Prolonged Lung Retention of Iodine-123-MIBG in Diabetic Patients

Mustafa Ünlü and Sabahat İnanir
Departments of Nuclear Medicine, Gazi University Medical Faculty; and Bayindir Medical Center, Ankara, Turkey

Iodine-123-MIBG has been introduced as a biochemical marker in assessing pulmonary endothelial cell integrity and myocardial β-adrenergic sympathetic innervation. The aim of this study was to evaluate ^{123}I-MIBG lung uptake in diabetic patients with and without coronary artery disease. **Methods:** Forty-four nonsmoking patients with normal respiratory function tests were included: 12 diabetics, 11 diabetics with coronary artery disease, 14 nondiabetic patients with coronary artery disease and 7 age-matched controls were imaged with ^{123}I-MIBG and ^{201}Tl scintigraphy. The lung retention of ^{123}I-MIBG, cardiac sympathetic innervation (heart-to-upper mediastinum ratio of ^{123}I-MIBG) and ^{201}Tl lung-to-heart ratio were determined in all cases. **Results:** In diabetics with coronary artery disease, significantly prolonged lung retention and decreased cardiac uptake of ^{123}I-MIBG were found. The lung retention of ^{123}I-MIBG was inversely correlated with the heart-to-upper mediastinum ratio in this group. Lung-to-heart ratios of ^{201}Tl were significantly increased in patients with coronary artery disease but there was no significant difference between diabetics and nondiabetics. **Conclusion:** Prolonged lung retention of ^{123}I-MIBG was associated with decreased cardiac sympathetic innervation in diabetic coronary artery disease patients. It seems that passive pulmonary congestion or cardiac dysfunction itself did not influence ^{123}I-MIBG lung uptake. Increased lung extraction of ^{123}I-MIBG is highly suggestive of ongoing pulmonary endothelial dysfunction together with ischemic events in diabetics.

Key Words: iodine-123-MIBG; Type II diabetes mellitus; pulmonary endothelium; sympathetic innervation

J Nucl Med 1998; 39:116–118

Radioiodinated metaiodobenzylguanidine (MIBG) has been introduced as a biochemical marker in the assessment of pulmonary endothelial cell integrity and cardiac β-adrenergic sympathetic innervation, in addition to its wide use in nuclear oncology (*1–7*). This agent, as an analog of adrenergic neuron-blocking agent guanetidine shares the same uptake, storage and release mechanisms as norepinephrine (*1–3,6,9*). Circulating biogenic amines, such as serotonin and norepinephrine, are actively taken up and metabolized by the lungs, and have been used to evaluate the functional state of pulmonary endothelium in the experimental models and clinical conditions. They are considered indicators of pulmonary endothelial cell integrity (*10–17*). The uptake mechanism of these amines includes a saturable, energy-requiring, sodium-dependent transport located in the endothelial cell membrane (*6,9*). It has been documented that MIBG is extracted by pulmonary endothelium through this transport system in the same way as norepinephrine (*6,9*). Therefore, ^{123}I-MIBG lung extraction may reflect pulmonary endothelial cell injury. Based on this hypothesis, abnormalities in the lung extraction of ^{123}I-MIBG have been reported after occurrence of bleomycin lung toxicity and hypoxia in the recent studies (*4–5*). Finally, the measurement of lung extraction of ^{123}I-MIBG has been proposed as a sensitive marker in enabling demonstration of the presence of minimal endothelial cell lesions (*4*). This study evaluated endothelial injury in diabetics and the effect of coronary artery disease on pulmonary ^{123}I-MIBG uptake.

Received Nov. 25, 1996; revision accepted Mar. 25, 1997.
For correspondence or reprints contact: Sabahat İnanir, MD, Bayindir Medical Centre, Department of Nuclear Medicine, TR-06520, Sogutozu, Ankara, Turkey.

MATERIALS AND METHODS

Forty-four nonsmoking patients with normal respiratory function tests were included: 12 diabetics, 11 diabetics with coronary artery disease, 14 nondiabetic patients with coronary artery disease and 7 age-matched normal volunteers were examined. Written informed consent was obtained in all cases before participation.

Normal coronary angiography or normal myocardial perfusion SPECT, with low probability for coronary artery disease, were the inclusion criteria for diabetics and control group. All diabetic patients had Type II diabetes mellitus and were using oral hypoglycemic drugs.

