Case Report

The potential for early diagnosis of pulmonary arterial hypertension using lung iodine-123-metaiodobenzylguanidine (\(^{123}\text{I-MIBG}\)) uptake: A case report

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**ABSTRACT**

Previous reports have found evidence that the lung uptake of iodine-123-metaiodobenzylguanidine (\(^{123}\text{I-MIBG}\)) represents pulmonary vascular endothelial function. Therefore, it was believed that the reduced lung uptake of \(^{123}\text{I-MIBG}\) in patients with pulmonary artery hypertension may indicate poor pulmonary vascular endothelial function in those patients. In our previous report, we analyzed the lung uptake of \(^{123}\text{I-MIBG}\) in patients with pulmonary hypertension, and demonstrated that it is lower in patients with pulmonary arterial hypertension (PAH) than in those with chronic thromboembolic pulmonary hypertension and controls, suggesting that reduced uptake of \(^{123}\text{I-MIBG}\) in patients with PAH indicates endothelial dysfunction of the pulmonary artery. In the current report, we describe a 46-year-old woman diagnosed with scleroderma whose lung uptake of \(^{123}\text{I-MIBG}\) was decreased on admission, but she was not diagnosed with pulmonary artery hypertension at that time because her pulmonary artery pressure during right heart catheterization was not elevated. However, she was diagnosed with borderline PAH 2 years later. The lung uptake of \(^{123}\text{I-MIBG}\) was reduced before a reduction in %DLCO was observed. This report suggests that the lung uptake of \(^{123}\text{I-MIBG}\) may be useful for the early diagnosis of pulmonary artery hypertension.

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We have previously reported that the lung uptake of iodine-123-metaiodobenzylguanidine (123I-MIBG) is reduced in patients with pulmonary artery hypertension (PAH) [1]. The lung uptake of 123I-MIBG in patients with PAH (early image: 1.54 ± 0.18, delayed image: 1.41 ± 0.16) was significantly lower than that of controls (early image: 2.32 ± 0.27, P < .0007; delayed image: 1.92 ± 0.19, P = .0007) [1]. Previous reports, including basic research [2,3] and clinical studies [4-9], have found evidence that the lung uptake of 123I-MIBG represents pulmonary vascular endothelial function; therefore, we believe that the reduced lung uptake of 123I-MIBG in patients with PAH might indicate poor pulmonary vascular endothelial function in those patients.

Herein, we report a case of PAH in which the lung uptake of 123I-MIBG was decreased on admission, but PAH was not diagnosed at that time because the pulmonary artery pressure during right heart catheterization was not elevated; however, the patient was diagnosed with borderline PAH 2 years later.

Case report

A 46-year-old woman visited a nearby doctor presenting with Raynaud’s phenomenon. She was diagnosed with scleroderma based on a positive test for antinuclear antibodies. The patient visited our hospital to be evaluated for the presence of pulmonary hypertension (PH). She did not have any chest symptoms. Her blood pressure at the first visit was 96/63 mmHg, heart rate was 73 beats per minute, and oxygen saturation (SpO2) was 99% on room air. In lab analysis, the brain natriuretic peptide level was 33.3 pg/mL (<18.4 pg/mL). The blood gas analysis on room air showed a pO2 of 104 mmHg and pCO2 of 36.7 mmHg. On chest X-ray, the cardio-thoracic ratio was 43% and pulmonary artery dilatation was not detected. An electrocardiogram showed sinus rhythm and no characteristic findings of PH, such as pulmonary p wave, negative T wave in the chest lead, or R wave increase in the chest lead. On echocardiography, the ejection fraction of the left ventricle was 78%. No characteristic findings of PH, such as right ventricle dilatation, were observed. The tricuspid regurgitation peak velocity was 2.1 m/s and right ventricle systolic pressure (RVSP) was 27.6 mmHg. In a respiratory function test, the vital capacity, measured using the standard spirometric method and expressed as the percentage of the predicted value, was 96.1%. The diffusing capacity for carbon monoxide (%DLCO), measured by the single-breath carbon monoxide gas transfer method and expressed as the percent of the predicted reference value, was 78%, which is within the normal range. During the right heart catheterization (RHC), the mean pulmonary artery pressure was 13 mmHg and pulmonary artery wedge pressure was 6 mmHg. Pulmonary vascular resistance was 143 dyn/s/cm²; thus, PH was not diagnosed at that time. We chose to proceed with follow-up observation only. At the initial visit, we also performed lung 123I-MIBG scintigraphy, which was approved by the institutional review board of our hospital, and the patient provided written informed consent [1]. Lung 123I-MIBG scintigraphy was performed as described in our previous report; early and delayed images were obtained 20 minutes and 4 hours after 123I-MIBG injection, respectively [1]. The lung uptake of 123I-MIBG in this patient, calculated as the lung-to-mediastinum ratio on the early and delayed images, was 1.18 on the early image and 1.12 on the delayed image, which was lower than that of the control group in our previous study [1]. The myocardial uptake of 123I-MIBG, represented by the heart-to-mediastinum (H/M) ratio, was also examined. The H/M ratio in this patient was 2.77 on the early image and 3.34 on the delayed image, which is similar to previous reports [10,14,15]; the heart washout rate of 123I-MIBG was 35.1%. Furthermore, we examined the 123I-MIBG uptake in specific regions of interest (ROIs) in the following areas of the left ventricle: the intraventricular septum, anterior wall, inferior wall, and lateral wall. The 123I-MIBG uptake in each region was comparable to that presented in past reports (25.4%, 25.4%, 21.0%, and 28.0% for the intraventricular septum, anterior wall, inferior wall, and lateral wall, respectively) [10].

