CLINICAL STUDY

Impairment of Iodine-123-Metaiodobenzylguanidine (^{123}I-MIBG) Uptake in Patients with Pulmonary Artery Hypertension

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Summary

According to recent studies, lung uptake of iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) is impaired in many lung diseases and low lung uptake of ^{123}I-MIBG suggests endothelial dysfunction of the pulmonary artery. ^{123}I-MIBG scintigraphy in patients with pulmonary hypertension (PH) has not yet been clinically evaluated. We hypothesized that the lung uptake of ^{123}I-MIBG is reduced in patients with PH and differs among PH subtypes. The purpose of the present study was to analyze the lung uptake of ^{123}I-MIBG in patients with PH and compare it with the data obtained by echocardiography or right heart catheterization. ^{123}I-MIBG scintigraphy was performed in 286 consecutive patients from 2003 to 2014. We enrolled 21 patients with PH and 8 control patients. The 21 patients with PH were categorized into those with pulmonary artery hypertension (PAH, n = 12) and those with chronic thromboembolic pulmonary hypertension (CTEPH, n = 9). The mean pulmonary artery pressure was not significantly different between patients with CTEPH and PAH (37.7 ± 6.8 versus 32.3 ± 5.3 mmHg respectively; P = 0.054). There were no significant differences in any other hemodynamic parameters between the two groups. The lung uptake of ^{123}I-MIBG in PAH patients (early image: 1.54 ± 0.18, delayed image: 1.41 ± 0.16) was significantly lower than that of CTEPH patients (early image: 2.17 ± 0.25, P < 0.0001; delayed image: 1.99 ± 0.20, P = 0.0001, adjusted for age and World Health Organization classification) and controls (early image: 2.32 ± 0.27, P = 0.0007; delayed image: 1.92 ± 0.19, P = 0.0007). In conclusion, we found for the first time that the lung uptake of ^{123}I-MIBG in patients with PAH is lower than that in patients with CTEPH and controls.

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Key words: Pulmonary hypertension, ^{123}I-MIBG scintigraphy, Endothelial dysfunction

Pulmonary hypertension (PH) is characterized by progressive remodeling of the distal pulmonary arteries, resulting in the loss of vascular area.[1)] New therapeutic options for patients with PH have recently been developed.[2,3)] Additionally, the therapeutic outcome of PH has notably improved,[2,3)] and long-term survival can be expected.[4)] However, PH is still a life-threatening disease.

Endothelial dysfunction, proliferation of vascular smooth muscle cells, and migration of inflammatory cells seem to play an integral role in the pathogenesis of PH.[5-8)] Several molecules are reportedly involved in the pathophysiology of PH.[9-12)] Therefore, certain biomarkers, such as asymmetric dimethylarginine, may represent pulmonary endothelial dysfunction and could be useful for early diagnosis of PH.[12)] However, some biomarkers may be not specific for pulmonary endothelial function because they are also increased in patients with other systemic vascular diseases, such as arteriosclerosis.[13)] Therefore, specific markers for pulmonary endothelial function are needed in patients with PH.

Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG), which acts as a tracer of norepinephrine, is used in scintigraphy to evaluate the activity of sympathetic nerve endings in many diseases (e.g., neuroendocrine tumors such as pheochromocytoma and neuroblastoma).[14)] In cardiology, ^{123}I-MIBG is utilized to evaluate the cardiac sympathetic status, arrhythmia risk, and prognosis of patients with heart failure.[15)] Slosman, *et al*.[16-18)] demonstrated that like norepinephrine, ^{123}I-MIBG was taken up and metabolized by the pulmonary endothelium in sheep and rat lungs. Furthermore, they analyzed ^{123}I-MIBG extraction in human lungs and suggested that ^{123}I-MIBG extraction might be a valuable tool for evaluating early metabolic changes that most likely reflect the pulmonary vascular endothelial function.[19)] Based on these reports, recent studies have demonstrated that the lung uptake of ^{123}I-MIBG is reduced in many pulmonary diseases and have suggested that this reduced lung uptake of ^{123}I-MIBG indicates pulmonary endothelial dysfunction.[20-27)]

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To date, ^{123}I-MIBG scintigraphy in patients with PH has not been clinically evaluated. We hypothesized that the lung uptake of ^{123}I-MIBG is reduced in patients with PH, differs among PH subtypes, and may be specific for the pulmonary endothelial status. The purpose of the present study was to analyze the lung uptake of ^{123}I-MIBG in patients with PH, including pulmonary artery hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), and compare it with the data obtained by echocardiography or right heart catheterization.

