Reduced lung uptake of iodine-123-MIBG in high-altitude pulmonary edema

Kazuhisa Urushihata, M.D., Tomonobu Koizumi, M.D., Masayuki Hanaoka, M.D., Keisaku Fujimoto, M.D., Keishi Kubo, M.D., Toshio Kobayashi, M.D., Tadashige Fujii, M.D.

First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, JAPAN

Name and address of corresponding author:

Tomonobu Koizumi, M.D.,
First Department of Internal Medicine
Shinshu University School of Medicine
3-1-1 Asahi Matsumoto, 390-8621, JAPAN
Tel: +81-263-37-2631, Fax: +81-263-36-3722
e-mail; tomonobu@hsp.md.shinshu-u.ac.jp

Abstract

Background : Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) lung uptake at early phase is a potentially suitable marker of pulmonary endothelial function because MIBG behaves quantitatively similar to norepinephrine in pulmonary circulation. In addition, hypoxia reduces ^{123}I-MIBG transport in pulmonary endothelial cell *in vitro*.

Objectives : The present study was undertaken to evaluate ^{123}I-MIBG lung uptake in patients with high-altitude pulmonary edema (HAPE).

Patients and Method : ^{123}I-MIBG scintigraphy was performed in 8 patients with HAPE. The findings were compared with those in 24 patients with congestive heart failure due to idiopathic dilated cardiomyopathy (DCM) or 13 normal controls. ^{123}I-MIBG examination in patients with HAPE was evaluated on days 7 to 14 following admission. Anterior planar images were acquired 15 min after injection of ^{123}I-MIBG and the total lung to upper mediastinum ratio (L/M ratio) was calculated in both lungs.

Results : The L/M ratio of patients with HAPE (1.39 ± 0.15, mean ± SD) was significantly lower than those with congestive heart failure/DCM (1.66 ± 0.16) and normal controls (1.53 ± 0.14). There were no significant differences in ^{123}I-MIBG accumulation in heart among the groups.

Conclusions : Although the mechanisms for the altered ^{123}I-MIBG kinetics remains obscure in HAPE, decreased ^{123}I-MIBG lung uptake might be a potentially suitable technique for the assessment of pathological conditions associated with pulmonary endothelium.

Key words : hypoxia, increased permeability pulmonary edema, MIBG, cardiogenic pulmonary edema, endothelial cell injury

Short Title ; ^{123}I-MIBG lung uptake in HAPE

Abbreviation List:

Iodine-123 metaiodobenzylguanidine : ^{123}MIBG,
high-altitude pulmonary edema : HAPE
idiopathic dilated cardiomyopathy : DCM
lung to upper mediastinum ratio in ^{123}MIBG uptake : L/M
bronchoalveolar lavage : BAL

INTRODUCTION

It has been demonstrated that radioiodinated metaiodobenzylguanidine (MIBG), an analog of the adrenergic blocking agent guanidine, shares many neuronal transport and storage mechanisms with norepinephrine [1,2]. Iodine-123 MIBG (^{123}I-MIBG) scintigraphy has been widely used for the detection of various neuroendocrine tumors and the evaluation of adrenergic dysfunction in the heart [3-5]. ^{123}I-MIBG is also taken up by lung through a saturable, energy-requiring, soduium-dependent transport mechanism similar to biogenic amines, such as serotonin and norepinephrine [6-8]. It is well known that transport of these biogenic amines requires normal endothelial cell integrity. Thus, ^{123}I-MIBG is regarded as an indicator of pulmonary endothelial function [6-9], because it behaves in a quantitatively similar manner to norepinephrine in pulmonary circulation [10,11]. Slosman et al. initially evaluated lung uptake of MIBG using animal models and demonstrated decreased MIBG lung extraction in bleomycin[9] – and endotoxin[12] – induced endothelial injury. Recently, several clinical studies using this property of ^{123}I-MIBG scintigraphy, showed that decreased ^{123}I-MIBG kinetic in lung could serve as a novel diagnostic tool to evaluate the endothelial damage in patients with pulmonary fibrosis[13] and myeloperoxidase antineutrophil cytoplasmic antibodies positive vascultis[14]. However, information on the potential value of pulmonary ^{123}I-MIBG uptake in pulmonary diseases remains limited.

