Increased Lung Uptake of Iodine-123-MIBG in Diabetics with Sympathetic Nervous Dysfunction

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Scintigraphy with ^{123}I-MIBG and ^{201}Tl was compared in patients with various diseases including diabetes mellitus, with and without sympathetic nervous dysfunction. This study was done to assess lung uptake of these tracers semiquantitatively. **Methods:** Thirty-eight patients with diabetes mellitus, seven patients with dilated cardiomyopathy (DCM), 12 patients with hypertrophic cardiomyopathy (HCM) and eight healthy subjects were studied. Sympathetic nervous dysfunction was observed in 13 of the 38 diabetic patients. Simultaneous imaging with ^{123}I-MIBG and ^{201}Tl was performed. The ratio of lung to total injected dose count and washout rate in the lung were calculated from dynamic images acquired in the initial 2 min and static images acquired at 15 min and at 4 hr after injection of the tracers. **Results:** Lung uptake of ^{123}I-MIBG at 4 hr was significantly increased in the diabetic group as compared with those in the other groups. In diabetic patients with sympathetic nervous dysfunction, the lung uptake ratio of ^{123}I-MIBG at 4 hr was significantly higher than that in the diabetic patients without sympathetic nervous dysfunction, due to decreased clearance of ^{123}I-MIBG from the lung. On the other hand, increased lung uptake of ^{201}Tl was observed in DCM patients at both 15 min and 4 hr. There was no significant difference between lung uptake of ^{201}Tl in diabetic patients and that in healthy subjects. **Conclusion:** Lung uptake of ^{123}I-MIBG was increased and lung washout of ^{123}I-MIBG was decreased in diabetic patients with sympathetic nervous dysfunction, while lung uptake of ^{201}Tl was not altered. Iodine-123-MIBG scintigraphy of the lung may provide information on sympathetic nervous activity in diabetic patients. It is a promising method for studying the kinetics of norepinephrine in the lung because MIBG is taken up in the lung by the same mechanism as norepinephrine.

Key Words: iodine-123-MIBG; thallium-201; lung uptake; diabetes mellitus; sympathetic nervous activity

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Autonomic neuropathy is one of the major complications in patients with diabetes mellitus. Postural hypotension is the most prominent cardiovascular symptom of sympathetic nervous dysfunction. The death rate in diabetic patients is markedly increased when postural hypotension is observed (*1*). Therefore, evaluation of sympathetic nervous activity is useful in the management of diabetic patients.

Metaiodobenzylguanidine (MIBG) is an analog of the adrenergic neuron-blocking agent guanethidine, and it shares the same uptake, storage and release mechanisms as norepinephrine in sympathetic nerve endings (*2–6*). Because the myocardium is richly supplied with sympathetic nerves, myocardial imaging using ^{123}I-MIBG has been performed to assess cardiac sympathetic nervous activity (*7–26*). We have already evaluated myocardial ^{123}I-MIBG uptake in diabetic patients, in our previous study, and reported that myocardial uptake of MIBG was decreased and myocardial washout of MIBG was increased in diabetic patients with sympathetic nervous dysfunction (*7*). These data were consistent with the results reported by Mäntysaari et al. (*8*).

The lung uptake of MIBG was initially studied by Slosman et al. (*27,28*) using animal models. They demonstrated that MIBG is taken up by the same sodium-dependent, energy-requiring transport system used for the extraction of norepinephrine in pulmonary capillary endothelial cells. They, therefore, suggested that scintigraphic evaluation of MIBG uptake and turnover in the lung may be useful for assessing pulmonary endothelial cell function. However, the influence of sympathetic nervous activity on the kinetics of MIBG in the lung has not been investigated.

We speculated that, if MIBG uptake in the systemic sympathetic nervous system decreases in diabetic patients with sympathetic nervous dysfunction as observed in the heart, lung accumulation of MIBG should increase because of excess MIBG circulating into the lung.

