Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintigraphic assessment of pulmonary vascular status in patients with chronic obstructive pulmonary disease (COPD)

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Short title: MIBG and pulmonary hypertension in COPD

Summary: The present study demonstrated that early uptake of ^{123}I-MIBG showed an inverse correlation with increases in pulmonary artery pressure during exercise in patients with COPD.

ABSTRACT

Background and Objectives: Lung uptake of iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) has been regarded as an indicator of pulmonary endothelial function. Decreased lung uptake of ^{123}I-MIBG was demonstrated in patients with chronic obstructive pulmonary disease (COPD) compared with normal subjects. The present study was performed to examine the relationship between ^{123}I-MIBG lung uptake and pulmonary artery pressure (Ppa) at rest and during exercise in patients with COPD. **Methods:** ^{123}I-MIBG scintigraphy was performed in 19 patients with COPD. Anterior planar images were acquired 15 min after injection of ^{123}I-MIBG and the total lung to upper mediastinum ratio (LMR) was calculated in both lungs. Ppa was monitored by right heart catheters continuously at rest and during exercise. Exercise was performed on an electrically braked bicycle ergometer with a constant workload of 25 W and for 3 min. **Results:** The LMR in COPD were not correlated with the detectable parameters of pulmonary function test before exercise, including FEV1, PaO_2, DLCO, and with Ppa at rest. However, the % increase in Ppa during exercise was significantly correlated with LMR. **Conclusion:** Evaluation of kinetic behaviour of ^{123}I-MIBG may be a novel scintigraphic tool for assessment of exercise-induced pulmonary hypertension in patients with COPD.

Key words: pulmonary artery pressure, pulmonary hypertension, airflow limitation, MIBG

1. Introduction

Radioiodinated metaiodobenzylguanidine (MIBG), an analogue of the adrenergic blocking agent guanidine, shares many neuronal transport and storage mechanisms with norepinephrine[1]. Iodine-123 MIBG (^{123}I-MIBG) has been widely used for the detection of various neuroendocrine tumours and for evaluation of adrenergic dysfunction in the heart [2-5]. ^{123}I-MIBG is taken up by the lung through a saturable, energy-requiring, sodium-dependent transport mechanism similar to biogenic amines, such as serotonin and norepinephrine [6,7]. 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 [6-8], because it behaves in a quantitatively similarly manner to norepinephrine in the pulmonary circulation [9].

Chronic obstructive pulmonary disease (COPD) is a common medical problem, and the mortality rate has been increasing in developed countries [10]. Pulmonary hypertension is a frequent complication in the clinical course of COPD [11-16]. Pulmonary hypertension is a significant prognostic factor in patients with COPD and is associated with poor survival [11-13]. Although many possible mechanisms for the development of pulmonary hypertension in COPD have been proposed, several studies have implicated dysfunction of pulmonary endothelial cells [14-19]. For example, expression of endothelial nitric oxide synthase in pulmonary arteries [17] and exhaled nitric oxide [18] were reduced in patients with COPD with pulmonary hypertension. In addition, expression of endothelin 1 (ET-1), an endogenous vasoconstrictor,

was increased in the pulmonary artery [19] and plasma ET-1 concentration was increased clinically in COPD patients with pulmonary hypertension [20].

Arao *et al.* [21] studied lung ^{123}I-MIBG uptake in patients with COPD and found that pulmonary uptake of ^{123}I-MIBG was significantly lower than that of control subjects. In addition, they measured the washout ratio of ^{123}I-MIBG, a more specific marker of pulmonary endothelial cell function, and showed a significant correlation with pulmonary function test, including % predicted values of forced expiratory volume in 1 s (% FEV1), carbon monoxide diffusing capacity/alveolar volume (DLCO/VA) and arterial blood oxygen tension (PaO_2).

