

Influence of age and gender on iodine-123 MIBG kinetics in normal lung

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Iodine-123 MIBG is a biochemical marker that can be used to monitor pulmonary norepinephrine (NE) metabolism. The purpose of this study was to characterize pulmonary I-123 MIBG kinetics in relation to age and gender.

Materials and Methods: Seventeen healthy volunteers and 14 patients with no cardiac or pulmonary disorders were included in this study (age range: 24 to 88 years, mean age 50.2 ± 17.6 years; 16 males, 15 females). Planar images were obtained 15 min (early) and 3 h (delayed) after injection of I-123 MIBG (111 MBq). Pulmonary uptake of I-123 MIBG was quantified based on the lung-to-mediastinum ratio (LMR) on early and delayed images. The lung clearance rate (LCR) was calculated from both the early and delayed images.

Results: Both early and delayed LMR values increased slightly, although they showed no significant correlations with age. There was a significant inverse correlation between LCR and age ($r = -0.57$, $p < 0.001$). Neither LCR nor LMR differed significantly between male and female patients, but the mean age of the men was lower than that of the women.

Conclusions: Pulmonary I-123 MIBG kinetics may reflect age-dependent changes in NE metabolism. The effects of age should be taken into account when assessing pulmonary NE metabolism with I-123 MIBG.

Key words: I-123 MIBG, lung uptake, norepinephrine metabolism, endothelial cell

INTRODUCTION

IODINE-123 metaiodobenzylguanidine (I-123 MIBG) is an analogue of guanethidine that is metabolized in a qualitatively similar manner to norepinephrine (NE),¹ and has been used for myocardial imaging to assess sympathetic activity. Reduced myocardial I-123 MIBG uptake in the inferior wall with aging, particularly in males, has been reported previously.² This suggests heterogeneity of sympathetic neuronal function in older patients. Lung uptake of I-123 MIBG, like NE, involves a sodium-dependent, energy-requiring active transporter located in the endothelial cell membrane.³⁻⁷ Therefore, I-123 MIBG has been used as a metabolic tracer of NE in pulmonary endothelial

cells. NE metabolism has been studied under a variety of conditions⁸ in order to assess physiologic or pathophysiologic changes in lung endothelial cell integrity. It has been reported that plasma NE kinetics in sympathetic nerve terminals may change with age.⁹ We hypothesized that I-123 MIBG metabolism in the lung may also undergo physiologic changes with aging, but this assessment of pulmonary endothelial cell function with I-123 MIBG has not yet been characterized. In this study, age- and gender-related changes in the kinetics of I-123 MIBG metabolism in normal lung were examined.

MATERIALS AND METHODS

Patients

Thirty-one subjects were enrolled (Table 1). They included 17 healthy volunteers, 12 patients with neuromuscular degenerative disease (NDD) without evidence of autonomic dysfunction, 1 patient with post-cerebrovas-

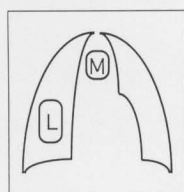
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Table 1 Patient characteristics

	20 to 40 years old		41 to 60 years old		Older than 60 years		Total
	Male	Female	Male	Female	Male	Female	
Normal volunteers	6	3	4	3	0	1	17
NDD	1		3	3	1	4	12
PCD					0	1	1
LC					1	0	1

NDD = neuromuscular degenerative disease, LC = lung cancer, PCD = post-cerebrovascular disease.



LMR : Lung (L) to mediastinum (M) ratio

LCR : Lung clearance rate

$$\text{LCR \%} = \frac{\text{Lung early count} - \text{Lung delayed count} \times 1.155}{\text{Lung early count}} \times 100$$

1.155 : coefficient for half - life correction

M= ROI in the Upper Mediastinum

L= ROI in the Middle-Lower Region in Right Lung

Fig. 1 Schematic representation of the anterior planar image. Pulmonary I-123 MIBG uptake and lung clearance rate were quantified as the LMR and LCR, respectively. ROIs were drawn over the right lung and upper mediastinum. Both LMR and LCR were calculated as mean counts per pixel.

