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Evaluation of Right Ventricular Overload by ^{123}I-MIBG, ^{123}I-BMIPP, and ^{99m}Tc-MIBI

Yoshiyuki MIYAHARA[1], Satoshi IKEDA[1], Tetsuro MATSUSHITA[2], Takuya MORIMITSU[1], Kyoji NISHIJIMA[1], Shigeru KOHNO[1]

1) Second Department of Internal Medicine, Nagasaki University School of Medicine

2) Department of General Medicine, Nagasaki University School of Medicine

It is important to evaluate the severity of right ventricular (RV) overload in patients with chronic pulmonary diseases or pulmonary thromboembolism because their prognosis depend on the severity of RV overload. Various examination methods have been used to non-invasively evaluate the severity of RV overload. We evaluated the usefulness of recently developed novel radiopharmaceuticals ^{123}I-MIBG, ^{123}I-BMIPP, and ^{99m}Tc-MIBI) in patients with chronic respiratory diseases or pulmonary thromboembolism. Myocardial scintigraphy using ^{123}I-MIBG revealed that the ratio of scintillation counts in the interventricular septum (IVS) to those in the left ventricle (LV) correlated negatively with the mean pulmonary arterial pressure (MPAP), suggesting the presence of sympathetic neuropathy due to RV overload. Myocardial scintigraphy using ^{123}I-BMIPP revealed that the ratio of scintillation counts in the RV to those in LV (RV/LV uptake ratio) correlated with MPAP. There was a negative correlation between RV metabolic index [RVMI = (RV/LV ratio of ^{123}I-BMIPP uptake) / (RV/LV ratio of ^{201}Tl uptake)] and MPAP. These findings suggested the presence of RV overload-induced fatty acid metabolic disorder. ^{99m}Tc-MIBI allows the simultaneous performance of both cardiac pool scintigraphy and myocardial single photon emission computed tomography. RV/LV ratio of ^{99m}Tc-MIBI uptake correlated with MPAP. Moreover, RV ejection fraction (RVEF) obtained by right cardiac pool scintigraphy correlated with the RVEF determined by the thermodilution method, suggesting the usefulness of ^{99m}Tc-MIBI.

Our findings suggest that these radiopharmaceuticals are useful for evaluating the severity of RV overload in patients with chronic respiratory diseases or pulmonary thromboembolism, as well as for evaluating RV overload-induced metabolic disorders.

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Address Correspondence: Yoshiyuki Miyahara, M.D.
Second Department of Internal Medicine, Nagasaki University, School of Medicine, 1-7-1, Sakamoto, Nagasaki, 852-8501, Japan
TEL and FAX: +81-95-849-7280
E-mail: miyayuki@net.nagasaki-u.ac.jp

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Introduction

Evaluation of the right heart system is important in patients with chronic pulmonary diseases or pulmonary vascular diseases because the severity of right ventricular (RV) overload correlates with prognosis. Invasive cardiac catheterization is mainly used to evaluate right cardiac function, and the procedure provides a high sensitivity and specificity. To date, various procedures have been used to evaluate non-invasively RV overload. These include echocardiography[1-4], electrocardiography[5-7], and nuclear medical examinations[8-11].

Myocardial scintigraphy using ^{201}T1 was developed initially to clinical evaluate of RV overload. Cohen *et al.*[8] first reported the usefulness of myocardial scintigraphy using ^{201}Tl for the diagnosis of cor pulmonale. Subsequently, various studies confirmed the usefulness of ^{201}Tl-myocardial scintigraphy for the evaluation of the severity of RV hypertrophy (RVH)[8-11].

In recent years, myocardial scintigraphy using novel radiopharmaceuticals, ^{99m}Tc-Sestamibi (^{99m}Tc-MIBI), ^{123}I-metaiodobenzyl guanidine (^{123}I-MIBG), and ^{123}I-β-meth yliodo phenyl pentadecanic acid (^{123}I-BMIPP) has been developed to evaluate the left heart system. However, only few studies have previously evaluated the right heart system using these radiopharmaceuticals. In the present study, we evaluated the severity of RV overload in patients with chronic pulmonary diseases or pulmonary vascular diseases using these radiopharmaceuticals. Based on our results, we discuss the usefulness of these radiopharmaceuticals for evaluating the right heart system.