Accordingly, the present study was performed to further characterise the pulmonary uptake of ^{123}I-MIBG in patients with COPD. Although lung washout ratio of ^{123}I-MIBG is a more suitable means of evaluating pulmonary endothelial function, decreased early uptake of ^{123}I-MIBG in COPD may reflect loss of pulmonary vascular area as well as pulmonary endothelial function [8]. The loss of the pulmonary vascular bed could be a contributing factor to the development of pulmonary hypertension in COPD [14-16]. Our hypothesis is that early uptake of ^{123}I-MIBG could be related to some parameters of pulmonary haemodynamics in patients with COPD. We focused on the relationship between pulmonary haemodynamics in patients with COPD and the early lung uptake of ^{123}I-MIBG. We evaluated whether ^{123}I-MIBG lung uptake is related to pulmonary hypertension in patients with COPD, especially pulmonary hypertension during exercise.

2. 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 written informed consent was obtained from each subject prior to study participation.

2.1. *Subjects*

Nineteen patients with stable COPD without α1-antitrypsin deficiency were enrolled in the present study. All patients were male with mean ages of 65 with ranging from 56 to 79 years olds. They had smoking histories (mean Brinkman index was 1,942.3 ± 743.7) but all were ex-smoker. The diagnosis of COPD was made on the basis of a clinical history of exertional dyspnoea and pulmonary function test. Patients with a history or presence of bronchial asthma and those with reversibility of > 15% and forced expiratory volume in 1 s (FEV1) of 200 ml after inhalation of ß-stimulator were excluded. Patients with multiple bullae or a single giant bulla on chest computed tomography and with clinically diagnosed acute exacerbation of COPD and/or pulmonary infection were also excluded from the present study. Although most patients were treated with several bronchodilators, including short-acting anticholinergic agents and/or theophylline, those treated with long-acting ß2-agonists were also excluded from the present study. In addition, there were no subjects with diabetes mellitus or ischemic heart disease in the present study population. Written informed consent for measurement of pulmonary haemodynamics and MIBG examinations were obtained from each subject. Although the study population included two

patients treated with home oxygen, pulmonary haemodynamic study and MIBG scintigraphy were performed without breathing oxygen.

The methods used for measurement of pulmonary haemodynamics were described in our previous reports [22,23]. Briefly, a 7 F Swan-Ganz thermodilution catheter (Becton Dickinson, Sandy, UT) was inserted through the internal jugular vein into the pulmonary artery for measurement of pulmonary artery pressure (Ppa). The Ppa was monitored continuously using a transducer system (SCK-580; Nihon Koden, Tokyo, Japan) and registered on a recording device (WT-685G; Nihon Koden). The zero pressure point was referenced to the midthoracic level and calibration was performed with a mercury manometer. Ppa was obtained at rest and during exercise in each subject. The exercise was performed on an electrically braked bicycle ergometer (Reclining Ergometer model WLP-300 ST; Lode BV, Groningen, The Netherlands) with a constant workload of 25 W. The exercise was usually continued for 3 min. During each experiment, the peripheral oxygen saturation (SpO_2) of all patients was monitored continuously with a Pulsox-8 SpO_2 monitor (Teijin, Osaka, Japan). Blood gas analysis was performed before and just after the end of exercise in each patient using a blood gas analyser (ABL-2; Radiometer, Copenhagen, Denmark).

2.2. *MIBG scintigraphy*

Use of inhaled ß2-agonist, which could influence sympathetic function, was prohibited in all subjects for at least 3 h before MIBG examination. A dose of 111 MBq of commercially available MIBG (Daiichi Radioisotopes Labs, Ltd., Tokyo, Japan) was administered intravenously after the patient lay in bed

undisturbed for at least 15 min. Anterior planar images were acquired 15 min after injection of ^{123}I-MIBG, and stored in a 64 × 64 matrix with a scintillation camera (ZLC 7500; Siemens, Solana, Sweden) equipped with a low-energy, general purpose collimator interfaced to a minicomputer (SCINTIPAC 2400; Shimadzu, Kyoto, Japan). The energy window was set at the 159 keV photopeak of ^{123}I. The region of interest (ROI) was placed on the upper mediastinum and on the right and left lungs in planar images. Referring to the isocount line, ROIs corresponding to the contours of the right and left lungs were assigned manually. Total counts of each lung were measured, and the geometric mean was calculated as counts per pixel. To quantify the degree of lung uptake of ^{123}I-MIBG, lung to upper mediastinum ratio in ^{123}I-MIBG uptake (LMR) was measured in the right and left lungs. The technical method of lung uptake of ^{123}I-MIBG was similar to those reported previously [21,24,25]. The LMR was examined to determine the correlations with parameters of pulmonary function test or pulmonary haemodynamics.

