterization.

123I-MIBG imaging also was performed in seven volunteers (six men and one woman; age, 66 ± 10 years [range, 52 to 78 years]) who served as the age-matched control group. Significant organic cardiopulmonary disease was ruled out in the control group by the findings of posteroanterior and lateral chest radiographs, routine blood examinations, and echocardiography. All patients were given an explanation of the purpose of the study, and informed consent was obtained.

Protocol for 123I-MIBG Imaging

Planar and single-photon emission CT (SPECT) images were obtained at rest in the anterior view at 15 min (early image) and

<table>
<thead>
<tr>
<th>Pulmonary Function Tests</th>
<th>Values</th>
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<tbody>
<tr>
<td>FVC</td>
<td>2.70 ± 0.81</td>
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<tr>
<td>% predicted</td>
<td>85.8 ± 19.0</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.62 ± 0.65</td>
</tr>
<tr>
<td>% predicted</td>
<td>59.2 ± 20.9</td>
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<tr>
<td>FEV1/FVC × 100, %</td>
<td>57.5 ± 13.0</td>
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<tr>
<td>FRC, %</td>
<td>98.5 ± 30.0</td>
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<tr>
<td>DLCO, % predicted</td>
<td>84.2 ± 33.6</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>76.5 ± 11.0</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>38.8 ± 6.2</td>
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*Values given as mean ± SD; FRC = functional residual capacity; DLCO = diffusing capacity of the lung for carbon monoxide.
4 h (delayed image) after the injection of 111 MBq $^{123}$I-MIBG, using a triple-headed gamma camera (MultiSPECT 3; Siemens; Erlangen, Germany) equipped with a low-energy, high-resolution collimator. The regions of interest in the heart were set manually on these planar images. A region (10 × 10 mm$^2$) in the upper mediastinum also was set in order to calculate the mean mediastinal counts on the planar images. The mean $^{123}$I-MIBG count of the heart from the early image and from the delayed image were calculated. Mean mediastinal counts also were obtained both from the early and the delayed image. The cardiac to mediastinal activity ratio was calculated for the early image (He/Me) and for the delayed image (H/M). The H/M was used as an index of the final myocardial uptake of MIBG. The WR was determined over 4 h, according to the formula: WR (%) = [(He/Me) − (H/M)] × 100/(He/Me). The distribution of MIBG accumulation in the myocardium was assessed using the short-axis SPECT image at the midventricular level.

Assessment of Severity of Pulmonary Dysfunction and Plasma NE in Patients With COPD

All patients with COPD were interviewed about their usual symptoms of dyspnea on exertion, which were classified by the shortness of breath scale of the American Thoracic Society (grade 0 = no dyspnea; grade 4 = very severe dyspnea).21 Diagnostic spirometry, including measurement of maximal voluntary ventilation (MVV) volume, functional residual capacity, and residual volume by the closed-circuit helium method, was performed on all the subjects in the COPD group.22 Arterial blood samples were drawn in all COPD patients at rest to measure both Pa$_o$ and PaCO$_2$ and to calculate alveolar-arterial partial oxygen pressure difference. The plasma NE concentration was measured in the morning while the subjects were awake and at rest in order to evaluate the sympathetic nervous system activity. The correlations between these data and the results of $^{123}$I-MIBG imaging of the heart were assessed.

Statistical Analysis

All data were presented as mean ± SD. Differences in H/M ratios and WRs of $^{123}$I-MIBG imaging between the control and COPD groups were analyzed using the Mann-Whitney U test and computer software (StatView, version 4.02; Abacus Concepts; Berkeley, CA). One-way analysis of variance and Fisher’s least-significant difference test were used to analyze the differences in $^{123}$I-MIBG imaging findings among the groups classified by the shortness of breath scale. Simple regression analysis was used to correlate $^{123}$I-MIBG imaging findings with pulmonary function test parameters or plasma NE concentrations. A cutoff value of p < 0.05 was used for the detection of a statistically significant difference.