In the present study, we focused on the pulmonary uptake of ^{123}I-MIBG in patients with high-altitude pulmonary edema (HAPE), a type of non-cardiogenic pulmonary edema. HAPE occurs in individuals who fail to acclimatize to altitudes above 2,500 m [15,16]. Although the mechanism of HAPE remains unknown, increases in pulmonary vascular pressure and/or microvascular permeability have been implicated in the pathophysiology of HAPE [17-20]. Thus, functional changes in the pulmonary vascular endothelium might be associated with the development of HAPE. Several in vitro studies demonstrated that hypoxia impaired pulmonary artery endothelial cell integrity [21] and serotonin uptake was reduced in lungs during hypoxic exposure [22]. More recently, Lee et al demonstrated *in vitro* that short-term exposure to hypoxia reduced ^{123}I-MIBG uptake in calf pulmonary artery endothelial cells [23]. Thus, we explored the potential for clinical application of ^{123}I-MIBG uptake in lung for the evaluation of patients with HAPE and compared the results with those of subjects with hydrostatic pulmonary edema and normal control.

MATERIALS AND METHODS

This study was conformed by the provisions of the Declaration of Helsinki in 1995. We informed the procedures, risk of this study and informed consent was obtained from each subject prior to study participation.

Subjects

The clinical characteristics of enrolled patients in this present study are summarized in Table 1. The study subjects were 8 patients with HAPE (6 males and 2 women, with a mean age of 44.6 years, range 21-58 years). All HAPE subjects were healthy athletic individuals at sea level who developed HAPE while climbing the Japan Alps. Altitudes at onset of HAPE ranged from 2,758 to 3,190 m above sea level. The diagnosis of HAPE was based on the Hultgren's criteria [16]. The subjects were transferred to our hospital and treated with oxygen and

adequate fluid therapy. Routine examination and related cardiovascular tests were conducted in hospital after their recovery to exclude any cardiopulmonary diseases. ^{123}I-MIBG scintigraphy was performed on days 7 to 14 after the admission. When ^{123}I-MIBG images were taken, chest infiltrates had almost disappeared. Oxygen therapy already discontinued because of sufficient oxygenation during breathing room air ($SpO_2 > 95\%$). They were discharged after the ^{123}I-MIBG examination. The results of ^{123}I-MIBG scintigraphy in HAPE were compared with those of congestive heart failure. These subjects were 24 patients with idiopathic dilated cardiomyopathy (DCM), consisted of 16 male and 8 female, ranging in age from 24 to 69 years with an average age of 50.5 years. Each of these patients had clinical symptoms consistent with New York Heart Association Class 2-3 heart failure. Almost all patients received medical treatment with digitalis and diuretics. None were received medications that could affect ^{123}I-MIBG uptake and metabolism, such as beta-adrenergic blocking drugs, catecholamine and angiotensin converting enzyme inhibitor. We also examined an additional 13 patients, including 7 males and 6 females with a mean age of 43.4 years (range, 20 – 64). They had arrhythmia (sustained ventricular tachycardia or premature ventricular contraction) and cardiac examination was taken. These subjects did not have any abnormal findings on chest radiographs, coronary arteriography and echocardiography nor did they have a history of congestive heart failure. They served as controls (normal volunteers) in the present study and ^{123}I-MIBG examination was performed. Medical treatments including specific anti-arrhythmic agents and/or beta-adrenergic blockers were not received in the control group.

MIBG scintigraphy

A dose of (111 MBq) of ^{123}I-MIBG (Daiichi Radioisotopes Labs, Tokyo, Japan) was intravenously administered after the patient had laid in bed undisturbed for 15 min. Anterior planar images were acquired 15 min after injection of ^{123}I-MIBG, and stored in a 64 x 64 matrix by a scintillation camera (ZLC 7500, Siemens, Solana, Sweden) equipped with a low-energy, general purpose collimator interfaced to a minicomputer (SCINTIPAC 2400, Shimazu, Kyoto, Japan). The energy window was set at the 159 keV photopeak of ^{123}I. Scintigraphic image acquired with ^{123}I-MIBG and method for heart and lung uptake were shown in Figure 1. The region of interest (ROI) was placed over the upper mediastinum, the right and left lung in planar images. ROIs corresponding to the contours of the right and left lungs were manually assigned with reference to the isocount line. Total counts of each lung and heart were measured and the genometric mean was calculated as counts per pixel. To quantify the degree of lung uptake of ^{123}I-MIBG, the lung to upper mediastinum ratio in ^{123}I-MIBG uptake (L/M) was measured for the right (R) and left (L) lungs. These data were used to calculate the mean value (R+L/2; L/M). To evaluate heart uptake of ^{123}I-MIBG, the heart to upper mediastinum ratio of ^{123}I-MIBG uptake (H/M) was similarly calculated.