Method

Patient background: ^{123}I-MIBG scintigraphy was performed in 286 consecutive patients from December 2003 to December 2014. We enrolled 21 patients with PH and 8 age- and sex-matched controls. The controls were analyzed by ^{123}I-MIBG scintigraphy because they were suspected to have Parkinson's disease, but were finally confirmed not to have Parkinson's disease. Moreover, they did not have PH, cardiac disease, pulmonary disease, or diabetes mellitus.

Diagnosis of PH was based on clinical and hemodynamic data according to current guidelines.[28,29] All patients underwent echocardiography, high-resolution chest computed tomography (CT), ^{99m}Tc-macroaggregated albumin scintigraphy, lung ventilation scintigraphy, and right heart catheterization to diagnose PH and determine the category of PH. Patients with PH due to lung disease and left heart disease were not included in this study.

Ethical approval was given by the institutional board of Kagoshima University Hospital. All patients provided written consent to participate in this study.

Echocardiography, 6-minute walk test, and B type natriuretic peptide measurement: Echocardiography was performed upon admission. We used GE Vivid 7, S6, and E9 Ultrasound Systems (GE Vingmed Ultrasound, Horten, Norway) or a Phillips IE33 system (Phillips Medical Systems, Andover, MA, USA) in the present study. The right ventricular systolic pressure, left ventricular ejection fraction, tricuspid annular plane systolic excursion, and tissue doppler-derived tricuspid lateral annular systolic velocity were obtained. The tricuspid annular plane systolic excursion was determined as the total excursion of the tricuspid annulus from its highest position to its deepest descent during ventricular systole. In addition, pulsed doppler tissue imaging was performed at the lateral corner of the tricuspid annulus, and the tricuspid lateral annular systolic velocity was measured. On the day after admission, blood samples were obtained and the plasma B type natriuretic peptide (BNP) concentration was measured. Three days after admission, the 6-minute walk test was carried out and the 6-minute walk distance was determined.

Pulmonary function test: The vital lung capacity was measured with the standard spirometric method and is expressed as the percentage of the predicted value. The diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath carbon monoxide gas transfer method and is expressed as the percentages of the predicted values.

Right heart catheterization and PH diagnosis: All patients underwent right heart catheterization within 1 week before or after ^{123}I-MIBG scintigraphy. The pulmonary capillary wedge pressure, pulmonary artery pressure, right ventricular pressure, and right atrial pressure were obtained. In addition, the mixed venous oxygen saturation was measured. Cardiac output was calculated by the Fick method. Pulmonary vascular resistance was calculated as follows: (mean pulmonary artery pressure-pulmonary capillary wedge pressure)/cardiac output.[30] None of the patients received oxygen therapy during right heart catheterization.

PH is defined as a resting mean pulmonary artery pressure of ≥ 25 mmHg demonstrated using right heart catheterization.[30] PAH is further defined as a mean pulmonary artery pressure of ≥ 25 mmHg in the presence of normal left-sided filling pressures, defined by a pulmonary capillary wedge pressure of < 15 mmHg.[30]

Connective tissue disease-related PH, portopulmonary hypertension, and congenital heart disease-related PH were diagnosed according to the right heart catheterization findings and patients' clinical manifestations. Pulmonary artery angiography was performed if the patient was suspected to have CTEPH, which is usually characterized by a perfusion defect in ^{99m}Tc-macroaggregated albumin scintigraphy with a normal ventilation scan (i.e., ventilation-perfusion mismatch). A definitive diagnosis of CTEPH was established when typical angiographic findings were observed, such as pouch defects, webs, bands, intimal irregularities, abrupt narrowing, or complete obstruction.[31,32]