Methods

Right heart cathetherization using Swan-Ganz balloon-tipped catheters (TF 002H-7F, Baxter, California, USA) were performed via the jugular vein or the femoral vein. RVEF was measured using the thermodilution method and a REF-1 RVEF CO computer (Baxter, California, USA)

^{99m}Tc-MIBI, ^{123}I-MIBG and ^{123}I-BMIPP scintigraphy was performed within 1 week of right heart catheterization. A triple-headed gamma camera (PRISM 3000, Picker International Inc., Ohio, USA) equipped with a low-energy, high resolution collimator was used for scintigraphy. On ^{123}I-MIBG and ^{123}I-BMIPP scintigraphy, single photon emission computed tomography (SPECT) imaging was obtained 15 min (early phase) and 4 h (late phase) after intravenous injection of 111 MBq radionuclides into the antecubital vein. SPECT images were acquired at an energy level of 159 keV, a window width of 20%, 40 sec per direction, with the step angle set at 5° x 24 steps. Data of a matrix size of 64 x 64 pixels and 360° were obtained. Following intravenous injection of 111MBq ^{201}Tl, SPECT was obtained a similar manner of ^{123}I-MIBG and ^{123}I-BMIPP scintigraphy, except that the energy level was set at 75 keV for the ^{201}Tl scans. On ^{99m}Tc-MIBI scintigraphy, 740 MBq of ^{99m}Tc-MIBI was bolus infused into the antecubital vein, and right heart pool scintigraphy was performed by the first-pass method using a multicristal-type portable gamma camera or a single-crystal gamma camera. Right ventricular ejection fraction was calculated from the end-diastolic count and end-systolic count. Regions of interest (ROI) were established at the RV, left ventricle (LV) and interventricular septum (IVS) (Fig.1).

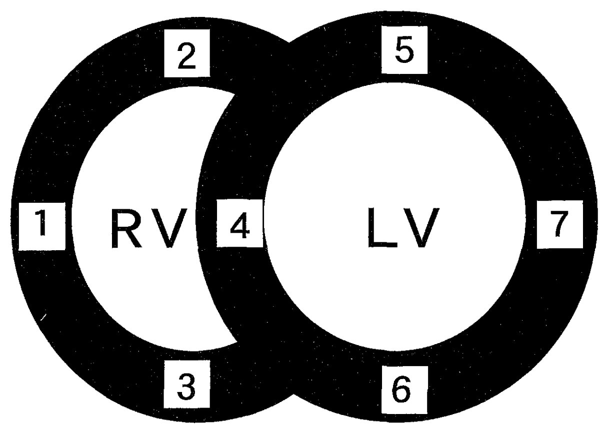

Fig. 1 Schematic diagram of regions of interest (ROI). ROIs were established on RV free wall (No. 1, 2, 3), interventricular septum (IVS, No. 4), and LV free wall (No. 5, 6, 7). RV: right ventricle, LV: left ventricle.

Each parameter on scintigraphy were calculated from scintillation counts using the following equations:

IVS/LV uptake ratio (%) = ROI 4 / (ROI 5 + ROI 6 + ROI 7) x 100

RV/LV uptake ratio (%) = (ROI 1 + ROI 2 + ROI 3)/ (ROI 5 + ROI 6 + ROI 7) x 100

RV metabolic index (RVMI) = (RV/LV ratio of ^{123}I-BMIPP uptake / RV/LV ratio of ^{201}Tl uptake)

1. ^{123}I-MIBG

It is considered that the uptake, storage, and release of ^{123}I-MIBG, a norepinephrine analog, are qualitatively similar to those of norepinephrine in the sympathetic nerve ending. Therefore, the level of ^{123}I-MIBG accumulation reflects cardiac sympathetic nerve function.

We performed ^{123}I-MIBG myocardial scintigraphy in 20 patients with chronic pulmonary diseases or pulmonary vascular diseases (Table 1). Our results showed a negative correlation between the mean pulmonary arterial pressure (MPAP) and the IVS/LV ratio of ^{123}I-MIBG uptake ($r=-0.78$, $p<0.01$) (Fig. 2)[12]. Previous studies reported that the severity of RVH could generally be evaluated by ^{201}Tl-myocardial scintigraphy based on the RV/LV ratio of scintillation counts, which correlated positively with the severity of RV overload[8-11]. Since the radioactivity of ^{123}I-MIBG decreases with the severity of RV overload, which is in contrast to ^{201}Tl, it is often difficult to establish ROIs in the RV. Thus, we used the IVS/LV ratio of ^{123}I-MIBG uptake to evaluate RV in this study. In contrast, ROIs are difficult to establish in the RV of patients with mild RV overload during ^{201}Tl-myocaridal scintigraphy. These findings suggested that the indices used in our study were useful for evaluating the severity of RV overload because they could be evaluated easily and accurately.