Statistical analysis

Data are expressed as mean ± SD. Unpaired t test was used to analyze differences in ^{123}I-MIBG scintigraphic data. A p value of <0.05 was considered statistically significant.

RESULTS

The mean and each value of L/M and H/M ratios in the three groups are shown in Table 1, Figures 2 and 3. The L/M ratio in HAPE was significantly lower than in DCM patients and controls (Figure 2). In relation to the H/M ratio, there were no significant differences between three groups, however, H/M ratio of DCM group was slightly lower than that of the other two groups (Figure 3). Anterior planar ^{123}I-MIBG scintigraphic images of HAPE patients are shown in Figure 4. The mean L/M ratios were 1.22 for the left side (Figure 4) and 1.31 for the right side (Figure 4). ^{123}I-MIBG images of patients with DCM are also shown in Figure 5. The mean L/M ratios were 1.64 for the left side (Figure 5) and 1.83 for the right side (Figure 5). Evaluation of the relationship between ^{123}I-MIBG uptake in lung and heart showed no significant correlation between the decreased H/M and increased L/M in DCM. Thus, the above results showed decreased lung ^{123}I-MIBG uptake during the early recovery phase in patients with HAPE.

In three cases of HAPE patients, we re-evaluated ^{123}I-MIBG lung uptake two months after the initial examination. The L/M ratios of these individuals showed slightly increased values at full recovery from HAPE. The L/M ratios measured in the initial phase and 2 months later were 1.22 and 1.36, 1.46 and 1.49, and 1.22 and 1.32, in the three individuals, respectively.

DISCUSSION

This study was undertaken to further characterize the behavior of ^{123}I-MIBG uptake in pulmonary diseases. We found that ^{123}I-MIBG lung uptake in HAPE was reduced during the recovery. The findings were different from those in congestive heart failure and normal controls. Although the ^{123}I-MIBG transport in pulmonary endothelial cells remains unsolved in the present study, decreased ^{123}I-MIBG lung uptake might be a potentially suitable technique for the assessment of pathophysiological conditions in HAPE.

The pathogenesis of HAPE is considered an altered permeability of alveolar-capillary barrier due to enhanced hypoxic pulmonary vasoconstriction and high capillary pressure [17-21]. In addition, several clinical studies suggest that individuals susceptible to HAPE have dysfunction in vascular endothelial nitric oxide (NO) vasodilator pathway during hypoxia [24,25]. These findings in HAPE strongly suggest an alteration in pulmonary endothelial cell function. Although we did not show any other specific biomarkers suggesting an impaired endothelial cell dysfunction in the present study, the decreased lung ^{123}I-MIBG uptake observed in our study might reflect the pathological conditions associated with pulmonary endothelial cell function in HAPE.

Our findings in patients with congestive heart failure and normal subjects were consistent with those of other studies [3,4]. Schofer et al. [3] and Glowniak et al. [4] showed that the lung uptake of ^{123}I-MIBG was slightly increased in DCM patients with congestive heart failure. Although the L/M ratio in patients with DCM was not always significantly higher than those with normal controls, the data showed a uniform increase in lung uptake of ^{123}I-MIBG in patients with congestive heart failure. Taken together, lung uptake in HAPE was significantly reduced in HAPE compared with that in congestive heart failure and/or normal controls. Pulmonary ^{123}I-MIBG uptake examination could be a novel technique for clinical assessment of various pathological mechanisms associated with endothelium.

However, there are several limitations in the present study to interpretation of our results. Richalet et al. [26] studied pulmonary ^{123}I-MIBG uptake in normal volunteers after exposure to hypoxic conditions of high altitude (4,350 m) for eight days. The subjects were rapidly transferred by helicopter and MIBG examination was performed 2 - 5 hours after the return to low altitude. Although none of them developed HAPE, the lung ^{123}I-MIBG uptake values were significantly lower than those of normal subjects who remained at the low altitude. These findings *in vivo* suggest that hypoxia is an important determinant of ^{123}I-MIBG uptake in lung, which was consistent with that in *in vitro* study by Lee et al [23]. In the present study, we did not compare the ^{123}I-MIBG lung uptake in HAPE with healthy control after exposure to high-altitude. Thus, it remains unclear whether the altered ^{123}I-MIBG kinetics in lung is due to hypoxia alone or recovery from well - developed HAPE.