In this study, serial ^{123}I-MIBG images of the lung were acquired to evaluate lung uptake of MIBG in diabetic patients, with and without postural hypotension, as compared with patients with idiopathic dilated cardiomyopathy (DCM), patients with idiopathic hypertrophic cardiomyopathy (HCM) and healthy subjects. We also compared ^{123}I-MIBG dynamics in the lung between these five groups and evaluated the influence of sympathetic nervous activity on ^{123}I-MIBG uptake in the lung. Moreover, we investigated the difference between lung uptake of ^{123}I-MIBG and ^{201}Tl.

MATERIALS AND METHODS

Subjects

Sixty-five subjects, including 38 patients with diabetes mellitus, seven patients with DCM, 12 patients with HCM and eight healthy subjects, were examined. Postural hypotension, which was defined as a fall in systolic blood pressure of 30 mmHg or more on standing, was found in 13 of the 38 diabetic patients. Diabetic patients with postural hypotension included five men and eight women, with a mean age of 57 ± 12 yr (range 34–71 yr), and the other 25 diabetic patients without postural hypotension included 13 men and 12 women with a mean age of 53 ± 12 yr (range 27–74 yr). In patients with postural hypotension, the duration of diabetes was longer than in patients without postural hypotension (17.2 ± 6.0 yr versus 11.5 ± 8.2 yr, $p < 0.05$). Other diabetic complications, such as nephropathy and retinopathy, were found in 13 diabetic patients with postural hypotension (100%) and in 11 diabetic patients without postural hypotension (44%). Eleven diabetic patients with postural hypotension and 12 patients without postural hypotension were treated with insulin. No diabetic patients had clinical histories of ischemic heart disease, and electrocardiographic and echocardiographic findings were normal in all diabetic patients.

DCM patients included six men and one woman with a mean age

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of 55 ± 12 yr (range 39–69 yr), and HCM patients included 10 men and two women with a mean age of 56 ± 13 yr (range 35–73 yr). The diagnosis of DCM and HCM was based on the findings of echocardiography and cardiac angiography. Heart valves and coronary arteries were normal in all patients. Myocardial biopsies showed no pathological findings. Clinically symptomatic congestive heart failure was observed in all DCM patients. Four patients had New York Heart Association Class 2 failure and three had Class 3 failure. Medical treatment was performed with digitalis in four patients (three DCM; one HCM), with diuretics in five patients (four DCM; one HCM), and with beta-adrenergic blocking drugs such as metoprolol, propranolol, nadolol and atenolol in five patients (one DCM; four HCM). Healthy subjects included eight men with a mean age of 57 ± 8 yr (range 49–72 yr). None of them had diabetes.

Study Protocol

Subjects were allowed to eat a normal breakfast on the day of the study. Each subject was placed in the supine position, and 111 MBq (3 mCi) ^{123}I-MIBG and 111 MBq (3 mCi) of ^{201}Tl were injected simultaneously through an antecubital vein. Serial dynamic imaging of the entire thorax was performed at 1 frame/sec during the initial 2 min after the rapid injection of these tracers followed by bolus injection of 20 ml saline. Thereafter, static images of the anterior chest with a digital resolution of 256 × 256 were acquired for 5 min, starting at 15 min and at 4 hr after injection. Imaging was performed with 20% energy windows centered at the ^{123}I-MIBG photopeak (160 keV) and the ^{201}Tl photopeak (80 keV), using a large field-of-view digital gamma camera equipped with a low-energy, parallel-hole collimator. Image data were transferred to a nuclear medicine data processor.

Image Analysis

Image data analysis was performed semiquantitatively. A region of interest (ROI) was placed over the entire thorax on the dynamic images to generate a time-activity curve according to the method reported by Ishii and MacIntyre et al. (*29*). The total injected dose was measured as the peak counts on the time-activity curve. Another ROI was placed over the right lung on static images to measure the lung uptake ratio. The lung uptake ratio at 15 min and at 4 hr after the injection and the lung washout rate from 15 min to 4 hr were calculated as follows:

Lung update ratio

$$= \frac{\text{Lung uptake (counts/pixel/5 min)}}{\text{Total injected dose (counts/sec)} \times 5(\text{min}) \times 60(\text{sec})} \times 100$$