I-123 MIBG: Iodine-123 metaiodobenzylguanidine, LMR: lung-to-mediastinum ratio, LCR: lung clearance rate, ROI: regions of interest

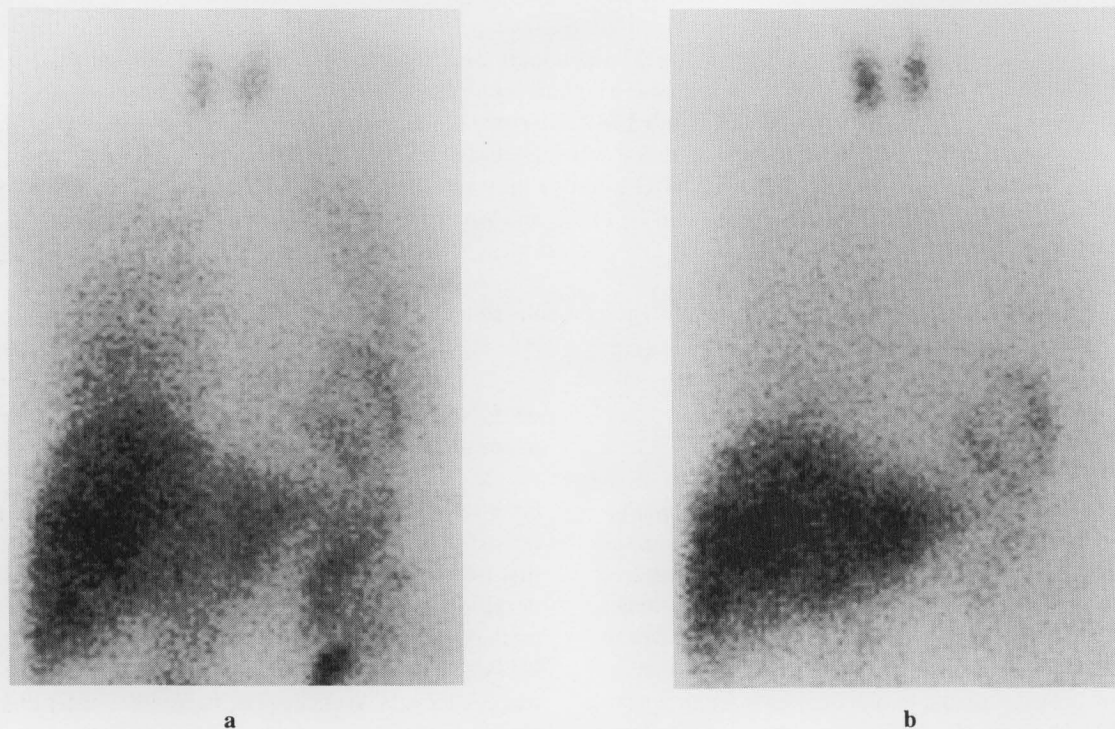


Fig. 2 I-123 MIBG planar early (a) and delayed (b) images of a 58-year-old healthy volunteer (non-smoker).

cular disease (PCD), and 1 patient with lung cancer (LC) affecting the left lung (age range: 24 to 88 years, mean age: 50.2 ± 17.6 years; 16 males, 15 females). Only three of the healthy volunteers were smokers. The patient with LC had not undergone chemotherapy or radiotherapy. The patients with NDD included 3 with Parkinson's

syndrome, 4 with amyotrophic lateral sclerosis, 2 with spinocerebellar degenerative disease, 2 with myotonic dystrophy, and 1 with Huntington's disease. None of the patients had a history of cardiac or pulmonary disease, diabetes mellitus, or hypertension. The healthy volunteers and patients with either NDD or PCD had no clinical

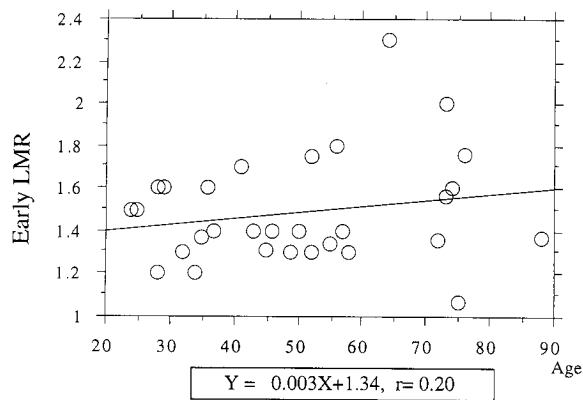


Fig. 3 Relationship between the early LMR and patient age. There was nonsignificant correlation between early LMR and age.