^{123}I-MIBG scintigraphy: Patients were placed in the supine position, and ^{123}I-MIBG (Fujifilm RI Pharma Co. Ltd., Tokyo, Japan) was intravenously injected at a dose of 111 MBq. Anterior planar images were obtained at 20 minutes (early image) and 4 hours (delayed image) after the injection of ^{123}I-MIBG in a 512 × 512 matrix using a dual-head gamma camera equipped with a low- to medium-energy general-purpose collimator (ECAM; Toshiba Medical Systems, Tochigi, Japan). The data were processed with an image processing system (e.soft; Toshiba Medical Systems). For enrolled patients in this study, regions of interest were set at the mediastinum (M), upper right lung (rt L), and upper left lung (lt L) (Figure 1). These regions of interest were determined with reference to previous reports.[20,24] The L/M ratio was calculated according to the following formula: L/M ratio = (rt L/M + lt L/M)/2. The lung washout rate of ^{123}I-MIBG was calculated as follows: [(early L/M ratio - delayed L/M ratio)/early L/M ratio] × 100.[20,24] Furthermore, the heart-to-mediastinum (H/M) ratio in early and delayed images was calculated by dividing the mean counts/pixels in the left ventricle by those in the mediastinum.[33] The heart washout rate of ^{123}I-MIBG was calculated as follows: [(early H count - delayed H count)/early H count] × 100.

Statistical analysis: Results are expressed as mean ± standard deviation. Statistical analysis was performed using JMP Statistical Discovery Software, version pro11 (SAS, Cary, NC, USA). Comparisons of baseline clinical characteristics between the two groups (CTEPH versus PAH) were performed using Student's t-test for parametric data or the Wilcoxon test for nonparametric data. Pearson's chi-square test was performed to compare sex and

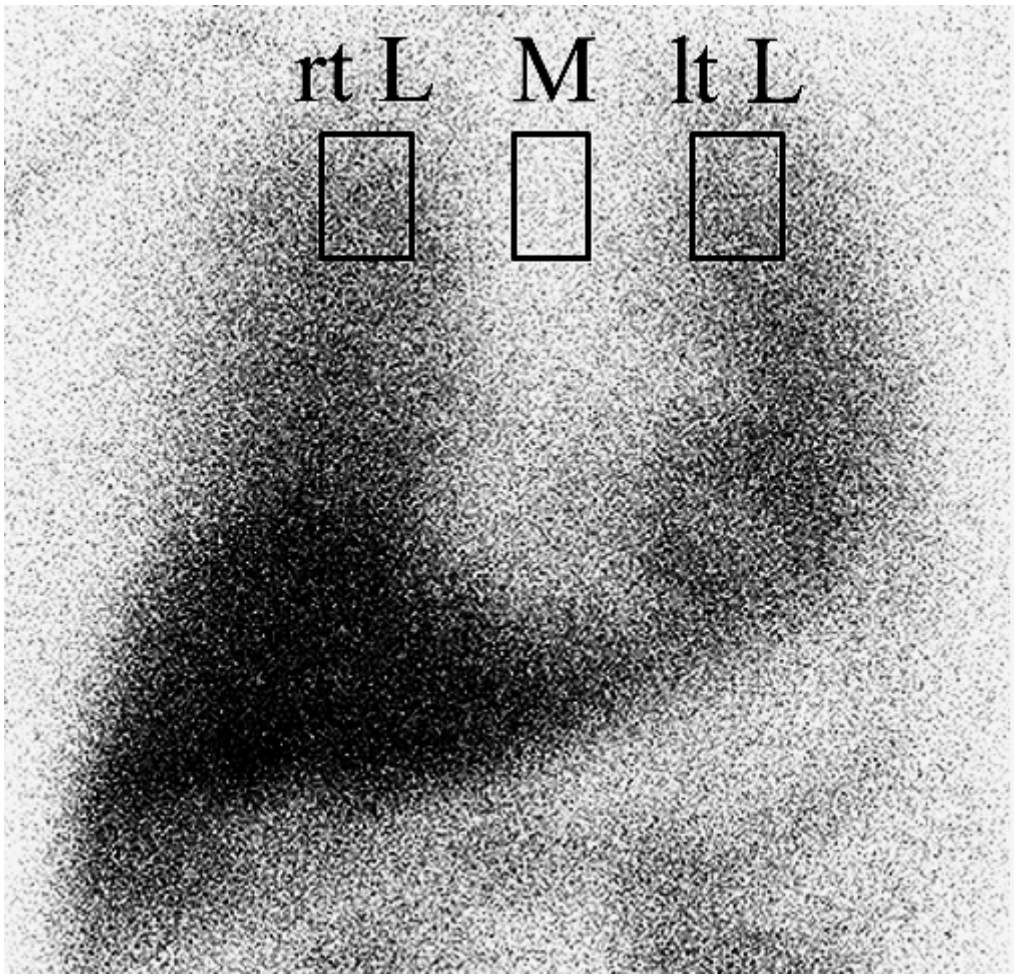

Figure 1. Anterior planar image of lung ^{123}I-MIBG scintigraphy and region of interest definition in the present study. An anterior planar image of lung ^{123}I-MIBG scintigraphy in a control subject is shown. rt L, lt L, and M indicate regions of interest in the right upper lung, left upper lung, and mediastinum, respectively. The L/M ratio was calculated as follows: (rt L/M + lt L/M) /2.