$(\times\ 10^{-4}\%)$. Eq. 1

Lung washout rate

$$= \frac{\text{Lung uptake ratio at 15 min-Lung uptake ratio at 4 hr}}{\text{Lung uptake ratio at 15 min}}$$

$\times\ 100(\%)$. Eq. 2

Statistical Analysis

Data were expressed as the mean value ± s.d. ANOVA was used to evaluate the statistical significance of the differences between the different groups. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Iodine-123-MIBG Uptake in the Lung

The lung uptake ratio of ^{123}I-MIBG is shown in Figure 1. At 15 min after injection of the tracers, the lung uptake ratio in diabetic patients with postural hypotension (13.8 ± 1.8 × 10^{-4}%) was significantly higher than that in healthy subjects

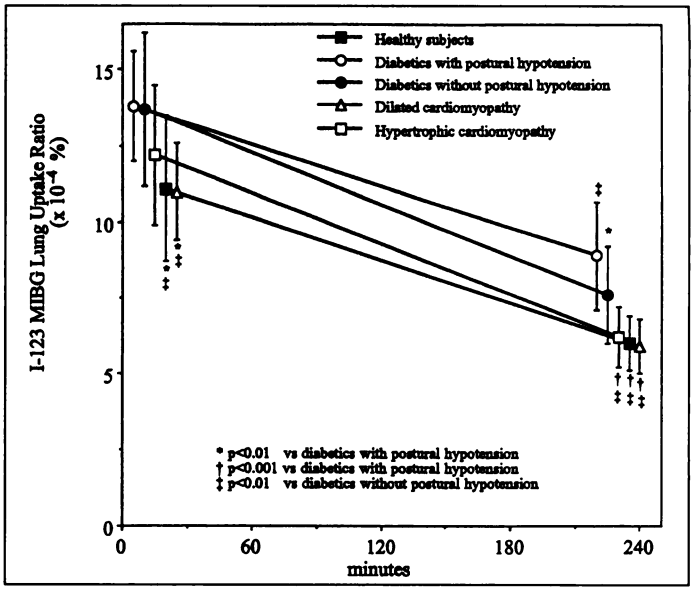

FIGURE 1. Lung uptake ratio of ^{123}I-MIBG: serial changes from 15 min to 4 hr after injection of tracer. Increased lung uptake of ^{123}I-MIBG in diabetic patients with and without postural hypotension is shown.

(11.2 ± 2.4 × 10^{-4}%, $p < 0.01$) or in DCM patients (11.0 ± 1.6 × 10^{-4}%, $p < 0.01$). The lung uptake ratio in diabetic patients without postural hypotension (13.7 ± 2.5 × 10^{-4}%) also was higher than those in healthy subjects ($p < 0.01$) and in DCM patients ($p < 0.01$). There were no significant differences in lung uptake ratio between diabetic patients with or without postural hypotension and HCM patients (12.2 ± 2.3 × 10^{-4}%).

At 4 hr after injection of the tracers, the lung uptake ratio in diabetic patients with postural hypotension (8.9 ± 1.8 × 10^{-4}%) was significantly higher than that in diabetic patients without postural hypotension (7.6 ± 1.6 × 10^{-4}%, $p < 0.01$), in DCM patients (5.9 ± 0.9 × 10^{-4}%, $p < 0.001$), in HCM patients (6.2 ± 1.0 × 10^{-4}%, $p < 0.001$), or in healthy subjects (6.0 ± 0.9 × 10^{-4}%, $p < 0.001$). The lung uptake ratio in diabetic patients without postural hypotension also was significantly higher than that in DCM patients ($p < 0.01$), in HCM patients ($p < 0.01$) or in healthy subjects ($p < 0.01$).

Interestingly, the lung uptake ratio of ^{123}I-MIBG in diabetic patients with postural hypotension was significantly higher than that in diabetic patients without postural hypotension at 4 hr, although there was no significant difference in lung uptake at 15 min. There were no significant differences in lung uptake ratio between healthy subjects, DCM patients and HCM patients at either 15 min or 4 hr after administration.