Second, ^{123}I-MIBG uptake in lung can be affected by endogenous norepinephrine concentrations, as high concentrations of catecholamine can competitively inhibit ^{123}I-MIBG uptake [2,5]. We showed previously that plasma catecholamine concentrations in patients with HAPE were high on hospital admission but returned to normal by the time of discharge [27]. Since ^{123}I-MIBG scintigraphy was performed 7 to 14 days after admission in the present study, it

was likely that plasma catecholamine concentrations were within normal range. The study by Richalet et al. [26] reported significant decreases in lung MIBG uptake in normal subjects exposed to high altitude, but the results were independent of high concentrations of circulating catecholamine. This is in line with our data indicating that the decreased lung uptake of ^{123}I-MIBG in HAPE appears to have no relationship to circulating catecholamine concentrations.

Finally, we have to consider a possibility of unperfused or collapsed areas due to residual pulmonary edema contributing to the decreased ^{123}I-MIBG uptake in patients with HAPE, whereas congestive heart failure might be related with increased pulmonary vascular surface area. It is reported that lung washout ratio of ^{123}I-MIBG is independent of the alteration in the pulmonary vascular surface area [28-30], although the examination is not done in the present study. However, MIBG examination in the present study was performed at fully recovery of HAPE and none of patients showed hypoxemia and abnormal findings on chest radiograph at the time. Furthermore, the ^{123}I-MIBG lung uptake was re-evaluated in three HAPE patients at two months after the initial examination. The changes of L/M ratio were slight in each patient even at full recovery and the values remained decreased. These findings also suggest that decreased lung ^{123}I-MIBG uptake reflects the pathological conditions in HAPE.

In summary, the present study showed that HAPE patients had low lung uptake of ^{123}I-MIBG, which was different from patients with congestive heart failure and normal subjects. Although we need to further investigate the exact mechanism of decreased ^{123}I-MIBG kinetics in HAPE, the finding might be associated with the pathological conditions including an impairment of pulmonary endothelial cell function or surface area in HAPE. Evaluation by lung uptake of ^{123}I-MIBG may be a reliable tool for assessing endothelial cell integrity in various pulmonary diseases.

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FIGURE LEGENDS

Figure 1. Scintigraphic image acquired with ^{123}I-MIBG at 15 min and methods for an evaluation of heart and lung uptake. The region of interest (ROI) was placed over the upper mediastinum (1), the right (2) and left lung (3) in planar images. ROIs corresponding to the contours of the right and left lungs were manually assigned with reference to the isocount line. Total counts of each lung and heart (4) were measured, and the genometric mean was calculated as counts per pixel.

Figure 2. Comparisons of ^{123}I-MIBG lung uptake to mediastinum (L/M) ratio in three groups. Data are mean ± SD.
HAPE; high-altitude pulmonary edema. DCM; idiopathic dilated cardiomyopathy.

Figure 3. Comparisons of ^{123}I-MIBG heart uptake to mediastinum (H/M) ratio in three groups. Data are mean ± SD.
HAPE; high-altitude pulmonary edema. DCM; idiopathic dilated cardiomyopathy.

Figure 4. ^{123}I-MIBG findings in patients with high-altitude pulmonary edema.
The L/M ratios were 1.22 for the subject on the left side and 1.31 on the right side.

Figure 5. ^{123}I-MIBG findings in patients with idiopathic dilated cardiomyopathy.
The L/M ratios were 1.64 for the subject on the left side, and 1.83 on right side case.

Table 1

Patients Characteristicus and MIBG uptake in lung and heart

	HAPE	DCM	Control
No.	8	24	13
gender (F, M)	(6 : 2)	(16 : 8)	(7 : 6)
age (yr)	44.6±17.0	50.5±17.0	43.4±17.0
H / M	2.11±0.28	1.82±0.22	1.98±0.22
L / M	1.39±0.15* §	1.66±0.16 §	1.53±0.14