Additionally, in all patients, stable potassium iodide was given to block thyroid uptake (two drops three times a day, 1 day before and 3 days after the administration of ^{123}I-MIBG) and interferring drugs were discontinued 48 hr before the study (*18*). Radiochemical and radionuclide purities were greater than 95% and 99.9%, respectively, at calibration time. Specific activity was in the range of 83–118 GBq/mmol 110 MBq ^{123}I-MIBG was slowly injected intravenously, within 2 hr of calibration time.

Anterior static images were acquired 30 min and 4 hr after the administration of ^{123}I-MIBG with a gamma camera using a low-energy, all-purpose collimator and setting the energy level to ^{123}I photopeak (159 keV) with a 20% window. Static images in 256 × 256 matrices were obtained by collecting one million counts.

Thallium-201 planar imaging also was performed to test the possible effect of passive congestion on ^{123}I-MIBG lung accumulation. Planar images were obtained 15 min after 110 MBq ^{201}Tl was injected intravenously.

Data Analysis

Iodine-123-MIBG lung retention was calculated for the mid zone of the right lung to avoid crosstalk of liver and cardiac activity. Appropriate regions of interest were drawn for this zone and after the corrections for acquisition time and decay, mean counts per pixel were used in the calculations. The following formula was used to quantify lung retention of ^{123}I-MIBG:

$$^{123}\text{I-MIBG lung retention} = \text{delay uptake/early uptake} \times 100.$$

The heart-to-upper mediastinum ratio also was calculated for evaluating cardiac sympathetic innervation. In ^{201}Tl rest images, the lung-to-heart uptake ratio was determined for the mid zone of the right lung as in the ^{123} I-MIBG study.

Statistical Analysis

Correlation among variables was evaluated using Pearson correlation analysis, and the correlation coefficient is considered as: r <0.25 = poor correlation, 0.25–0.49 = moderate, 0.50–0.75 = good and >0.75 = strong correlation. Continuous variables were reported as mean ± 1 s.d. Differences were considered significant at $p < 0.05$ in the Mann-Whitney U test.

TABLE 1
Clinical Characteristics of Study Groups

	Controls n = 7	Diabetics n = 12	CAD n = 14	DCAD n = 11
Age	53 ± 5.5	51 ± 6.3	52 ± 5.4	51.5 ± 4.9
Sex (M:F)	5:2	9:3	12:2	9:2
Duration of diabetes (yr)	—	12.5 ± 2.3	—	13.2 ± 3.2
Blood glucose (mg/dl)	79.9 ± 14.9	179 ± 25.5*	—	184 ± 38.7*
HbA1c (%)†	—	7.4 ± 0.9	—	7.5 ± 0.8

*$p < 0.05$ compared to controls, Mann-Whitney U test.
†Normal laboratory range: 3.3–6.6%.
CAD = nondiabetics with coronary artery disease; DCAD = diabetics with coronary artery disease.

RESULTS

The clinical characteristics and laboratory data of the study groups were compared and the results summarized (Table 1). No significant differences were found in the metabolic control of diabetes and disease duration among the diabetic groups.

The scintigraphic results are shown in Table 2. In diabetics with coronary artery disease, both prolonged lung retention and decreased cardiac uptake of ^{123}I-MIBG were revealed (Fig. 1, Table 2). In these patients, the lung retention and cardiac uptake of ^{123}I-MIBG were calculated as 80.1 ± 4.1 and 1.7 ± 0.15, respectively, and both reached significance statistically compared to other groups. Interestingly, lung retention of ^{123}I-MIBG was inversely correlated with the heart-to-upper mediastinum ratio in this group ($r = -0.76$, $p = 0.024$). Such a correlation could not be found in normal volunteers and in diabetic and nondiabetic patients with coronary artery disease. In comparing lung-to-heart ratios of ^{201}Tl, increased ^{201}Tl accumulation was identified in patients who had coronary artery disease with or without diabetes mellitus (0.64 ± 0.14 and 0.63 ± 0.23, respectively; Table 2), in which the results of coronary angiography were similar (Table 3). The lung retention of diabetics without coronary artery disease was not different from normals and nondiabetic patients with coronary artery disease (Table 2). The decreased cardiac ^{123}I-MIBG uptake also was found in both diabetics and patients with coronary artery disease when compared to normals (2.0 ± 0.27, 2.1 ± 0.34 and 2.5 ± 0.24, respectively, $p < 0.05$). An inverse correlation was observed between ^{201}Tl lung accumulation and cardiac sympathetic innervation ($r = -0.53$, $p < 0.001$).

