OPEN

Original article

Nuclear Medicine Communications

# Three-dimensional fractal analysis of $^{99m}$Tc-MAA SPECT images in chronic thromboembolic pulmonary hypertension for evaluation of response to balloon pulmonary angioplasty: association with pulmonary arterial pressure

Yasuhiro Maruoka[a], Michinobu Nagao[d], Shingo Baba[a], Takuro Isoda[a], Yoshiyuki Kitamura[a], Yuzo Yamazaki[a], Koichiro Abe[d], Masayuki Sasaki[b], Kohtaro Abe[c] and Hiroshi Honda[a]

***Objective*** Balloon pulmonary angioplasty (BPA) is used for inoperable chronic thromboembolic pulmonary hypertension (CTEPH), but its effect cannot be evaluated noninvasively. We devised a noninvasive quantitative index of response to BPA using three-dimensional fractal analysis (3D-FA) of technetium-99m-macroaggregated albumin ($^{99m}$Tc-MAA) single-photon emission computed tomography (SPECT).

***Patients and methods*** Forty CTEPH patients who underwent pulmonary perfusion scintigraphy and mean pulmonary arterial pressure (mPAP) measurement by right heart catheterization before and after BPA were studied. The total uptake volume (TUV) in bilateral lungs was determined from maximum intensity projection $^{99m}$Tc-MAA SPECT images. Fractal dimension was assessed by 3D-FA. Parameters were compared before and after BPA, and between patients with post-BPA mPAP more than 30 mmHg and less than or equal to 30 mmHg. Receiver operating characteristic analysis was carried out.

***Results*** BPA significantly improved TUV (595 ± 204–885 ± 214 ml, $P<0.001$) and reduced the laterality of uptake (238 ± 147–135 ± 131 ml, $P<0.001$). Patients with poor therapeutic response (post-BPA mPAP ≥ 30 mmHg, $n=16$) showed a significantly smaller TUV increase ($P=0.044$) and a significantly greater post-BPA fractal dimension ($P<0.001$) than the low-mPAP group. Fractal dimension correlated with mPAP values before and after BPA ($P=0.013$ and 0.001, respectively). A post-BPA fractal dimension threshold of 2.4 distinguished between BPA success and failure with 75% sensitivity, 79% specificity, 78% accuracy, and area under the curve of 0.85.

***Conclusion*** 3D-FA using $^{99m}$Tc-MAA SPECT pulmonary perfusion scintigraphy enables a noninvasive evaluation of the response of CTEPH patients to BPA. *Nucl Med Commun* 38:480–486 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

Nuclear Medicine Communications 2017, **38**:480–486

**Keywords:** $^{99m}$Tc-MAA SPECT, balloon pulmonary angioplasty, chronic thromboembolic pulmonary hypertension, fractal analysis

Departments of [a]Clinical Radiology, [b]Health Sciences, [c]Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka and [d]Department of Diagnostic Imaging and Nuclear Medicine, Tokyo Women's Medical University, Tokyo, Japan

Correspondence to Yasuhiro Maruoka, MD, Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka City, Fukuoka 812-8582, Japan
Tel: +81 92 642 5695; fax: +81 92 642 5820;
e-mail: ymaruoka@radiol.med.kyushu-u.ac.jp

**Received** 4 November 2016 **Revised** 14 March 2017 **Accepted** 24 March 2017

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as pulmonary hypertension because of stenosis or obstruction of the pulmonary arteries, and can cause right heart failure and death [1,2]. The prognosis of CTEPH patients with a mean pulmonary arterial pressure (mPAP) of more than 30 mmHg is poor [3]. Although pulmonary thromboendarterectomy has been established as the definitive surgical treatment for CTEPH, ~40% of cases are inoperable because of surgically inaccessible distal thrombi or comorbid illness [4,5]. In these cases, balloon pulmonary angioplasty (BPA) is used as an alternative strategy for improving hemodynamic parameters and symptoms [6–8]. The treatment response to BPA is evaluated by measuring mPAP by cardiac catheterization in these high-risk patients. Therefore, there remains a need for simple, noninvasive, quantitative tools that can be used in an outpatient setting to evaluate the therapeutic effects of BPA.