World Health Organization functional class (WHO FC) between the CTEPH and PAH groups. Kruskal-Wallis analysis of variance (ANOVA) for nonparametric data was used to compare the lung and myocardial uptake of ^{123}I-MIBG among control subjects, patients with CTEPH, and patients with PAH. Steel-Dwass analysis was used for post hoc analysis. Multivariate analysis was performed to adjust for the differences in age and WHO FC between the CTEPH and PAH groups. Linear regression analysis was employed to evaluate the correlation of planar L/M and hemodynamic data obtained by right heart catheterization or echocardiography indices. Statistical significance was assumed at a P-value of < 0.05.

Results

The average age of the 21 patients with PH was 60.6 ± 13.4 years (range, 22-78 years). This study included 5 male and 16 female patients with PH, and we compared the backgrounds between the CTEPH and PAH groups (Table I). There were 12 patients with PAH and 9 patients with CTEPH. All CTEPH patients in this study had class III CTEPH of the San Diego classification according to the results of pulmonary artery angiography, suggesting that all of the CTEPH patients in the present study had a relative indication for not pulmonary endarterectomy but balloon pulmonary angioplasty. No patients had San Diego classification I or II CTEPH, representing a massive perfusion defect in $^{99\ m}$Tc-macroaggregated albumin scintigraphy. PAH patients were classified into connective tissue disease-related PH (n = 7), portopulmonary hypertension (n = 3), congenital heart disease-related PH (n = 1), and idiopathic pulmonary artery hypertension (n = 1). The causative diseases in patients with connective tissue disease-related PH were systemic sclerosis (n = 3), systemic lupus erythematosus (n = 2), polymyositis (n = 1), and mixed connective tissue disease (n = 1). No patients exhibited interstitial pneumonia on chest CT images. The patients with CTEPH were significantly older than those with PAH (P = 0.008). The WHO FC was significantly different between the CTEPH and PAH groups (P = 0.009). Both, patients with CTEPH and PAH, showed nor-

Table I. Characteristics of Patients with Pulmonary Hypertension

	CTEPH (n = 9)	PAH (n = 12)	P
Age (years)	69.1 ± 7.5	54.1 ± 13.4	0.008
Sex (male/female)	2/7	3/9	0.882
WHO FC (I/II/III)	0/1/8	1/8/3	0.009
6MWD (m)	360.4 ± 69.3	427.8 ± 134.6	0.243
BNP (pg/mL)	83.4 ± 47.9	74.8 ± 120.7	0.095
RVSP (mmHg)	67.2 ± 18.7	53.9 ± 18.9	0.135
TAPSE (cm)	1.4 ± 0.4	1.7 ± 0.4	0.217
S' (mm)	12.3 ± 3.8	10.4 ± 1.6	0.590
LVEF (%)	67.4 ± 7.0	72.6 ± 7.0	0.118
meanPAP (mmHg)	37.7 ± 6.8	32.3 ± 5.3	0.054
RAP (mmHg)	6.1 ± 3.1	5.2 ± 3.8	0.519
CO (L/min)	3.60 ± 0.9	4.3 ± 0.9	0.110
PVR (dynes•sec•cm^{-5})	652.0 ± 397.1	453.7 ± 155.1	0.214
SV (mL)	46.6 ± 10.1	59.2 ± 17.8	0.145
SVO_2 (%)	71.8 ± 5.8	71.2 ± 4.9	0.972
%VC (%)	91.4 ± 15.7	89.8 ± 15.2	0.887
%DLCO (%)	85.3 ± 12.6	54.7 ± 19.1	0.001

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary artery hypertension; WHO FC, World Health Organization functional class; 6MWD, 6-minute walk distance; BNP, B type natriuretic peptides; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annual plane systolic excursion; S', tissue doppler-derived tricuspid lateral annular systolic velocity; LVEF, left ventricular ejection fraction; mean PAP, mean pulmonary artery pressure; RAP, right atrium pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SV, stroke volume; SVO_2, mixed venous oxygen saturation; VC, vital capacity; and DLCO, diffusing capacity for the lung carbon monoxide.