DISCUSSION

The lungs actively take up ^{123}I-MIBG through a saturable, energy-requiring, sodium-dependent transport mechanism similar to biogenic amines (*6–9*). Previous studies confirmed the diagnostic value of MIBG as an excellent marker of minimal endothelial cell lesions (*4–9*). Our study demonstrated the increased lung retention of ^{123}I-MIBG in diabetic patients with coronary artery disease, which was associated with impaired cardiac sympathetic innervation. It seems that pulmonary passive congestion itself does not affect lung uptake of ^{123}I-MIBG. There was no difference between ^{201}Tl lung accumulation in diabetic and nondiabetic coronary artery disease patients, which has been considered a useful indicator of cardiac dysfunction (*19*).

In the previous reports (*4,20*), ^{99m}Tc-human serum albumin and ^{201}Tl were used to differentiate ^{123}I-MIBG lung uptake from residual nonspecific lung activity and passive pooling. The results supported the concept that ^{123}I-MIBG was accumulated by the lungs through a specific mechanism, different from ^{201}Tl and ^{99m}Tc-human serum albumin. It is likely that the association of diabetes with coronary artery disease may have an additive effect on the ability of pulmonary endothelium to sequester radioiodinated MIBG. In other words, the results are highly suggestive of ongoing pulmonary endothelial dysfunction in diabetics with ischemia. A slight increase in MIBG

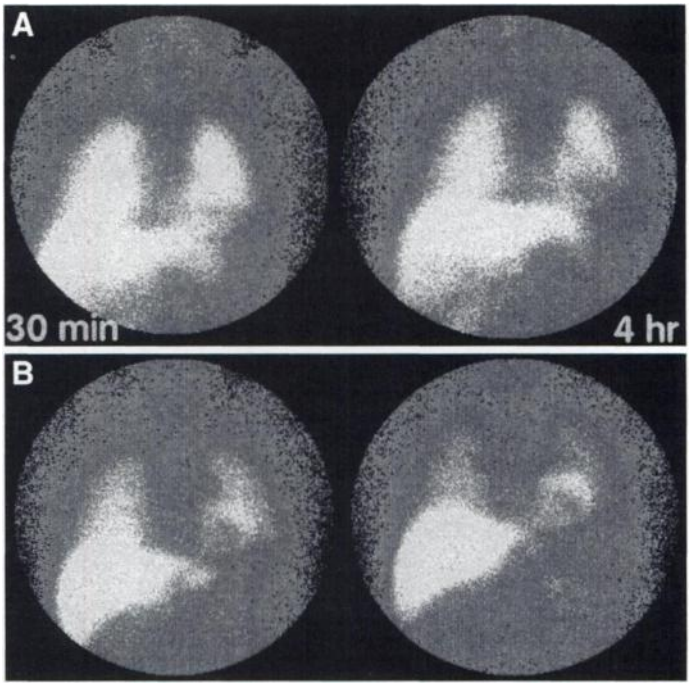

FIGURE 1. Planar ^{123}I-MIBG images 30 min and 4 hr after MIBG injection in a diabetic patient with CAD (A) and a nondiabetic patient with CAD (B). Both patients had two-vessel coronary artery disease (LAD + CX). Note the higher lung retention of MIBG as well as lower cardiac sympathetic innervation in the diabetic with coronary artery disease when compared to a (B) nondiabetic patient.

TABLE 2
Scintigraphic Study Results

	Controls n = 7	Diabetics n = 12	CAD n = 14	DCAD n = 11
MIBG lung retention (delay/early) × 100	70.7 ± 1.8	74.6 ± 8.7	74 ± 8.7	80.1 ± 4.1*
^{201}Tl lung-to-heart ratio	0.34 ± 0.06	0.42 ± 0.07	0.63 ± 0.23†	0.64 ± 0.14†
MIBG heart-to-upper mediastinum ratio	2.5 ± 0.24	2 ± 0.27‡	2.1 ± 0.34†	1.7 ± 0.15*

*Compared to other groups, $p = 0.05$, Mann-Whitney U test.
†Compared to controls and diabetics, $p = 0.05$, Mann-Whitney U test.
‡Compared to controls, $p = 0.05$, Mann-Whitney U test.
CAD = nondiabetics with coronary artery disease; DCAD = diabetics with coronary artery disease.