values are mean±SD
* p<0.01 vs DCM
§ p<0.05 vs Control

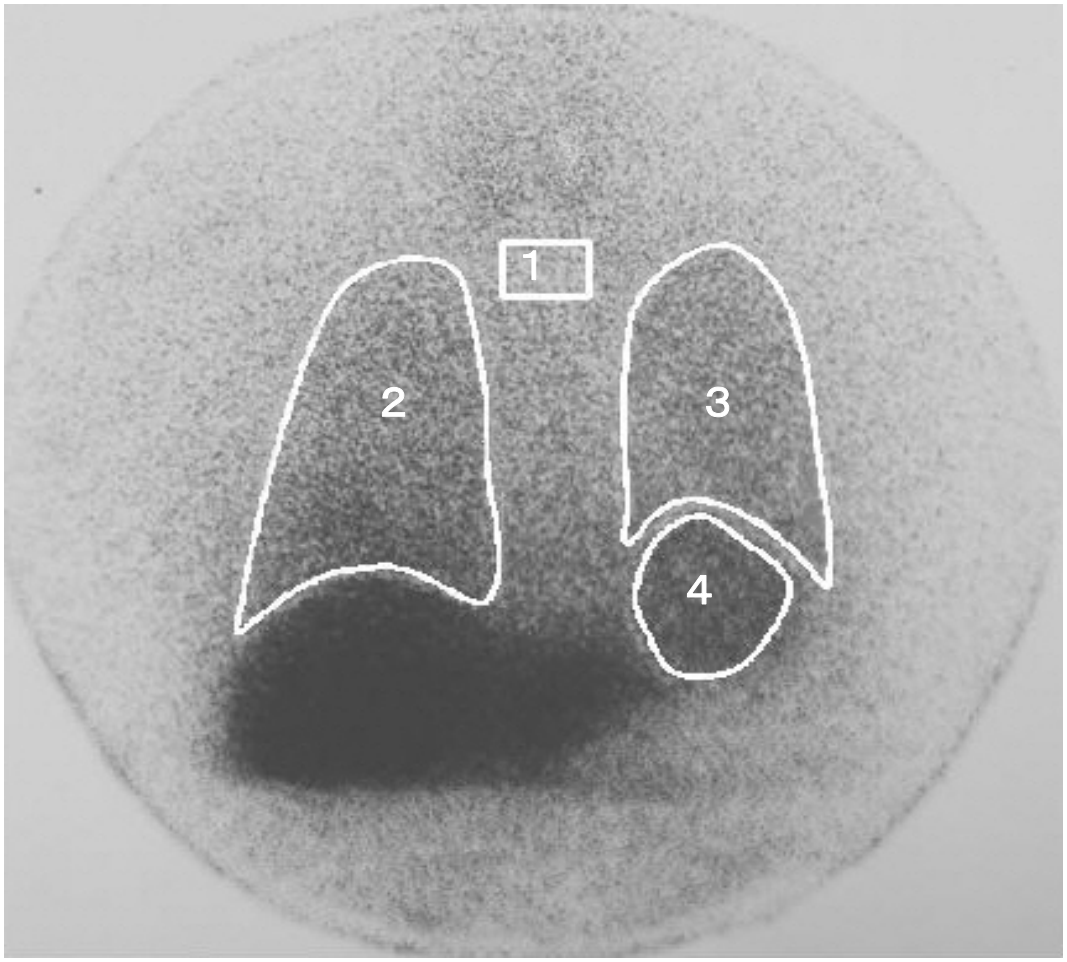