Iodine-123-MIBG Washout from the Lung

The lung washout rate of ^{123}I-MIBG is shown in Figure 2. The lung washout rate in diabetic patients with postural hypotension (35.6% ± 9.8%) was significantly lower than that in diabetic patients without postural hypotension (44.6% ± 4.6%, $p < 0.001$), in healthy subjects (45.2% ± 8.4%, $p < 0.005$), in DCM patients (45.8% ± 7.5%, $p < 0.005$) or in HCM patients (48.2% ± 7.4%, $p < 0.001$). There were no significant differences in the lung washout rate of ^{123}I-MIBG between healthy subjects, diabetic patients without postural hypotension, DCM patients and HCM patients.

Thallium-201 Uptake in the Lung

The lung uptake ratio of ^{201}Tl is shown in Figure 3. At 15 min after injection of the tracers, the lung uptake ratio of ^{201}Tl in DCM patients (13.2 ± 1.6 × 10^{-4}%) was significantly higher than that in healthy subjects (10.9 ± 1.5 × 10^{-4}%, $p < 0.005$),

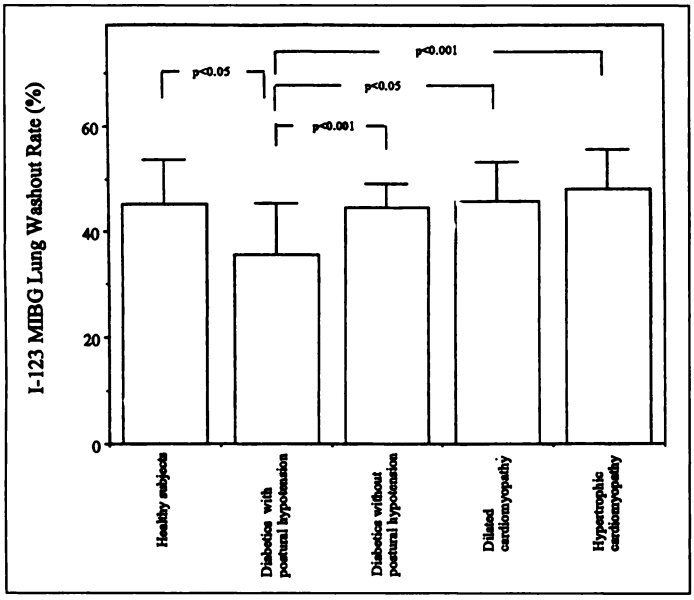

FIGURE 2. Lung washout rate of ^{123}I-MIBG from 15 min to 4 hr. Decreased lung washout of ^{123}I-MIBG in diabetic patients with postural hypotension is shown.

in diabetic patients with and without postural hypotension ($9.9 \pm 1.0 \times 10^{-4}$%, $p < 0.001$, and $10.3 \pm 1.3 \times 10^{-4}$%, $p < 0.001$, respectively), or in HCM patients ($10.0 \pm 1.6 \times 10^{-4}$%, $p < 0.001$). In addition, the ^{201}Tl lung uptake ratio at 4 hr in DCM patients ($7.4 \pm 0.7 \times 10^{-4}$%) was still significantly higher than that in healthy subjects ($6.0 \pm 0.7 \times 10^{-4}$%, $p < 0.005$), in diabetic patients with and without postural hypotension ($6.1 \pm 0.7 \times 10^{-4}$%, $p < 0.005$, and $6.1 \pm 0.9 \times 10^{-4}$%, $p < 0.001$, respectively), or in HCM patients ($5.4 \pm 0.7 \times 10^{-4}$%, $p < 0.001$). There were no significant differences in lung uptake of ^{201}Tl between healthy subjects, diabetic patients with or without postural hypotension and HCM patients.