2.3. *Statistical analysis*

The data are shown as means ± SEM. Unpaired *t* test analysis of variance was used to analyse the differences in clinical and ^{123}I-MIBG scintigraphic data. Correlations between the scintigraphic data and clinical parameters, including pulmonary function test and haemodynamics, were assessed by linear regression analysis. In all analyses, $P < 0.05$ was considered statistically significant.

3. Results

3.1. *Respiratory parameters and ^{123}I-MIBG scintigraphic findings.*

Parameters in pulmonary function tests and pulmonary haemodynamics in patients with COPD are summarised in Table 1 and 2, respectively. In terms of the severity of GOLD classification, 2 cases were Stage II (50% < %FEV1 < 80%), 6 were stage III (30% < %FEV1 < 50%), 11 were stage IV (%FEV1 < 30%). Mean PaO_2 was 68.3 ± 2.2 mmHg (range 52.0 – 93.1) before exercise and decreased significantly to 52.5 ± 2.0 mmHg (range 41.0 – 74.9) after exercise (Table 1). Mean Ppa at rest was 24.1 ± 1.0 mmHg and increased significantly to 43.9 ± 2.2 mmHg after exercise (Table 2). On the other hand, mean LMR was 1.17 ± 0.03 (range 0.99 – 1.36) in the present study. We calculated the relationships between the parameters in pulmonary function test and MIBG scintigraphic images, and the data are summarised in Table 3. In terms of the relationship with the parameters in pulmonary function test, the lung uptake of ^{123}I-MIBG did not show a significant correlation with the severity of airflow limitation or the diffusion capacity in pulmonary function tests.

3.2. *Interaction of ^{123}I-MIBG lung uptake with pulmonary haemodynamics*

The interaction of ^{123}I-MIGB lung uptake with pulmonary haemodynamics was calculated and the data are summarised in Table 4. As likely in parameters of pulmonary function test, there were no significant correlations between ^{123}I-MIBG lung uptake and pulmonary haemodynamic parameters at rest and during exercise in patients with COPD. However, the ^{123}I-MIBG lung uptake showed a negative correlation with the % increase in

pulmonary artery pressure during exercise (Ppa during exercise – Ppa at rest)/Ppa) (Figure 1). Correlations between the % increase in Ppa and each parameter in pulmonary function test were also evaluated. However, there were no significant relationships between the ^{123}I-MIBG lung uptake and these parameters.

Thus, ^{123}I-MIBG lung uptake showed a significant correlation with exercise-induced pulmonary hypertension in patients with COPD.

4. Discussion

In the present study, early lung uptake of ^{123}I-MIBG was not significantly correlated with the parameters of pulmonary function tests or pulmonary artery pressure at rest. In addition, the parameters of pulmonary function tests, including PaO_2, also failed to estimate the pulmonary haemodynamics at rest, during exercise and the changes during exercise. However, the changes in pulmonary artery pressure during exercise were significantly correlated with lung uptake of ^{123}I-MIBG in patients with COPD. These findings suggest that early lung uptake of ^{123}I-MIBG is a useful radioscintigraphic method for semiquantitative assessment of pulmonary vascular status, especially exercise-induced pulmonary hypertension in patients with COPD.