Two years later, during her annual examination for PH, her %DLCO fell from 96.1% to 57.8%. Since some reports suggest that a decrease in %DLCO may indicate PH, she again visited our hospital to be re-evaluated for PH. Chest radiography showed a cardio-thoracic ratio of 46%, and electrocardiogram showed sinus rhythm and negative T waves at V1-2, which are similar findings to her previous examination. The brain natriuretic peptide value was 27.1 pg/ml, which was not significantly different from the previous value (33 pg/ml). However, on echocardiography, the tricuspid regurgitation peak velocity and RVSP rose from 2.1 to 3.1 m/s and from 27.6 to 48.4 mmHg, respectively, suggesting that her pulmonary artery pressure may have increased. RHC revealed that the mean pulmonary artery pressure increased from 13 to 21 mmHg, indicating borderline PH. The pulmonary vascular resistance also increased from 143 to 200 dyns/cm². A comparison of these parameters between this and her initial visit is presented in Table 1. We determined that bosentan should be administered.

Echocardiography 1 year later showed that her TR improved from 3.1 to 2 m/s and the RVSP improved from 48.4 to 20 mmHg.

Discussion

In this case, the lung uptake of 123I-MIBG was decreased before borderline PH was detected by RHC, suggesting that the

Table 1 - Comparison of right heart catheter and echocardiographic results between initial examination and 1-year reexamination.

|                      | On 1st admission | One year later |
|----------------------|------------------|----------------|
| DLCO (%)             | 78               | 57.8           |
| TRPV (m/s)           | 2.1              | 3.1            |
| RVSP (mmHg)          | 27.6             | 48.4           |
| mPAP (mmHg)          | 13               | 21             |
| PVR (dyn·s/cm²)      | 143              | 200            |
| PCWP (mmHg)          | 6                | 8              |

DLCO, diffusing capacity for carbon monoxide; TRPV, tricuspid regurgitation peak velocity; RVSP, right ventricle systolic pressure; mPAP, mean pulmonary artery pressure; pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure.
Table 2 – Past reports about iodine-123-metaiodobenzylguanidine (123I-MIBG) in patients with pulmonary hypertension.

| Author          | Published year | Studied uptake site of 123I-MIBG | Study population of patients with PH | Included patients (N) | What 123I-MIBG uptake represented                           |
|-----------------|----------------|---------------------------------|-------------------------------------|------------------------|-----------------------------------------------------------|
| Morimitsu et al.| 1997           | Left ventricle                  | Chronic lung disease and pulmonary vascular disease with PH | 10                     | Cardiac sympathetic neuronal dysfunction                   |
| Sakamaki et al. | 2000           | Left ventricle                  | PAH and CTEPH                        | 55                     | Cardiac sympathetic neuronal dysfunction                   |
| Higo et al.     | 2018           | Lung                            | PAH and CTEPH                        | 21                     | Pulmonary endothelial dysfunction                         |
| Gimelli et al.  | 2019           | Lung                            | PAH                                 | 13                     | Pulmonary endothelial dysfunction                         |

PH, pulmonary hypertension; PAH, pulmonary artery hypertension; CTEPH, chronic thromboembolic pulmonary artery hypertension.