Fig. 1

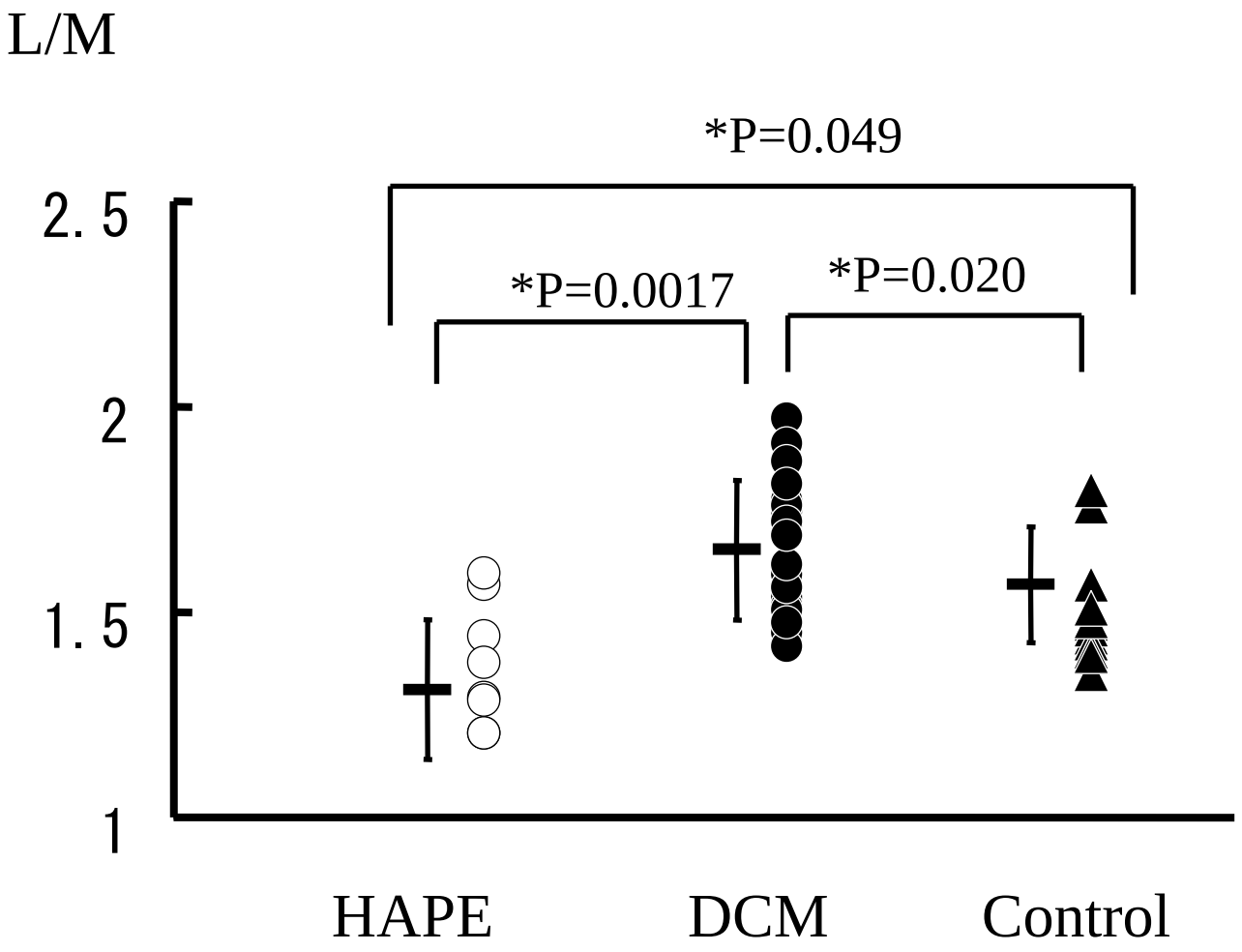
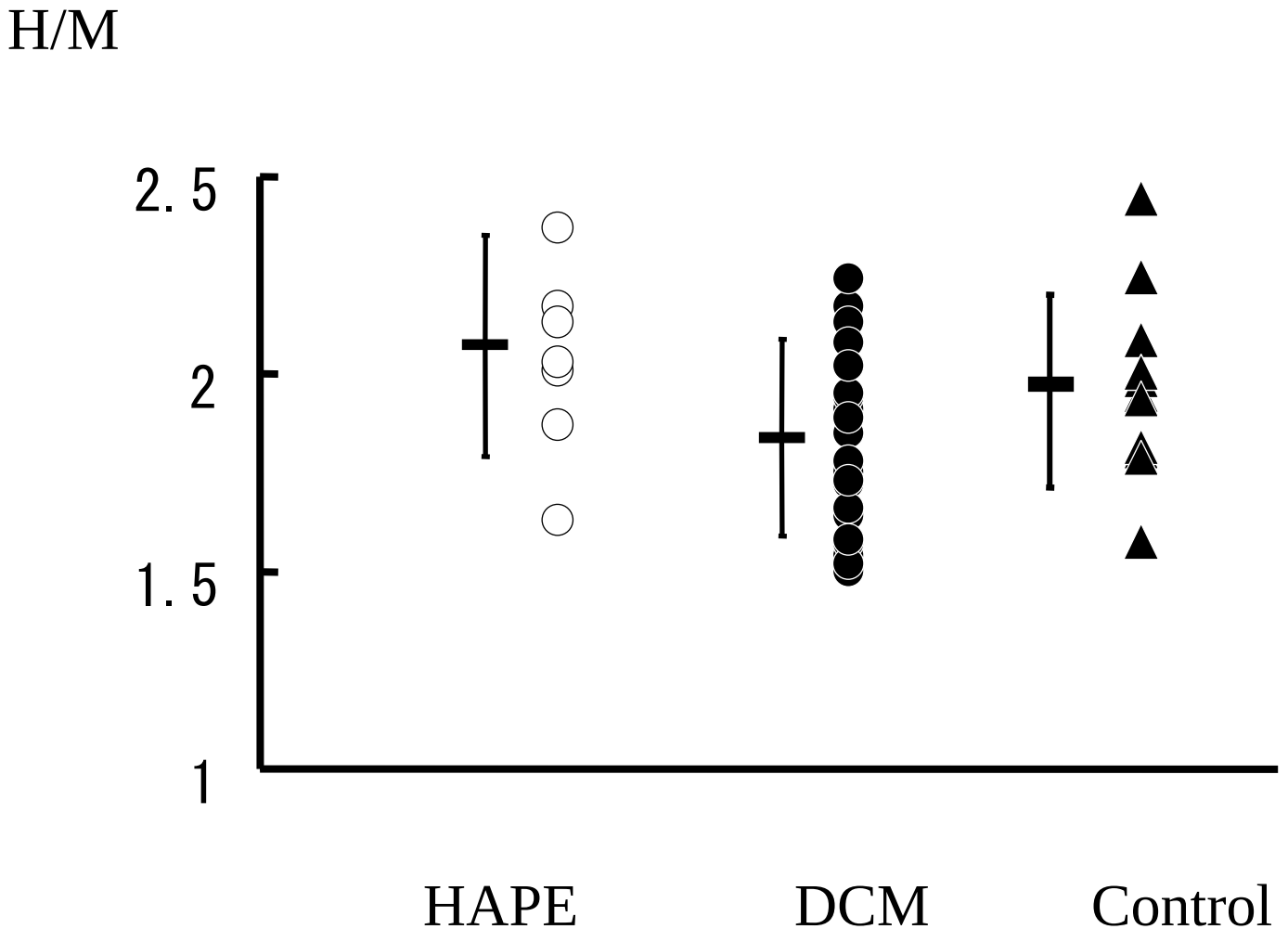