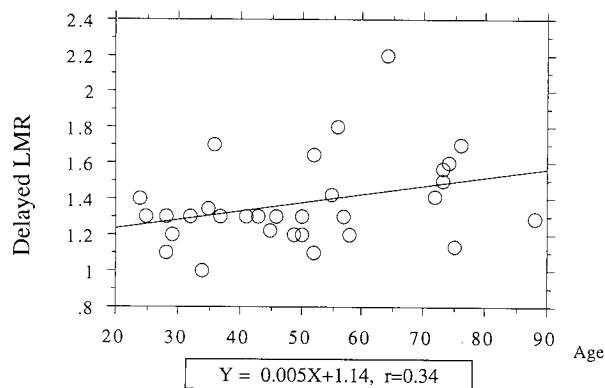


Fig. 4 Relationship between the delayed LMR and patient age. There was nonsignificant correlation between delayed LMR and age.

symptoms and no abnormalities on chest radiographs. The patient with LC had no abnormalities affecting the right lung or mediastinum. None of the patients had electrocardiographic abnormalities. The patients with NDD, PCD or LC had no perfusion defects on resting myocardial Tc-99m sestamibi (600 MBq) imaging. The right and left ventricular ejection fractions, assessed by the dynamic first-pass acquisition technique, were normal in all patients. None of the patients were taking medication which reduced myocardial uptake of I-123 MIBG. Informed consent was obtained from all patients.

I-123 MIBG study

In order to block tracer uptake in the thyroid gland, 2 mg of potassium iodine was administered orally for 3 days before and 7 days after the I-123 MIBG study. I-123 MIBG (111 MBq) was injected intravenously, and anterior planar images were obtained 15 min (early) and 3 h (delayed) later. The images were acquired over a 5-min interval and stored in a 256 × 256 matrix by using a single-head gamma camera (SNC-500R, Shimadzu, Japan)

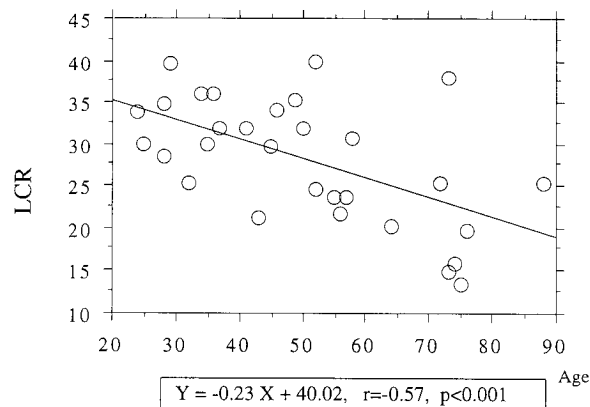


Fig. 5 Relationship between the LCR and patient age. There was a significant inverse correlation between LCR and age.

equipped with a low-energy, general purpose collimator interfaced to a minicomputer (Scintipac 700, Shimadzu). A symmetric 20% energy window centered on the 159 keV photon peak of I-123 was used for acquisition. Regions of interest were placed over the upper mediastinum and the middle-lower region of the right lung in planar images (Fig. 1), and the lung to mediastinum ratio (LMR) was determined. The lung clearance rate (LCR) for I-123 MIBG was determined after correction for I-123 physical decay by calculating the percent change in I-123 MIBG uptake from the early and delayed images. An example for a healthy volunteer is shown in Fig. 2.

Statistical analysis

The data are expressed as the mean ± standard deviation. Linear regression analysis was performed to determine the relationships between age and both LMR and LCR. The Mann-Whitney U test was used to determine the significance of differences between groups, and a probability value of < 0.05 was considered to indicate statistical significance.

RESULTS

Although both the early and delayed LMR values increased slightly, these values were not significantly correlated with age (Figs. 3 and 4), but the LCR was significantly correlated with age (Fig. 5) ($r = -0.57$, $p < 0.001$, mean LCR: 28.3 ± 7.2 , range: 13.5 to 40). When the normal volunteers were divided into two groups, those aged 40 years or younger and those aged over 40 years, the early LMR and LCR did not significantly differ between the normal volunteers aged over 40 years and patients with NDD, PCD or LC, but the delayed LMR was significantly lower in normal volunteers over 40 years of age ($p < 0.05$, Table 2). Both LCR and LMR were similar in both male and female patients, although the mean age of the men was lower than that of the women ($p < 0.05$, Table 3).

Table 2 Differences in LMR and LCR between normal volunteers and patients with NDD, PCD or LC

	Normal volunteers		NDD+PCD+LC
	≤ 40 years	40 years <	
No. of patients	9	8	14
Early LMR	1.45 ± 0.14	1.36 ± 0.05	* 1.58 ± 0.33
Delayed LMR	1.33 ± 0.16	1.24 ± 0.07	1.44 ± 0.34
LCR	32.2 ± 4.3	30.2 ± 6.4	24.8 ± 7.8
Age	30.4 ± 4.8	55.4 ± 14.1	60.0 ± 14.3

LMR = lung to mediastinum ratio, LCR = lung clearance rate, NDD = neuromuscular degenerative disease, LC = lung cancer, PCD = post-cerebrovascular disease, *p < 0.05.