mal vital capacity, suggesting that no patients had restrictive lung disease in the present study. Moreover, patients with PAH showed a lower DLCO on pulmonary function tests than did patients with CTEPH (P = 0.001). There were no statistically significant differences between the two groups in sex, 6-minute walk distance, BNP, hemodynamic data obtained by right heart catheterization, or echocardiographic indices such as the right ventricular systolic pressure, tricuspid annular plane systolic excursion, tricuspid lateral annular systolic velocity, and left ventricular ejection fraction.

Representative early-phase lung ^{123}I-MIBG scintigraphy images are shown in Figure 2. The control subject showed homogeneous and symmetrical distribution of ^{123}I-MIBG throughout the lung. In the patient with PAH, uptake in the upper lung was reduced compared with that in the patient with CTEPH and the control subject.

We compared the lung uptake of ^{123}I-MIBG between the 21 patients with PH and the 8 controls (mean age, 69.6 ± 7.1 years; 7 female). The lung uptake of ^{123}I-MIBG in patients with PH was significantly lower than that of controls in early images (1.80 ± 0.38 versus 2.32 ± 0.27; P = 0.006) and delayed images (1.67 ± 0.34 versus 1.92 ± 0.19; P = 0.048). Furthermore, we compared the lung uptake of ^{123}I-MIBG among controls, patients with CTEPH, and patients with PAH. Kruskal-Wallis ANOVA showed significant differences in the lung uptake of ^{123}I-MIBG among these three groups. Steel-Dwass analysis demonstrated that the lung uptake of ^{123}I-MIBG in patients with PAH was significantly lower than that in patients with CTEPH and controls in both early and delayed images (Table II and Figure 3). We found no significant difference in the lung uptake of ^{123}I-MIBG between patients with CTEPH and controls. Age and WHO FC were significantly different between patients with PAH and CTEPH. Therefore, we performed a multivariate analysis with adjustment for age and WHO FC between the two groups and demonstrated that the significant difference in the lung uptake of ^{123}I-MIBG between the CTEPH and PAH groups was conserved. There was no significant difference in the washout rate of ^{123}I-MIBG among controls, patients with CTEPH, and patients with PAH (Table II).

The myocardial uptake of ^{123}I-MIBG in patients with PH was significantly lower than that in controls in both early images (2.40 ± 0.39 versus 3.35 ± 0.62, respectively; P = 0.0003) and delayed images (2.28 ± 0.60 versus 3.37 ± 0.69, respectively; P = 0.0008). Kruskal-Wallis ANOVA showed significant differences in the myocardial uptake and washout rate of ^{123}I-MIBG among controls, patients with CTEPH, and patients with PAH. Steel-Dwass analysis demonstrated significant differences in the myocardial uptake of ^{123}I-MIBG between controls and patients with either CTEPH or PAH. Furthermore, there was a significant difference in the myocardial washout rate of ^{123}I-MIBG between controls and patients with CTEPH. After adjustment for age and WHO FC, there was no significant difference in the myocardial uptake or washout rate of ^{123}I-MIBG between patients with CTEPH and PAH (Table III).

Table IV shows the results of linear regression analysis between lung uptake of ^{123}I-MIBG and BNP, 6-minute walk distance, hemodynamic data obtained by right heart catheterization, and echocardiographic indices. There was no significant correlation between the lung uptake of ^{123}I-