TABLE 3
Coronary Angiography Results in Patients with Coronary Artery Disease

	LAD + CX + RCA	LAD + CX	LAD + RCA	LAD
Nondiabetics with coronary artery disease	5	2	2	2
Diabetics with coronary artery disease	5	3	3	3

retention in the lungs of patients with diabetes without coronary artery disease and of nondiabetic patients with coronary artery disease was not significant. The increased pulmonary capillary wedge pressure, which has been demonstrated to be correlated with resting increases in lung thallium activity (*21*), may alter pulmonary endothelium, but the effect of diabetes on pulmonary endothelium and its clinical importance remains to be elucidated. Limited data suggest that the lung is a target organ in diabetes (*22,23*). It has been reported that the thickening of the capillary basal membrane, nonenzymatic glycolysis of proteins, endothelial changes, platelet alterations and free radicals might lead to damage in the lungs of diabetic patients (*24–26*).

Caner et al. (*23*) found longer clearance times of ^{99m}Tc-DTPA aerosol in diabetics. In a recent study performed by Murashima et al. (*20*), increased ^{123}I-MIBG retention has been reported in diabetics but there is no information as to whether their patients also had ischemic heart disease. They concluded that increased ^{123}I-MIBG lung extraction suggested sympathetic dysfunction in pulmonary vasculature. In the lung toxicity of bleomycin and chronic exposure to hypoxia, decreased pulmonary retention of ^{123}I-MIBG has been noted and attributed to intracytoplasmic edema and endothelial blebbing, both detected by electron microscopy (*4,5*). Slosman et al. (*4*) have used the first-pass extraction of ^{123}I-MIBG in the measurements but delay images (from 15 min to 240 min) also have been used by other investigators (*5,20*). The result of these studies was that radioiodinated MIBG could detect endothelial injury using either early- or late-phase images after injection.

It is known that transport of biogenic amines requires normal endothelial cell integrity. The decrease of ^{123}I-MIBG extraction by the lung in chronic hypoxia has been attributed to the changes in pulmonary circulation involving an alteration of either vascular surface area or endothelial cell function according to Richalet et al. (*5*). In contrast, the increased lung extraction of ^{123}I-MIBG in diabetic patients with coronary artery disease may possibly be due to the thickening of the capillary basal membrane, which causes a delay in the clearence of this compound rather than any abnormality in uptake. Delayed ^{99m}Tc-DTPA aerosol clearance detected in diabetics also supports this hypothesis (*23*).

CONCLUSION

Prolonged lung retention of ^{123}I-MIBG was associated with decreased cardiac sympathetic innervation in diabetic coronary artery disease patients. It seems that pulmonary congestion or cardiac dysfunction itself did not affect ^{123}I-MIBG lung uptake. Pulmonary retention of ^{123}I-MIBG seems rather to be influenced by ongoing pulmonary endothelial dysfuction and ischemic events in diabetics.