Table 3 Comparison of scintigraphic parameters with respect to gender

	Mean age	Early LMR	Delayed LMR	LCR
Male	43.7 ± 14.9	1.55 ± 0.26	1.40 ± 0.29	30.0 ± 6.90
Female	57.2 ± 18.1	1.42 ± 0.23	1.34 ± 0.20	26.5 ± 7.32
Significance	p < 0.05	ns	ns	ns

LMR = lung to mediastinum ratio, LCR = lung clearance rate, ns = not significant.

DISCUSSION

This study demonstrated a tendency for the LCR to decrease with increasing age, but neither the early nor the delayed LMR was affected by age. These findings may have resulted from normal I-123 MIBG uptake across the endothelial cell membrane, but there was decreased I-123 MIBG lung clearance in the older patients. Because the lung endothelium has no vesicles and cannot store NE, the clearance of I-123 MIBG from the lung is relatively rapid compared to the heart.¹⁰

The site of NE uptake in the lung is the endothelium of capillaries and small venules.¹¹ Numerous sympathetic nerves innervate vessels as small as 30 μm in the lung.¹² While autonomic vascular neuroeffector junctions exist in the adventitial-medial borders of small veins, the neural-endothelial relationships in the capillaries are less well characterized. It has been hypothesized that the interaction between neural and endothelial cells may regulate vascular tone.¹³⁻¹⁵ Neurotransmitters released from sympathetic neurons can potentially affect endothelial cells. In contrast, the endothelium plays an important role in inhibiting adrenergic transmitter release from sympathetic terminals. Further, endothelium-derived factors can modify the release of neurotransmitters, and thereby control vascular tone. Based on these findings, we hypothesized that altered pulmonary sympathetic nervous activity may exist in older subjects.

Although this study included patients with NDD or PCD without autonomic dysfunction, none of them had

evidence of cardiac or pulmonary disease. This study demonstrated a significant correlation between LCR and age. While neither LCR nor LMR measurements in men and women differed significantly, the mean age for the men and women was different, but the difference in mean age may be explained by the relatively small number of patients studied.

While I-123 MIBG is a useful index for evaluating NE metabolism in the pulmonary endothelium,³⁻⁷ I-123 MIBG is not metabolized by either monoamine oxidase or catechol-*o*-methyl transferase. In addition, the distribution of I-123 MIBG after it is taken up into endothelial cells remains undefined. Because the LMR is determined by variables which affect the pulmonary uptake of I-123 MIBG, the LMR may be influenced by several factors: 1) The vascularity of the pulmonary circulation may affect the LMR, but it has been reported that the pulmonary uptake of I-123 MIBG tends to be increased in cardiac transplant patients, although any difference is not significant.^{16,17} Glowniak et al.¹⁶ have suggested that the tendency for I-123 MIBG uptake to increase is caused by increases in pulmonary artery pressure. Although comparisons between I-123 MIBG lung scans and perfusion lung scans were needed, such studies were not performed. 2) The LMR may be affected by the available pulmonary vascular surface area. Slosman et al.⁷ have suggested that both endothelial cell function and the vascular surface area that is accessible to the blood pool may influence I-123 MIBG lung accumulation. 3) Lung volume and gas exchange parameters that change with age may influence I-123 MIBG uptake. Vital capacity, carbon monoxide diffusing capacity, membrane diffusing capacity and arterial oxygen pressure decrease with age. Comparisons between the LMR and LCR versus these parameters are also needed, although these parameters were not determined. 4) The LMR may be affected by endogenous NE concentrations. High concentrations of catecholamine can competitively inhibit I-123 MIBG uptake. Although comparisons between I-123 MIBG and NE concentrations are necessary, the concentration of NE in the pulmonary circulation was not determined. 5) Exposure to tobacco smoke, which affects the respiratory tract, may influence I-123 MIBG uptake. Only 3 smokers were enrolled in this study, and so a comparison of smokers with non-smokers is needed.

In addition, other factors related to pulmonary physiological and anatomical changes with age may potentially influence this tracer. Further studies on a larger number of patients are necessary. The kinetic behavior of I-123 MIBG following endothelial cell uptake remains to be explained.

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