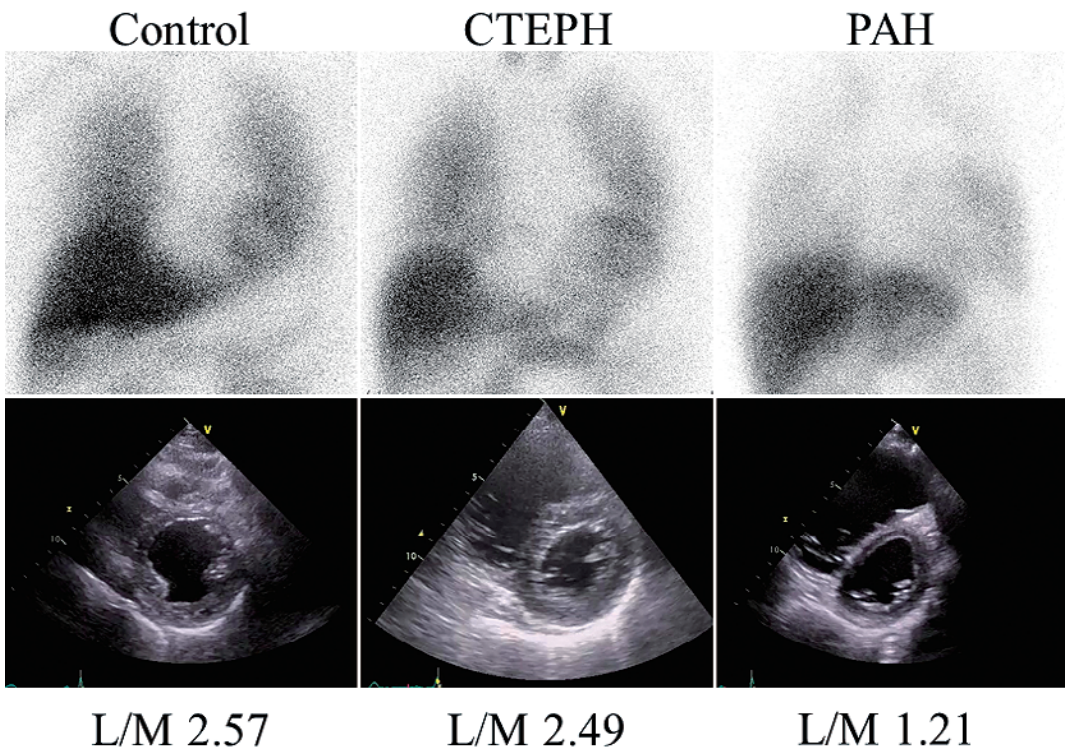

Figure 2. Representative anterior planar images of lung ^{123}I-MIBG scintigraphy and echocardiography images from a patient with pulmonary artery hypertension (PAH), a patient with chronic thromboembolic pulmonary hypertension (CTEPH), and a control subject. The control subject showed homogeneous and symmetrical distribution of ^{123}I-MIBG throughout the lung. In the patient with PAH, the uptake in the upper lung was reduced compared with that in the patient with CTEPH and the control subject.

Table II. Comparison of Lung Uptake of ^{123}I-MIBG among Patients with Pulmonary Artery Hypertension (PAH), Patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH), and Controls

	Control	CTEPH	PAH
Early L/M ratio	2.32 ± 0.27	2.17 ± 0.25	1.54 ± 0.18 *
Delayed L/M ratio	1.92 ± 0.19	1.99 ± 0.20	1.41 ± 0.16 **
Washout ratio	46.3 ± 6.28	42.0 ± 7.47	43.6 ± 6.70

Kruskal-Wallis ANOVA showed significant differences in the lung uptake of ^{123}I-MIBG in the early and delayed phases among controls, patients with CTEPH, and patients with PAH. Steel-Dwass analysis demonstrated that the lung uptake of ^{123}I-MIBG in patients with PAH was significantly lower than that in controls in the early phase (*P = 0.0007) and delayed phase (**P = 0.0007). Multivariate analysis with adjustment for age and WHO classification showed that the lung uptake of ^{123}I-MIBG in patients with PAH was significantly lower than that in patients with CTEPH in the early phase (*P < 0.0001) and delayed phase (**P = 0.0001).