In a previous study in our laboratory, the mean value of early lung accumulation of ^{123}I-MIBG in normal healthy volunteers was 1.45 ± 0.03 [24]. The mean value of LMR in subjects with COPD in the present study (1.17 ± 0.03) was less than that in the normal controls, which was consistent with the report by Arao *et al.* [21]. Thus, we confirmed that early pulmonary ^{123}I-MIBG accumulation was significantly decreased in patients with COPD compared with normal subjects. Arao *et al.* [21] examined the late phase of ^{123}I-MIBG accumulation as well as the early phase, and reported that the lung washout ratio of MIBG was correlated with DLCO/VA and PaO_2 in patients with COPD. Although the washout ratio was not evaluated in the present study, the washout of ^{123}I-MIBG may be a more suitable indicator of clinical manifestations, especially pulmonary function parameters, in

patients with COPD than early ^{123}I-MIBG uptake.

However, we found that early accumulation of ^{123}I-MIBG could be a predictor of exercise-induced pulmonary hypertension in patients with COPD. Early accumulation of ^{123}I-MIBG may be dependent on the pulmonary vascular surface area as well as endothelial cell function. In rats with an experimentally decreased pulmonary vascular surface, a linear relationship was found between reduced MIBG uptake and loss of pulmonary vascular area [8]. Therefore, the decrease in early ^{123}I-MIBG accumulation observed in the present study may reflect a reduced pulmonary vascular area in patients with COPD. The destruction of vascular area due to emphysematous alterations is a contributing factor to the development of pulmonary hypertension at rest and/or during exercise [14-19]. We have shown previously that the increase in pulmonary hypertension during exercise is prominent in patients with severe air flow limitation (< 35% of FEV1), but is not correlated with the parameters of pulmonary function tests at rest, such as FEV1 and DLCO [23]. These findings were consistent with those of other previous studies [26,27]. In contrast, improvements in airflow limitation by lung volume reduction surgery failed to relieve pulmonary hypertension during exercise in patients with COPD [22,27]. Therefore, neither pulmonary function test parameters nor other clinical methods are available for assessment of exercise-induced pulmonary hypertension in patients with COPD. Furthermore, other specific biomarkers or methods useful for evaluating endothelial cell dysfunction or loss of vascular area in patients with COPD were limited in clinical studies. The mechanisms underlying the decreased

^{123}I-MIBG lung uptake in the early phase and exercise induced pulmonary hypertension in patients with COPD remain uncertain, but we suggest that early ^{123}I-MIBG lung uptake evaluation may be a useful, semiquantitative and noninvasive assessment for pulmonary hypertension during exercise in patients with COPD. In future, further studies to define the critical values of the decreased ^{123}I-MIBG lung uptake suggesting the presence of pulmonary hypertension in patients with COPD are needed.

Several previous studies, including those performed in our laboratory, showed that pulmonary hypertension during exercise is a predictive factor of the development of persistent pulmonary hypertension in patients with COPD [22,23,26,27]. The elevation of pulmonary artery pressure during exercise is a contributing factor for exercise limitation in patients with COPD [23]. Thus, pulmonary hypertension is likely to be latent and can easily be unmasked by exercise. Right-heart catheterisation is the gold standard for diagnosis of pulmonary hypertension in patients with COPD. However, because it is an invasive procedure, it is not routinely recommended for use in assessment of patients with COPD. Sakamaki *et al.* [30] reported that decreased heart ^{123}I-MIBG imaging was correlated with the severity of pulmonary hypertension in patients with primary and chronic thromboembolic pulmonary hypertension. The results of this previous study in addition to our results suggest that scintigraphic examination of ^{123}I-MIBG acclimatisation in the heart and lung could be a reliable means of assessing several the clinical condition of pulmonary circulation in cases of pulmonary disease.

In summary, we demonstrated that the decreased uptake of ^{123}I-MIBG

was correlated with the severity of pulmonary hypertension during exercise in patients with COPD. Evaluation by lung uptake of ^{123}I-MIBG may be a useful noninvasive means of estimating pulmonary vascular status in various pulmonary diseases.

Conflicts of interest: None.

Statement: Tomonobu Koizumi, and Kenji Tsushima invested right-heart catheterisation and exercise test. Kazuhisa Urushihata, Masayuki Hanaoka and Tadashige Fujii examined lung uptake of ^{123}I-MIBG. Keisaku Fujimoto analysed the pulmonary function test results. Keishi Kubo organised the study design.