Fig. 2



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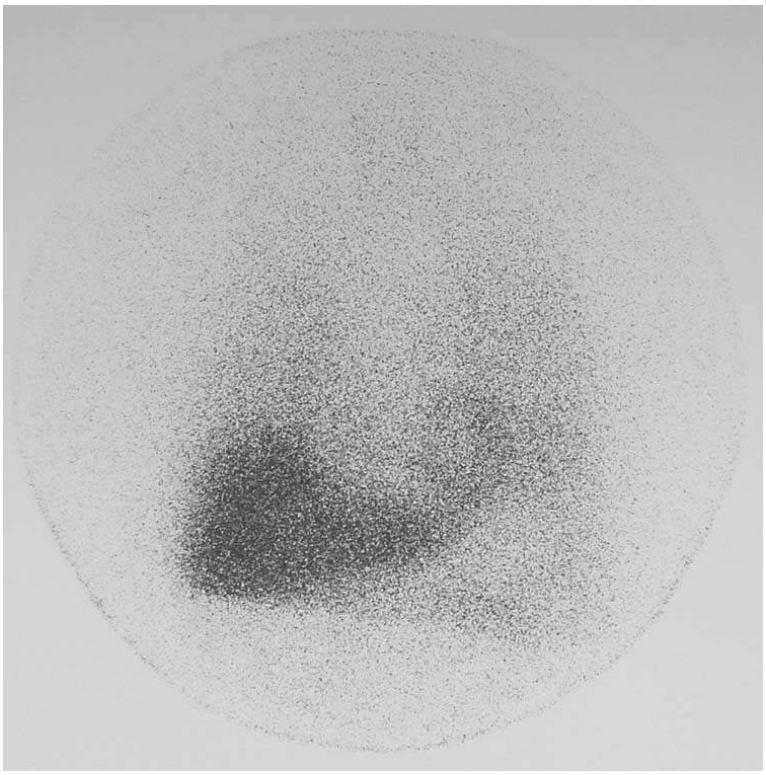