RESULTS

H/Ms and WRs from $^{123}$I-MIBG images in the control and COPD groups are presented in Figure 1. The H/M was significantly lower in the COPD group (1.96 ± 0.62; n = 28) than in the control group (2.49 ± 0.16; n = 7; p < 0.05). The WR was significantly higher in the COPD group (44.1 ± 14.9%) than in the control group (22.3 ± 3.9%; p < 0.01). The heart rate was 9% higher in patients with COPD compared with control subjects (75 ± 9 vs 69 ± 6, respectively), but this difference was not quite significant statistically (p = 0.06). The heart rates for both groups did not correlate with either the H/Ms (p = 0.43; r = 0.14) or the WRs (p = 0.15; r = 0.25). The duration from the diagnosis to the $^{123}$I-MIBG imaging test also did not correlate with these two parameters of $^{123}$I-MIBG imaging. There was no significant difference in the H/M and WR between patients who inhaled anticholinergic agents (H/M, 2.17 ± 0.51; WR, 39.4 ± 10.3; n = 16) and those who did not (H/M, 1.89 ± 10.3; WR, 46.4 ± 16.4; n = 12). There also was no significant difference between patients who received β-stimulants (H/M, 1.93 ± 0.48; WR, 41.9 ± 13.1; n = 17)

**Figure 1. Left:** cardiac $^{123}$I-MIBG uptake assessed as the cardiac to mediastinal accumulation ratio (MIBG: H/M) in patients in the control and COPD groups is presented. **Right:** myocardial MIBG turnover expressed as the percentage of washout from 15 to 240 min (MIBG: WR). Data are shown as mean ± SD. H/M was significantly lower in the COPD group than in the control group (∗ = p < 0.05 vs control group). WR was significantly higher in the COPD group than in the control group (**) = p < 0.01 vs control group).
and those who did not (H/M, 2.06 ± 0.82; WR, 47.5 ± 17.5; n = 11). In all the patients with COPD, MIBG uptake was decreased in the region of the interventricular septum (IVS) and inferior wall of the LV on SPECT imaging. Two representative cases of 123I-MIBG SPECT imaging (bull’s-eye display) from the COPD group are presented in Figure 2.

The patients with COPD were classified into the following three subgroups according to the American Thoracic Society shortness of breath scale: grade 1 (n = 5); grade 2 (n = 17); and grade 3 (n = 6). H/M and WR were compared among these three groups. H/M in the grade 2 group (1.89 ± 0.51) was lower than that in the grade 1 group (2.60 ± 0.91), and H/M in the grade 3 group (1.72 ± 0.33) was even lower than that in the grade 2 group (p < 0.05). WR in the grade 3 group (54.4 ± 12.7) was significantly higher than that in the grade 1 group (35.8 ± 11.7). These results are presented in Figure 3.

WR in the COPD group correlated with some of the parameters of pulmonary function. The percentage of measured FVC over the predicted value correlated with the WR (p = 0.013; r = −0.47). The percentage of residual volume over total lung capacity also correlated significantly with the WR (p = 0.047; r = 0.39). There was a significant correlation between the percentage of MVV over the predicted value and the WR (p = 0.033; r = −0.41). There was no significant correlation between the WR and other parameters of pulmonary function. The H/M did not correlate with any parameters of pulmonary function in the COPD group.

The mean plasma NE concentration in the COPD group (449.4 ± 196.7 pg/mL; n = 28) was higher than that in the control group (68.9 ± 31.9; p < 0.01; n = 7). Plasma NE concentrations were compared among patients classified according to the shortness of breath scale. The plasma NE concentration in the grade 3 group (551.5 ± 196.1; n = 6) was significantly higher than that in the grade 1

Figure 2. Left: an 123I-MIBG image (bull’s-eye display) of one case, a 73-year-old man with mild dyspnea (grade 1) in the COPD group, is shown. FVC and FEV1 were 60.1% and 38.4% of predicted value, respectively. On 123I-MIBG imaging, the H/M was 2.14 and the WR was 34%. Right: an 123I-MIBG image of another case, a 82-year-old man with severe dyspnea (grade 3) in the COPD group, is shown. FVC and FEV1 were 55.2% and 49.3% of predicted value, respectively. On 123I-MIBG imaging, the H/M was 1.61 and the WR was 52%. Decreased 123I-MIBG uptake in the myocardium is demonstrated as the green or blue color in the region of the IVS in both patients and in the inferior LV wall in the image on the right (arrows). Top: diagram shows the coronary arterial territory on this short-axis image. LAD = left anterior coronary artery; L = left circumflex coronary artery; RCA = right coronary artery.
In this study, we have demonstrated that cardiac $^{123}$I-MIBG imaging showed a decreased ratio of cardiac to mediastinal accumulation and a higher WR from the LV in patients with COPD.

MIBG metabolism and washout may be affected by heart rate or cardiac output. The higher WR in the COPD group might be due to higher heart rates, because COPD patients have a faster heart rate in general. However, in the present study, there was no statistically significant difference in heart rate between the control and COPD groups. Further, heart rate did not correlate with either H/M or WR in our study. These results suggest that the high WR in the COPD group cannot be explained by higher heart rates or higher cardiac output alone.