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Figure Legends

Figure 1

Relationship between % changes in pulmonary artery pressure during exercise and at rest and ^{123}I-MIBG lung uptake in patients with COPD.

LMR: lung to mediastinal ratio in ^{123}I-MIBG accumulation.

Table 1

Pulmonary function test

Parameters in pulmonary function test	Values
VC (l)	2.61 ± 0.09
% VC (% predicted)	78.1 ± 2.2
FVC (l)	2.35 ± 0.13
% FVC (% predicted)	69.9 ± 3.8
FEV1 (l)	0.76 ± 0.08
FEV1%	34.9 ± 2.1
% FEV1 (% predicted)	30.7 ± 3.7
% RV (% predicted)	209.3 ± 15.8
DLco ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	9.8 ± 0.9
% DLco (% predicted)	40.3 ± 4.1
DLco/VA ($ml \cdot min^{-1} \cdot mmHg^{-1} \cdot l^{-1}$)	1.69 ± 0.20
PaO_2 at rest	68.3 ± 2.2
PaO_2 during exercise	52.5 ± 2.0

Values were mean ± SEM. VC, vital capacity, FVC, forced vital capacity, FEV1, forced expiratory volume in 1s, RV, residual volume, DLco, carbon monoxide diffusing capacity, DLco/VA, carbon monoxide diffusing capacity/alveolar volume, Pao_2, partial arterial oxygen tension.

Table 2

Pulmonary haemodynamics at rest and during exercise

Pulmonary Hemodynamics	at rest	during exercise
Pulmonary artery pressure (mmHg)	24.1 ± 1.0	43.9 ± 2.2
Cardiac index (l ・ min^{-1} ・ m^{-2})	3.72 ± 0.26	5.26 ± 0.28
Pulmonary occlusive pressure (mmHg)	9.0 ± 0.6	19.4 ± 1.8

Values were mean ± SEM.

Table 3

Correlation between parameters in pulmonary function test and ^{123}I-MIBG lung uptake in patients with COPD.

Parameters in pulmonary function test	Correlation with ^{123}I-MIBG lung uptake	
	p value	R
VC (l)	0.23	-0.18
% VC (% predicted)	0.29	-0.14
FVC (l)	0.41	0.06
% FVC (% predicted)	0.33	-0.11
FEV1 (l)	0.19	-0.21
FEV1%	0.29	-0.24
% FEV (% predicted)	0.42	-0.05
% RV (% predicted)	0.11	0.30
DLCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	0.42	-0.05
% DLCO (% predicted)	0.38	-0.07
DLCO/VA ($ml \cdot min^{-1} \cdot mmHg^{-1} \cdot l^{-1}$)	0.39	-0.07

Values were mean ± SEM. VC, vital capacity, FVC, forced vital capacity, FEV1, forced expiratory volume in 1s, RV, residual volume, DLco, carbon monoxide diffusing capacity, DLco/VA, carbon monoxide diffusing capacity/alveolar volume.

Table 4

Correlation between parameters in pulmonary haemodynamics and ^{123}I-MIBG lung uptake in patients with COPD.

Parameters in pulmonary hemodynamics	Correlation with ^{123}I-MIBG lung uptake	
	p value	R
Pulmonary artery pressure		
at rest	0.08	0.34
during exercise	0.32	-0.12
% change	0.02	-0.47
Cardiac index		
at rest	0.07	0.35
during exercise	0.21	-0.16
% change	0.20	0.20
Pulmonary occlusive pressure		
at rest	0.16	0.25
during exercise	0.34	0.10
% change	0.19	-0.22
PaO_2		
at rest	0.41	-0.06
during exercise	0.16	0.24
% change	0.06	-0.37

Values were mean ± SEM. Pao_2, partial arterial oxygen tension.