Table 1 Characteristics of patients

	Mean±SD
Sex (male/female)	10/10
Age (years)	61.8±2.5
PaO_2 (torr)	71.0±2.2
$PaCO_2$ (torr)	37.6±1.2
%VC (%)	86.0±7.0
FEV1.0% (%)	61.8±4.9

PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbondioxide; %VC, % vital capacity; FEV1.0%, % forced expiratory volume in 1s

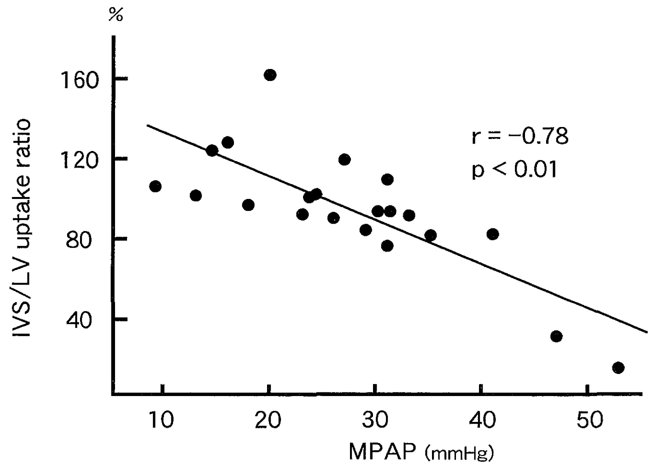

Fig. 2 Correlation between the IVS/LV uptake ratio determined by [123]I-MIBG image and MPAP. MPAP: mean pulmonary arterial pressure.

Previous studies concluded that β-adrenoreceptors are downregulated in patients with heart failure, resulting in reduced accumulation of [123]I-MIBG[13-15]. Yoshie *et al.*[16] used rats with monocrotaline-induced pulmonary hypertension and showed that the level of β-adrenoreceptor decreased with increased severity of pulmonary hypertension. Furthermore, Sakamaki *et al.*[17] reported that myocardial sympathetic neuropathy was induced by excessive systemic sympathetic nerve activity based on a lower heart/mediastinum activity of [123]I-MIBG, although plasma norepinephrine levels were higher in patients with chronic obstructive pulmonary diseases than in the controls. Therefore, our data also suggested that cardiac sympathetic neuropathy could be induced by chronic RV overload.

2. [123]I-BMIPP

Fatty acids and glucose are major energy sources for cardiac muscle. The energy efficiency of fatty acid β-oxidation is high, and more than 80% of its energy substrate depends on fatty acid metabolism. Since myocardial fatty acid metabolic imaging facilitates the evaluation of myocardial metabolism, this procedure is useful for elucidating the pathological conditions in various heart diseases. [123]I-BMIPP is a radiopharmaceutical developed to evaluate myocardial fatty acid metabolism by myocardial scintigraphy.

[201]Tl and [123]I-BMIPP myocardial scintigraphy was performed in 46 patients with chronic pulmonary diseases or pulmonary vascular diseases (Table 2). The RV/LV uptake ratio of [123]I-BMIPP and MPAP showed a positive correlation (r=0.67, p<0.01) (Fig. 3, left)[18]. Since the RV visualized by [123]I-BMIPP-myocardial scintigraphy was similar to that by [201]Tl-myocardial scintigraphy, the severity of RV overload was favorably evaluated by [123]I-BMIPP-myocardial scintigraphy. On [123]I-BMIPP imaging, RV fatty acid metabolism seemed to be enhanced because of RVH. Therefore, the RVMI was calculated to exclude the influence of RVH. The results showed a negative correlation between RVMI and MPAP (r=-0.50, p<0.01) (Fig. 3, right)[18]. In this regard, Kim *et al.*[19] suggested that [123]I-BMIPP uptake in the RV decreased in patients with severe RVH, in which the RV was clearly depicted by [201]Tl-myocardial scintigraphy, demonstrating the presence of fatty acid metabolic disorder. In addition, the level of [123]I-BMIPP uptake in the IVS and in the free walls near the IVS in the LV, not in the RV, correlated with the severity of pulmonary hypertension, suggesting the presence of myocardial metabolic disorder in these regions[20]. Thus, the decrease in RVMI associated with the severity of RV overload suggests the presence of RV overload-induced fatty acid metabolic disorder in the RV.

Table 2 Characteristics of patients

	Mean±SD
Sex (male/female)	26/20
Age (years)	64.0±11.8
PaO_2 (torr)	74.0±18.5
$PaCO_2$ (torr)	42.6±11.3
%VC (%)	80.0±24.8
$FEV_{1.0\%}$ (%)	62.7±2.8

Abbreviations as in Table1.