REFERENCES

1. Kline RC, Swanson DP, Wieland DM, et al. Myocardial imaging in man with I-123 metaiodobenzylguanidine. *J Nucl Med* 1981;22:129–132.
2. Sisson JC, Wieland DM, Sherman P, Tobes MJ. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620–1624.
3. Wafelman AR, Hoefnagel CA, Mals RAA, Bejinen JH. Radioiodinated metaiodobenzylguanidine: a review of its distribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry. *Eur J Nucl Med* 1994;21:545–559.
4. Slosman DO, Polla BS, Donath A. ^{123}I-MIBG pulmonary removal: a biochemical marker of minimal endothelial cell lesions. *Eur J Nucl Med* 1990;16:633–637.
5. Richalet JP, Merlet P, Boutguignon M, et al. MIBG scintigraphic assessment of cardiac adrenergic activity in response to altitude hypoxia. *J Nucl Med* 1990;31:34–37.
6. Slosman DO, Davidson D, Brill AB, Alderson PO. Pulmonary accumulation of ^{131}I-MIBG studied in an isolated perfused rat lung model. *J Nucl Med* 1986;133:1076,A664.
7. Slosman DO, Davidson D, Brill AB, Alderson PO. ^{131}I-metaiodo-benzylguanidine in the isolated perfused lung: a potential marker of endothelial cell function. *Eur J Nucl Med* 1988;13:543–547.
8. Slosman DO, Morel DR, Mo Costabella P, Suter PM, Donath D. Lung uptake of 131-metaiodobenzylguanidine in sheep. An in vivo measurement of pulmonary metabolic function. *Eur J Nucl Med* 1988b;14:65–70.
9. Pitt BR, Hadden P, Gillis CN. In line assessment of pulmonary extraction of of ^{125}I-metaiodobenzylguanidine (MIBG) by perfused rabbit lung. *Fed Proc* 1987;46:665.
10. Junod AF. Uptake, metabolism and efflux of ^{14}C-5-hydroxytryptamine in isolated perfused rat lungs. *J Pharmacol Exp Ther* 1972;183:341–355.
11. Junod AF. Hydroxytryptamine and other amines in the lung. Circulation and nonrespiratory function. In: Fishman AP, Fischer AB, eds. *Handbook of physiology.* Section 3. The respiratory system. Bethesda, MD: American Physiology Society; 1985:337–349.
12. Dollery CT Junod AF. Concentration of (±)-propranolol in isolated, perfused lungs of rat. *Br J Pharmacol* 1976;57:67–71.
13. Catravas JD, Lazo JS, Gillis CN. Biochemical markers of bleomycin toxicity: clearence of [^{14}C]-5-hydroxytryptamine and [^{3}H]-norepinephrine by rabbit lung in vivo. *J Pharmacol Exp Ther* 1981;217:524–529.
14. Catravas JD, Lazo JS, Dobuler KJ, Gillis CN. Pulmonary endothelial dysfunction in the presence or absence of endothelial cell injury by intratracheally injected bleomycin in rabbits. *Am Rev Respir Dis* 1983;128:740–748.
15. Dargent F, Gardaz JP, Morel P, Suter PM, Junod AF. Effects of atelectasis and vascular occlusion on the simultaneous measurement of serotonin and propranolol pulmonary extraction in dogs. *Clin Sci* 1985;69:279–286.
16. Dargent F, Neidhart P, Bachman S, Suter PM, Junod AF. Simultaneous measurement of serotonin and propranolol pulmonary extraction in patients after extracorporeal circulation and surgery. *Am Rev Respir Dis* 1985;131:242–245.
17. Morel DR, Dargent F, Bachman M, Suter PM, Junod AF. Pulmonary extraction of serotonin and propronalol in patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1985;132:479–484.
18. Solanki KK, Bomanji J, Moyes J, Mather J, Trainer PJ, Britton KE. A pharmacological guide to interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). *Nucl Med Commun* 1992;13:512–521.
19. Tamaki N, Itoh H, Ishii Y, et al. Hemodynamic significance of increased lung uptake of thallium-201. *AJR* 1982;138:223–228.
20. Murashima S, Takeda K, Matsumura K, et al. Increased lung uptake of iodine-123 metaiodobenzylguanidine in diabetics [Abstract]. *J Nucl Med* 1995;36:35P.
21. Martinez EE, Horowitz SF, Castello HJ, et al. Lung and myocardial thallium-201 kinetics in resting patients with congestive heart failure: correlation with pulmonary capillary wedge pressure. *Am Heart J* 1972;123:427–432.
22. Sandler M. Is the lung a target organ in diabetes mellitus? *Arch Intern Med* 1990;150:1385–1388.
23. Caner B, Uğur Ö, Bayraktar M, Ulutuncel N, Menteş T, Telatar F, Bekdik C. Impaired lung endothelial permeability in diabetics detected by tehnetium-99m-DTPA aerosol scintigraphy. *J Nucl Med* 1994;35:204–206.
24. Lysenko LV, Lysenko AL, Kulik VP. Ultrastructural and ultrachemical changes in diabetic lungs. *Byulleten Experimental'noi Biologii Meditsiny* 1988;109:75–78.
25. Vrakko R, Thorning D, Huang TW. Basal lamina of alveolar endothelium and capillaries: quantitative changes with aging and diabetes mellitus. *Am Rev Respir Dis* 1979;120:973–983.
26. Weir DC, Jennings PE, Henny MS, Barnett AH, Sherwood BP. Transfer factor for carbon monoxide in patients with diabetes with and without microangiopathy. *Thorax* 1988;43:725–726.