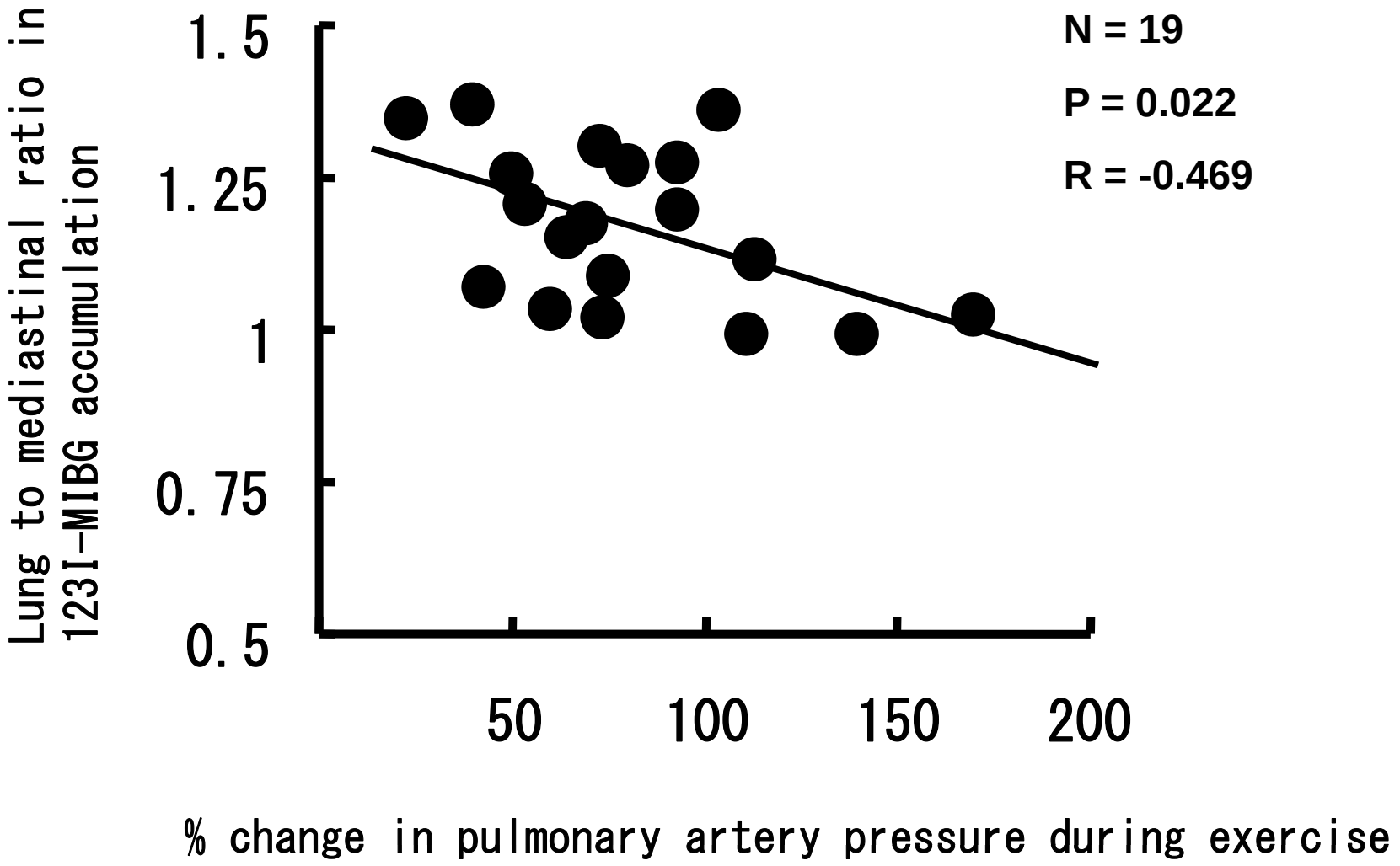
Lung to mediastinal ratio in 123I-MIBG accumulation
1.5
1.25
1
0.75
0.5
50
100
150
200
N = 19
P = 0.022
R = -0.469
% change in pulmonary artery pressure during exercise

Figure 1