Fig. 1 – The anterior planar images of lung 123I-MIBG scintigraphy in the current patient are shown. In this case, the uptake of 123I-MIBG was severely reduced throughout the lung. The uptake of 123I-MIBG in this case, represented by the lung-to-mediastinum (L/M) ratio on early and delayed images, was 1.18 on the early image and 1.12 on the delayed image, which is appreciably lower than that of the control group in our previous study. Furthermore, the myocardial uptake of 123I-MIBG, represented by the heart-to-mediastinum (H/M) ratio, was 2.77 on the early image and 3.34 on the delayed image, which is similar to previous reports.

L/M early 1.18  
L/M delayed 1.12  
Washout rate 50.5%

H/M early 2.77  
L/M delayed 3.34  
Washout rate 35.1%

Lung uptake of 123I-MIBG might be able to detect PH earlier than RHC. Over the course of PAH development, pulmonary vascular endothelium injury progresses but pulmonary arterial pressure does not rise, which makes the early diagnosis of PAH very difficult. We speculate that lung 123I-MIBG scintigraphy may be useful for the early diagnosis of PAH. Furthermore, although it is reported that a reduction in the %DLCO is useful for the early diagnosis of PAH in patients with collagen disease [11,12], it should be noted that, in this case, the lung uptake of 123I-MIBG was reduced before a reduction in %DLCO was observed.

In our previous study [1], the lung uptake of 123I-MIBG did not correlate with echocardiographic indices or hemodynamic indicators obtained from RHC. Reports have found that the pulmonary blood vessels are not associated with an increase in pulmonary arterial pressure until approximately 70% of the vascular bed is damaged [13]. Thus, the duration of latent pulmonary angioopathy is long, which may make 123I-MIBG worthwhile because it has the potential to reveal pulmonary vascular injury at an earlier stage.

There have been 4 reports of 123I-MIBG scintigraphy in patients with PH [1,10,14,15] (Table 2). Of these, 2 studies examined the myocardial uptake of 123I-MIBG. Sakamaki et al. [14] demonstrated that, in patients with idiopathic PAH and chronic thromboembolic PH, uptake of 123I-MIBG in the left ventricle was reduced and the washout rate was increased, suggesting dysfunction of the cardiac sympathetic nerve. They reported that the myocardial uptake of 123I-MIBG was useful for assessing severity and prognosis in patients with PH because the indices obtained by 123I-MIBG myocardial scintigraphy were correlated with the hemodynamic indices obtained by RHC. Moreover, Morimitsu et al. [10] divided
the left ventricle into regions of interest corresponding to the septal wall, anterior wall, lateral wall, and posterior wall, and compared the myocardial uptake of $^{123}$I-MIBG in patients with PH between each of these areas. They reported that in patients with PH, the myocardial uptake of $^{123}$I-MIBG in the left ventricular septum, which is the site that borders the right ventricle, was significantly decreased. Recently, we for the first time focused on the uptake of $^{123}$I-MIBG, which may represent pulmonary endothelial function, in patients with PH [1]. This was a completely new concept in $^{123}$I-MIBG scintigraphy in patients with PH. Similarly, Gimelli et al. recently reported that the lung uptake of $^{123}$I-MIBG was lower in patients with PAH than patients with dilated cardiomyopathies, suggesting that lung uptake of $^{123}$I-MIBG may identify pulmonary vascular remodeling [15], which is consistent with our findings. An important aspect of lung $^{123}$I-MIBG is that it evaluates the pulmonary blood vessels themselves, rather than the myocardial damage resulting from PH. Furthermore, lung $^{123}$I-MIBG scintigraphy focuses not on the rise in pulmonary arterial pressure as the result of pulmonary angiopathy, but on the underlying pulmonary angiopathy itself, which emphasizes its utility for the early diagnosis of PH. In our case, there was no significant decline in the $^{123}$I-MIBG H/M ratio in the left ventricle as a whole or in the septal wall compared to previous reports. This is consistent with our finding that there was no increase in pulmonary artery pressure at the time when pulmonary $^{123}$I-MIBG was decreased in our case. However, reports of $^{123}$I-MIBG scintigraphy in patients with PH have only included a small number of cases. In the future, it will be necessary to examine a larger number of patients. Despite the small number of patients studied, it is a promising avenue for research. Additionally, the pathological picture of PAH is slightly different for each underlying disease. Therefore, the value of pulmonary $^{123}$I-MIBG may differ between PAH due to collagen disease, as in our case, and PAH due to other underlying diseases. Further study is necessary (Fig. 1).

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