Figure 4 shows representative scintigraphic images. In diabetic patients with postural hypotension (C), lung washout of ^{123}I-MIBG was reduced and lung uptake of ^{123}I-MIBG at 4 hr was increased, as compared with the other four scintigrams. The

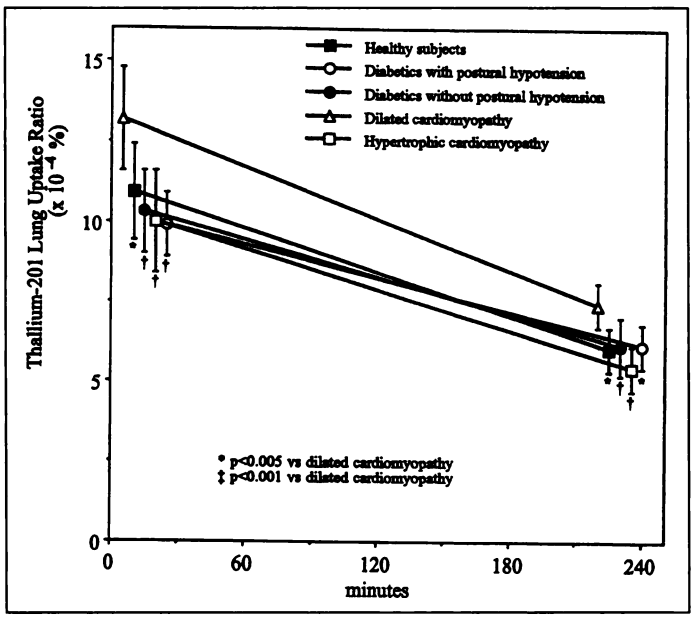

FIGURE 3. Lung uptake ratio of ^{201}Tl: serial changes from 15 min to 4 hr after injection of tracer. Increased lung uptake of ^{201}Tl in DCM patients at both 15 min and 4 hr is shown.

lung uptake of ^{201}Tl was not increased in diabetic patients, but was increased in DCM patients (D). In addition, decreased myocardial uptake of ^{123}I-MIBG is shown in the diabetic patient with postural hypotension at 4 hr after the injection of the tracer.

DISCUSSION

Norepinephrine Kinetics in the Lung and Pulmonary Sympathetic Nervous System

The fate of norepinephrine within the pulmonary circulation has been described by Gillis et al. (*30*). In the lung, approximately 25%–50% of norepinephrine is extracted and degraded during a single pass through the pulmonary circulation. The primary site for removal of norepinephrine is pulmonary capillary endothelial cells. Since inactivation of norepinephrine in the lung affects systemic arterial blood concentration of norepinephrine, the lung can be regarded as a biochemical filtration system in regulating the effects of norepinephrine. On the other hand, sympathetic nerves are present in the walls of 30- to 300-μm pulmonary arteries and of larger pulmonary veins (*31*), and stimulation of the sympathetic nerves causes pulmonary vasoconstriction and increased transcapillary lymph and protein flow in the lung. Therefore, norepinephrine kinetics in the lung may be involved in regulating arterial norepinephrine concentrations, pulmonary vascular resistance and transcapillary fluid exchange. Since MIBG is taken up in the lung by the same mechanism as norepinephrine, the assessment of MIBG uptake and washout in the lung provide some information concerning such neurohormonal regulations in the lung.

Relation Between Lung Uptake of MIBG and Sympathetic Nervous Activity

In our previous article (*7*), we reported myocardial MIBG uptake was decreased in diabetic patients with sympathetic nervous dysfunction. Since sympathetic nerves are affected systemically in diabetic patients with sympathetic nervous dysfunction (*32*), the total amount of MIBG taken up by sympathetic nerves is likely to decrease as well as in the heart. On the other hand, we demonstrated that uptake of MIBG was increased and washout of MIBG was decreased in the lungs of diabetic patients with sympathetic nervous dysfunction. Excess MIBG, not taken up by the sympathetic nervous system, may accumulate in the lung because the lung is considered to be a filtration system for MIBG, like norepinephrine.