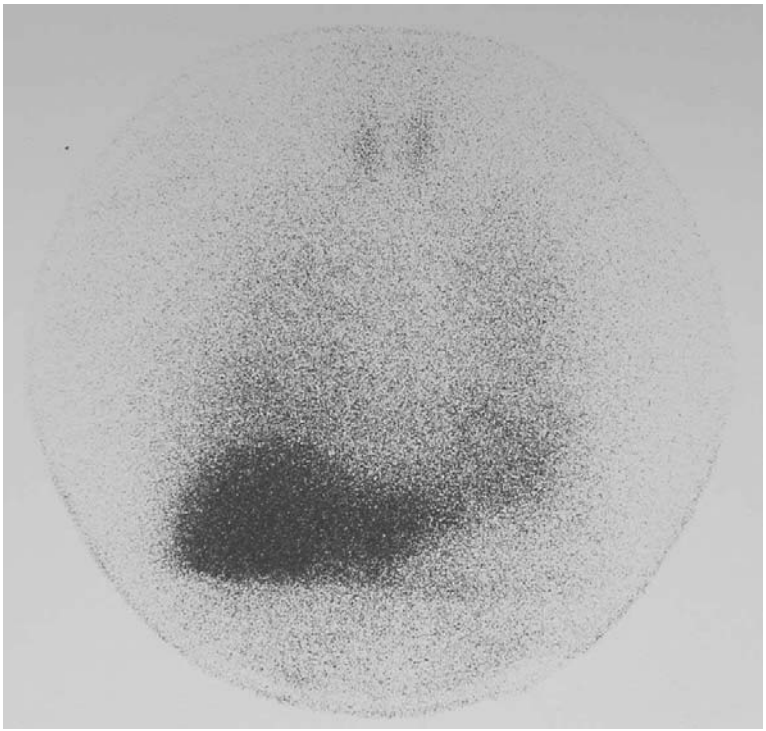
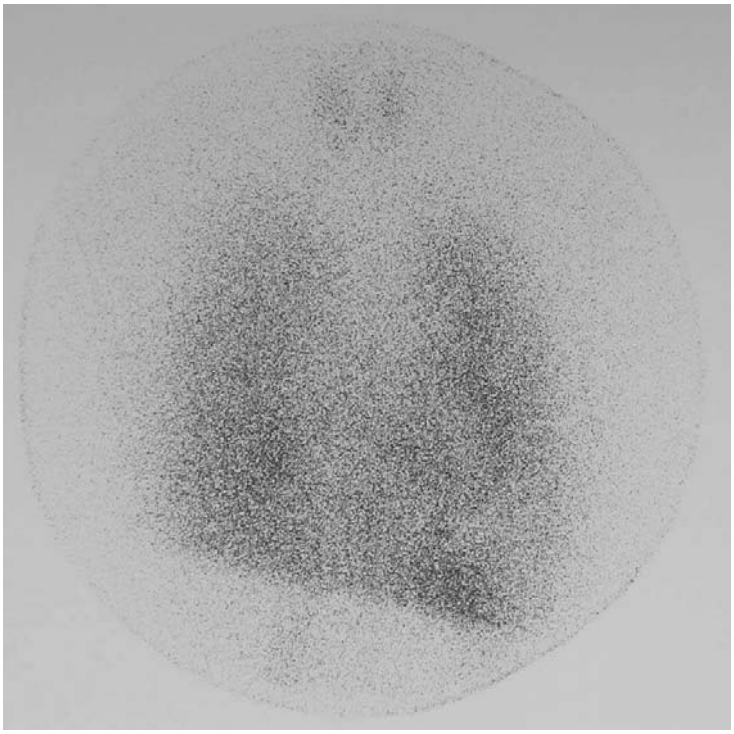


Figure 4



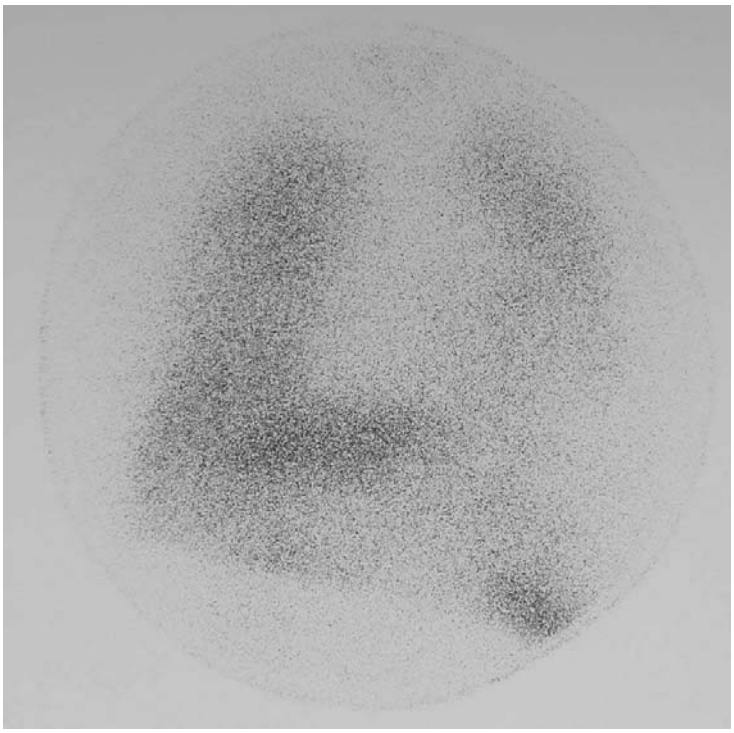


Figure 5