The duration of COPD and the use of inhaled β-stimulating or anticholinergic agents may impact on the abnormal findings of $^{123}$I-MIBG imaging. Indeed, the interval from the diagnosis to the $^{123}$I-MIBG imaging test was extremely variable, 7.7 ± 5.5 years (range, 1 to 20 years). The duration of disease, however, did not correlate with either H/M or WR of $^{123}$I-MIBG. There were no significant differences in H/M and WR of $^{123}$I-MIBG according to the use of anticholinergic and β-stimulating agents, and there also was no significant difference in plasma NE concentration according to the use of the bronchodilators. These results suggest that the results of $^{123}$I-MIBG imaging are not greatly affected by bronchodilators. Therefore, it is conceivable that abnormal LV sympathetic function assessed by $^{123}$I-MIBG imaging could reflect cardiac sympathetic nervous alterations secondary to COPD.

The decreased H/M and increased WR of $^{123}$I-MIBG in our study support the existence of subclinical LV alterations in patients with COPD, although it is controversial whether LV function is compromised in patients with COPD. Rao and coworkers clearly showed LV failure secondary to COPD, as assessed by cardiac catheterization or autopsy, for the first time. Baum et al demonstrated that LV end-diastolic BP was elevated, that LV hypertrophy was suggested on left ventriculography in COPD, and that the degree of impairment of LV function was not influenced by the presence or degree of right-sided heart failure. Abnormal results of blood gas measurements, increased collateral circulation to the lungs (“left-to-right shunt”) with resultant LV overwork, and mechanical interference with LV performance of a hypertrophied, dilated RV are thought to be possible mechanisms. We speculate that intrathoracic damage to sympathetic neurons also would play a major role in sympathetic denervation. Gas trapping due to rapid breathing in patients with COPD increases lung volume and increases the pressure in the cardiac fossa around the heart, with resulting biventricular dysfunction.

In addition to these mechanisms, systemic ANS overactivity may be causative or contributory to the development of LV alterations in patients with COPD. Indeed, in our study, plasma NE concentrations, which may reflect an abnormality of systemic sympathetic nervous function, were significantly increased in the COPD group. It has been demon-
strated that increased sympathetic activity can contribute significantly to the pathophysiology of myocardial infarction, arrhythmia, and heart failure.28–30

In all the patients with COPD, myocardial 123I-MIBG uptake was decreased in the region of the IVS and inferior wall on SPECT images. It remains controversial why relative sympathetic denervation was detected in these regions. Morimitsu and co-workers31 reported that the ratio of 123I-MIBG uptake in the IVS to the LV was decreased in patients with pulmonary arterial hypertension. Therefore, reduced 123I-MIBG uptake in the IVS and inferior wall may be due to possible RV pressure overload. We cannot completely rule out the existence of ischemic coronary artery disease because coronary angiography was not performed in all the COPD patients. If many of the patients with COPD in our study had significant coronary artery disease, however, an MIBG study might have revealed, in a few cases, reduced uptake in other regions, including the anterior or posterior wall of the LV. These results indicate that the reduced H/Ms and higher WRs in our study were not affected by ischemic coronary artery disease but mainly by COPD.

COPD patients with more severe symptoms had lower H/Ms and higher WRs. All pulmonary function test parameters, except for percentages of FVC, residual volume/TLC ratio, and MVV volume, did not correlate with the parameters of 123I-MIBG imaging. This result may indicate that the severity of symptoms in COPD is affected not only by pulmonary function, but also by ANS alterations that may be related to increased respiratory effort.

There are several limitations of the present study. First, since cardiac catheterization was performed in only 8 patients in the COPD group, and although RV hypertrophy or overload and abnormal LV wall motion were not found on echocardiography in any subjects, RV hypertrophy or alterations as well as ischemic coronary artery disease were not completely ruled out in the other 20 patients. Mild pulmonary hypertension might be associated in some patients in the COPD group. In order to study COPD patients without cardiac complications, right heart catheterization and coronary angiography would have to be performed in all patients in the COPD group. Second, the patients with COPD who were involved in this study had mild to moderate COPD. Investigations that extend to populations with more advanced COPD would produce more useful findings.

In conclusion, our data indicate that patients with COPD demonstrated abnormal results in 123I-MIBG imaging, which may suggest the existence of LV myocardial sympathetic nervous alterations due to generalized sympathetic ANS overactivity. Further studies are needed to clarify the relationship between the ANS abnormality assessed by 123I-MIBG and the severity and prognosis of COPD.

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