Wieland et al. (*3*) studied the distribution of ^{125}I-MIBG in the heart and blood in dogs pretreated with reserpine, which selectively blocks the uptake of norepinephrine and guanethidine into the storage vesicles of adrenergic nerves. They observed that the concentration of ^{125}I-MIBG was decreased in the heart but increased in the blood in the reserpine-treated dogs. These results suggest that large amounts of MIBG may be retained in the blood when uptake of MIBG by the sympathetic nervous system is reduced. Nakajo et al. (*9*) studied tissue concentration of ^{131}I-MIBG, in the reserpine-treated rats, and reported that ^{131}I-MIBG uptake was increased in the lungs but decreased in the myocardium. Sisson et al. (*10*) conducted a clinical study with ^{123}I-MIBG scintigrams and reported the uptake of ^{123}I-MIBG was increased in the lungs but markedly decreased in the heart in patients with generalized autonomic neuropathy including diabetic patients. These findings seem to support our hypothesis that the increase in MIBG accumulation in the lung results from an increase of MIBG without being taken up by the sympathetic nervous system.

Circulating catecholamines might influence the tissue uptake of MIBG. Nakajo et al. (*11*) observed an inverse relationship

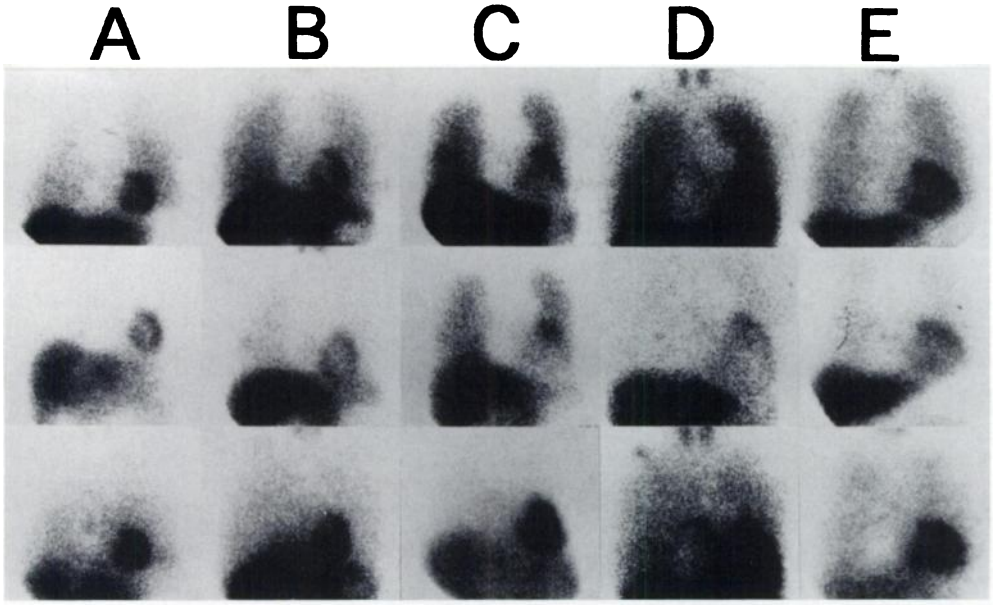

FIGURE 4. Scintigraphic images acquired with ^{123}I-MIBG at 15 min (upper) and at 4 hr (middle), and with ^{201}Tl at 15 min (lower) after injection of the tracers are shown. A = healthy subject, B = diabetic patient without postural hypotension, C = diabetic patient with postural hypotension, D = patient with dilated cardiomyopathy, E = patient with hypertrophic cardiomyopathy.

between ^{131}I-MIBG uptake in the heart and concentrations of plasma catecholamines in patients with suspected pheochromocytoma. Competitive uptake of ^{131}I-MIBG and circulating catecholamines in the heart is one explanation for these findings. On the other hand, there have been several reports that plasma catecholamine concentrations were not related to myocardial MIBG uptake (*8,12,13*) or lung MIBG uptake (*13*). Therefore, the relationship of circulating catecholamines and lung uptake of MIBG is still controversial.