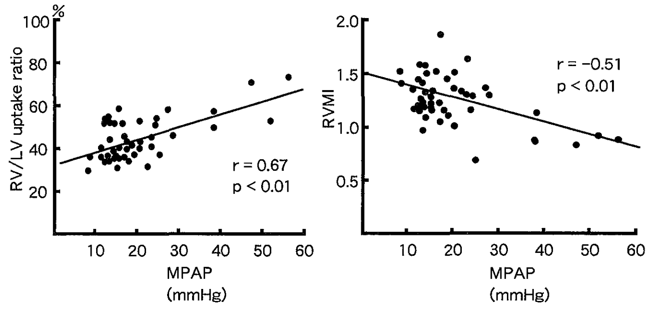

Fig. 3 Correlation between MPAP and the RV/LV uptake ratio of [123]I-BMIPP (left), and RVMI (right). MPAP: mean pulmonary arterial pressure, RVMI: right ventricular metabolic index.

3. ^{99m}Tc-MIBI

^{99m}Tc-MIBI, which has excellent radiophysical properties such as a short half-life of 6 hours and gamma ray energy of 140 keV, is suitable for scintigraphy and SPECT. Furthermore, cardiac pool scintigraphy and myocardial SPECT can be performed simultaneously using ^{99m}Tc-MIBI. In 23 patients with chronic pulmonary diseases or pulmonary vascular diseases (Table 3), we compared ^{99m}Tc-MIBI-myocardial scintigraphy with both right cardiac pool scintigraphy, using the first-pass method, and myocardial SPECT[21]. The RV/LV ratio of ^{99m}Tc-MIBI uptake correlated positively with MPAP (r=0.81, p<0.01, Fig. 4, left)[21]. ^{99m}Tc-MIBI diffuses passively, and binds to the mitochondria in myocardial cells after its uptake in the myocardium. In comparison, ^{201}Tl accumulate in the myocardium through an active transport process involving the Na-K pump. Since the half-life of ^{99m}Tc is shorter than that of ^{201}Tl, the dose of ^{99m}Tc-MIBI can be increased to a level more than five times larger than that of ^{201}Tl, and the higher radionuclide energy facilitates the acquisition of qualitatively more useful scintigrams. Moreover, ^{99m}Tc-MIBI-myocardial scintigraphy can be used more safely than ^{201}Tl-myocardial scintigraphy because the dose of exposure is lower in ^{99m}Tc-MIBI than in ^{201}Tl[22]. Furthermore, the RVEF obtained by right cardiac pool scintigraphy using ^{99m}Tc-MIBI correlates with the RVEF obtained by right cardiac catheterization using the thermodilution method (r=0.68, p<0.01, Fig. 4, right)[21]. Combined together, these findings suggest that ^{99m}Tc-MIBI-myocardial scintigraphy facilitates the simultaneous evaluation of RVEF and the severity of RVH, together with the evaluation of the right heart system.

Table 3 Characteristics and hemodynamic findings of patients

	Mean±SD
Sex (male/female)	14/9
Age (years)	59.4±13.9
MPAP (mmHg)	24.4±13.6
CO (l/min)	4.9±1.2
TPR (dynes)	5.5±4.2

MPAP, mean pulmonary arterial pressure; CO, cardiac output; TPR, total pulmonary artery resistance.

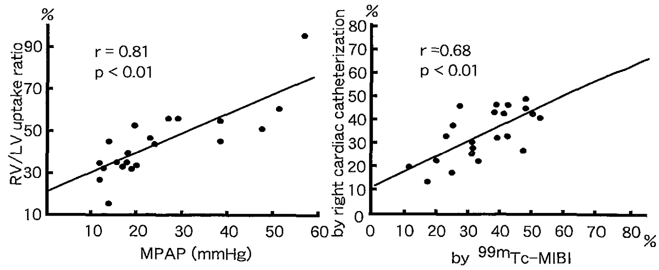

Fig. 4 Left: correlation between MPAP and RV/LV uptake ratio determined by ^{99m}Tc-MIBI image. Right: correlation between right ventricular ejection fraction measured by right cardiac catheterization and right heart pool scintigraphy using ^{99m}Tc-MIBI. MPAP: mean pulmonary arterial pressure.

Conclusions

The respective radiopharmaceuticals correlated significantly with pulmonary arterial pressure. Furthermore, ^{123}I-MIBG facilitated the evaluation of cardiac sympathetic nerve function in RV overload, whereas ^{123}I-BMIPP facilitated the evaluation of RV fatty acid metabolism. Moreover, another advantage of ^{99m}Tc-MIBI was that it facilitates the simultaneous evaluation of right cardiac function and morphological changes after administration of a single radiopharmaceutical. Using these radiopharmaceuticals the severity of RV overload can be evaluated non-invasively from different perspectives.

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