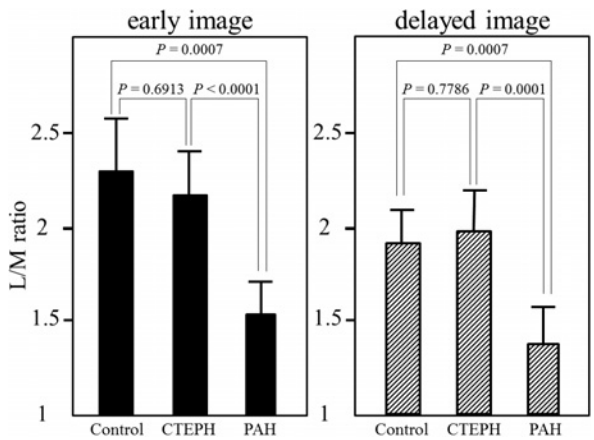

Figure 3. Comparison of lung uptake of ^{123}I-MIBG among patients with pulmonary artery hypertension (PAH), patients with chronic thromboembolic pulmonary hypertension (CTEPH), and control subjects. Kruskal-Wallis ANOVA showed significant differences in the lung uptake of ^{123}I-MIBG in the early and delayed phases among controls, patients with CTEPH, and patients with PAH. Steel-Dwass analysis demonstrated that the lung uptake of ^{123}I-MIBG in patients with PAH was significantly lower than that in controls in the early phase (P = 0.0007) and delayed phase (P = 0.0007). Multivariate analysis adjusted for age and World Health Organization functional class showed that the lung uptake of ^{123}I-MIBG in patients with PAH was significantly lower than that in patients with CTEPH in the early phase (P < 0.0001) and delayed phase (P = 0.0001).

MIBG and these parameters.

Discussion

In the present study, we demonstrated that ^{123}I-MIBG uptake in patients with PAH was significantly lower than that in controls. Previous studies reported that reduced lung uptake of ^{123}I-MIBG correlated with pulmonary endothelial dysfunction in animals and humans.[16-19] Therefore,

Table III. Comparison of Myocardial Uptake of ^{123}I-MIBG among Patients with Pulmonary Artery Hypertension (PAH), Patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH), and Controls

	Control	CTEPH	PAH
Early H/M ratio	3.35 ± 0.62	2.31 ± 0.49*1	2.47 ± 0.30*2
Delayed H/M ratio	3.37 ± 0.69	1.90 ± 0.56*3	2.57 ± 0.47*4
Washout ratio	34.03 ± 4.32	45.70 ± 8.00*5	35.47 ± 7.44

Kruskal-Wallis ANOVA showed significant differences in the myocardial uptake of ^{123}I-MIBG in the early phase, uptake of ^{123}I-MIBG in the delayed phase, and washout rate of ^{123}I-MIBG among controls, patients with CTEPH, and patients with PAH. Steel-Dwass analysis showed significant differences in the myocardial uptake of ^{123}I-MIBG in the early phase between controls and patients with CTEPH (*1P = 0.0094) or patients with PAH (*2P = 0.0030). Steel-Dwass analysis demonstrated significant differences in the myocardial uptake of ^{123}I-MIBG in the delayed phase between controls and patients with CTEPH (*3P = 0.0026) or patients with PAH (*4P = 0.0264). Steel-Dwass analysis also revealed significant differences in the myocardial washout rate of ^{123}I-MIBG between controls and patients with CTEPH (*5P = 0.0168).

Table IV. Comparison between the Lung Uptake of the ^{123}I-MIBG and Clinical Parameters

Parameters	r^2	P
BNP (pg/mL)	0.003	0.817
6MWD (m)	0.014	0.657
RVSP (mmHg)	0.182	0.054
TAPSE (cm)	0.060	0.403
S' (mm)	0.066	0.262
LVEF (%)	0.012	0.638
mean PAP (mmHg)	0.180	0.056
PVR (dyne•sec•cm^{-5})	0.044	0.363
RAP (mmHg)	0.080	0.222
CO (L/minute)	0.126	0.115
SV (L/minute)	0.046	0.356

BNP indicates B type natriuretic peptides; 6MWD, 6-minute walk distance; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annual plane systolic excursion; S', tissue doppler-derived tricuspid lateral annular systolic velocity; LVEF, left ventricular ejection fraction; mean PAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrium pressure; CO, cardiac output; and SV, stroke volume.

we suggest that reduced uptake of ^{123}I-MIBG in patients with PAH indicates endothelial dysfunction of the pulmonary artery.

Because the lung receives the entire venous return, it can take up and regulate many circulating substances, including norepinephrine.[34] During a single pass through the pulmonary circulation, norepinephrine is rapidly extracted and degraded.[35] Sole, *et al*.[36] directly measured the pulmonary extraction of circulating norepinephrine in controls and patients with PH, excluding those with CTEPH. They demonstrated that 25% of circulating norepinephrine is extracted during passage through the normal lung, but the metabolic function of the lung appears to be lost in patients with PH. These results are compatible with the present study, because ^{123}I-MIBG acts as a tracer of norepinephrine during scintigraphy.

In patients with chronic obstructive pulmonary disease, ^{123}I-MIBG defects were shown even when there were no perfusion defects in scintigraphy or morphologic abnormalities in CT, suggesting that ^{123}I-MIBG uptake may be more sensitive than perfusion scintigraphy and CT.[23] Pulmonary endothelial dysfunction is one of the pathogeneses of PAH,[1,37] and we suggest that ^{123}I-MIBG can detect endothelial dysfunction early in the disease course of PAH.