Possible Mechanism of Decreased MIBG Washout in the Lungs

Nakajo et al. (*9*) studied ^{131}I-MIBG accumulation in the storage vesicles of sympathetic neurons (intravesicular accumulation) and in other sites (extravesicular compartment). The intravesicular MIBG is retained for a prolonged period, while the extravesicular MIBG shows considerably rapid decrease within several hours after injection of the tracer. In an experimental study using a diabetic rat model, Ganguly (*33*) showed a decrease in [^{3}H] norepinephrine in the storage vesicles and an increase in the extravesicular compartment. In our clinical study, we reported that myocardial washout of ^{123}I-MIBG was accelerated in diabetic patients with postural hypotension (*7*). Our results might be caused by an increase in the extravesicular compartment of MIBG accumulation, as observed in rats. Since the same phenomenon is considered to occur in systemic sympathetic neurons, release of ^{123}I-MIBG from the extravesicular compartment might increase during the first several hours after injection of the tracer in diabetic patients with postural hypotension. This increase in MIBG release might lead to the decrease in lung washout of ^{123}I-MIBG from 15 min to 4 hr in those patients.

Pulmonary Angiopathy in Diabetic Patients

Evidence of pulmonary angiopathy has been reported in diabetic patients. Sandler et al. (*34*) demonstrated a decreased pulmonary capillary blood volume in diabetic patients, and they suggested that pulmonary dysfunction is an early complication of diabetes. Pathologically, Vracko et al. (*35*) reported thickening of the basal lamina of pulmonary capillaries. Uchida et al. (*36*) demonstrated reduced perfusion and normal ventilation in diabetic patients in the study using lung images with ^{99m}Tc-MAA and ^{133}Xe, suggesting the presence of pulmonary microangiopathy in those patients.

If pulmonary abnormalities are an early complication of diabetes, as Sandler mentioned, the patients with postural hypotension in our study might have had pulmonary angiopathy. As previously mentioned, MIBG is taken up by pulmonary capillary endothelial cells, and injury to pulmonary capillary endothelial cells reduces lung uptake of MIBG. Therefore, we expected, before initiating this study, that the lung uptake of MIBG would be decreased in diabetic patients with postural hypotension. However, the lung uptake of ^{123}I-MIBG actually was increased in diabetic patients in this study. It is possible, therefore, that pulmonary microangiopathy in diabetic patients has little influence on the lung uptake of MIBG.

Lung Congestion and Pulmonary Hypertension

Tamaki et al. (*37*) reported that the increase in lung ^{201}Tl activity may be related to pulmonary congestion and edema. In this study, all patients with DCM had symptomatic congestive heart failure of New York Heart Association Class 2 or 3. The lung uptake of ^{201}Tl was significantly increased in these patients compared with the other subjects, as shown in Figure 3. Glowniak et al. (*14*) and Dae et al. (*15*) reported that the lung uptake of ^{123}I-MIBG was increased in patients with DCM. They suggested that increased MIBG uptake in the lung might result from pulmonary hypertension in those patients, since increased norepinephrine removal in the lung was observed in patients with pulmonary hypertension.

The results of this study showed no significant differences in the lung uptake of ^{123}I-MIBG between DCM patients and healthy subjects. On the other hand, the lung uptake of ^{123}I-MIBG was increased in diabetic patients. There were no echocardiographic findings suggestive of pulmonary hypertension in these diabetic patients. Therefore, we thought that lung uptake of MIBG might not be influenced by lung congestion or pulmonary hypertension in our DCM patients.

CONCLUSION

We evaluated ^{123}I-MIBG scintigraphy and observed increased lung uptake and reduced lung washout of the tracer in diabetic patients with sympathetic nervous dysfunction. Lung congestion in our DCM patients, which is related to lung uptake of ^{201}Tl, had little influence on the lung uptake of ^{123}I-MIBG. Iodine-123-MIBG scintigraphy, which has been used to evaluate the cardiac sympathetic nervous function, may provide information on systemic sympathetic nervous activity in dia-

betic patients by estimating lung uptake of the tracer. We hope that ^{123}I-MIBG scintigraphy is a promising method for evaluating norepinephrine kinetics in the lung.

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