Langleben, *et al*.[38] studied the pulmonary capillary bed and metabolism of the pulmonary endothelium with angiotensin-converting enzyme in patients with idiopathic PAH and patients with connective tissue disease-related PH. They demonstrated that the pulmonary capillary bed was reduced to an equal extent in patients with idiopathic PAH and those with connective tissue disease-related PH; however, the metabolism of the pulmonary endothelium with angiotensin-converting enzyme was reduced in patients with connective tissue disease-related PH but not in patients with idiopathic PAH. Their findings suggest that pulmonary endothelial metabolic function differs between PAH types. We believe that in the present study, the lung uptake of ^{123}I-MIBG in patients with PAH was markedly lower than that in patients with CTEPH, because most patients with PAH had connective tissue disease-related PH. The validation of reduced lung uptake of ^{123}I-MIBG between different types of PAH should be examined in further studies.

A similar study of CTEPH was performed by Orfanos, *et al*.[39] They demonstrated that the vascular bed was decreased in patients with CTEPH but that the metabolism of the pulmonary endothelium with angiotensin-converting enzyme was maintained. These results suggest that pulmonary endothelial metabolic function may be maintained in patients with CTEPH. Conversely, it was recently proposed that CTEPH is not simply a thromboembolic disease but also a microvascular disease. Some reports have indicated that the progression of PH in patients with CTEPH results from progressive pulmonary artery remodeling. Both the extent of proximal occlusion of the

pulmonary arteries and secondary small-vessel arteriopathy are considered to contribute to the elevated pulmonary artery resistance.[31] Thus, many aspects of endothelial function in patients with CTEPH remain unclear. In the present study, ^{123}I-MIBG uptake in patients with San Diego class III CTEPH was not significantly different from that in controls. The lung uptake of ^{123}I-MIBG in patients with San Diego class I, II, and III CTEPH should be examined in a further study, and the endothelial function among patients with various San Diego classes of CTEPH should be discussed.

In this study, the patients with CTEPH were significantly older than the patients with PAH, and the WHO FC was significantly different between the CTEPH and PAH groups. Therefore, we performed multivariate analysis adjusting for age and WHO FC between patients with CTEPH and PAH. As a result, we demonstrated that the differences in the lung uptake of ^{123}I-MIBG between CTEPH and PAH patients were conserved. This suggests that the lung uptake of ^{123}I-MIBG between the two groups were independent from age and WHO FC. Furthermore, it was reported that the lung uptake of ^{123}I-MIBG showed no significant correlations with age.[40] Therefore, we think that the difference of age between CTEPH and PAH patients may not have affected the lung uptake of ^{123}I-MIBG in the present study.

In this study, lung uptake of ^{123}I-MIBG was not correlated with any parameters, such as the BNP level, 6-minute walk distance, hemodynamic data obtained by right heart catheterization, or echocardiographic indices. No reports have described the correlation between endothelial function and these parameters in patients with PH. Therefore, we speculate that lung uptake of ^{123}I-MIBG, which indicates pulmonary endothelial function, may not be associated with right ventricular function in patients with PH. Further studies are required.

Limitations: This study has some limitations. First, the number of cases was small. Second, the study was retrospective. Third, whether ^{123}I-MIBG uptake changes according to the endothelial status after treatment remains unclear because this was a cross-sectional study. Therefore, a prospective, longitudinal study of many patients with PH is necessary to clarify the clinical validity of lung uptake of ^{123}I-MIBG in patients with PH. Fourth, we did not compare the relationship between the lung uptake of ^{123}I-MIBG and levels of certain biomarkers, such as asymmetric dimethylarginine that may be considered to indicate pulmonary endothelial dysfunction. Such associations should be analyzed in future research. Finally, in this study, the lung uptake of MIBG was evaluated by planar images because many previous reports studied the lung MIBG uptake in patients with lung diseases using this method. Measurement of lung MIBG uptake is not yet well established, and more studies are needed.

Conclusion

We found for the first time that lung uptake of ^{123}I-MIBG in patients with PAH is lower than that of patients with CTEPH and controls, suggesting the presence of endothelial dysfunction of the pulmonary artery in patients with PAH.

Disclosures

Conflicts of Interest: None.

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