Recently, the evaluation of image heterogeneity in nuclear medicine imaging has been used in the differential diagnosis and prognosis of various diseases such as pulmonary nodules, non-small-cell lung cancer, and esophageal cancer [9–11]. Furthermore, fractal analysis has been proposed as a method for assessing heterogeneity in single-photon emission computed tomography (SPECT) images [10,12,13]. For example, three-dimensional fractal analysis (3D-FA) of SPECT images has been used to quantify the distribution of cerebral blood flow in patients with Alzheimer's disease [12] and evaluate emphysematous lung quantitatively [13]. Pulmonary perfusion scintigraphy is useful in the diagnosis of CTEPH [14], but its value in determining the therapeutic effects of BPA remains unclear.

The aim of this study was to develop a noninvasive, quantitative index for assessing the response to BPA in CTEPH patients using 3D-FA of technetium-99m-macroaggregated albumin ($^{99m}$Tc-MAA) SPECT as pulmonary perfusion scintigraphy.

## Patients and methods

### Patient selection

This single-center, retrospective observational study was approved by the institutional review board of Kyushu University and written informed consent from each patient was obtained. Forty-six patients from our hospital with a diagnosis of inoperable CTEPH between August 2012 and October 2015 were considered for this study. All patients were evaluated by a multidisciplinary team of pulmonologists, surgeons, and radiologists using pulmonary ventilation/perfusion scintigraphy, conventional and computed tomography (CT) pulmonary angiography, and right heart catheterization (RHC). All patients also underwent a complete workup, including echocardiography, to exclude left-sided heart disease, and high-resolution CT, to exclude pulmonary diseases as underlying causes of pulmonary hypertension.

Inclusion criteria comprised a diagnosis of CTEPH (mPAP $\geq$ 25 mmHg) and eligibility for BPA, as per established definitions and criteria [8,15], and a minimum follow-up of 3 months after BPA. Pulmonary perfusion scintigraphy findings were judged as CTEPH by the consensus of two nuclear medicine specialists with both planar and SPECT/CT images. Inoperable CTEPH was defined as (a) distal, surgically inaccessible vascular occlusions, or (b) pulmonary hypertension severity greater than that predicted from the degree of vascular obstruction. Exclusion criteria were surgical indications for pulmonary thromboendarterectomy, informed refusal, and pregnancy or breast-feeding in women.

After applying these selection criteria, a total of 40 patients were enrolled in this study. The study outline is presented in Fig. 1. Pulmonary vasodilator therapy was fixed at least 1 month before BPA and remained unchanged until the follow-up $^{99m}$Tc-MAA SPECT and RHC. $^{99m}$Tc-MAA SPECT and the first RHC were performed, with mPAP measurement, within 1 month before the BPA session. A follow-up $^{99m}$Tc-MAA SPECT was also performed at 3–6 months after BPA, and within 1 month of this, a follow-up RHC was also performed to measure mPAP [16]. At the end of the study, therapeutic outcomes of BPA were assessed by dividing patients into those with a mean post-BPA mPAP more than 30 mmHg (high-mPAP group) and those with a mean post-BPA mPAP less than or equal to 30 mmHg (low-mPAP group) [17]. Table 1 summarizes the baseline characteristics of the patients.

### Pulmonary perfusion scintigraphy

All patients underwent a planar scan and SPECT/CT with a hybrid camera involving a dual-head c-camera and a six-slice spiral CT (Symbia T6; Siemens, Hoffman Estates, Illinois, USA). Scans were performed after an intravenous injection of 185 MBq (5 mCi) $^{99m}$Tc-MAA. Anterior planar images were acquired with low – medium-energy parallel-hole collimators, a 256 × 256 matrix, and a 140 keV photopeak with 15% windows. SPECT images were acquired with 60 projections (a duration of 20 s at each projection), low – medium-energy parallel-hole collimators, a 128 × 128 matrix, and a 140 keV photopeak with 15% windows.

Next, 3D ordered-subset expectation–maximization iterative reconstruction was performed, with eight iterations and 10 subsets; CT-based attenuation correction was applied without scattered correction. CT scans were acquired at 130 keV, 30 mAs, or less (for minimization of radiation exposure) using a 512 × 512 matrix and a 2 × 2.5 mm collimation.

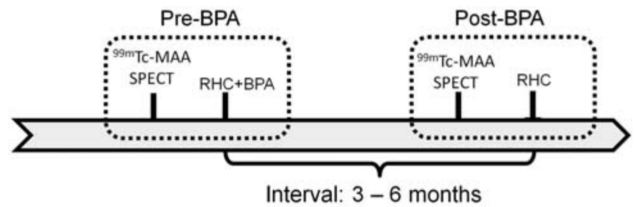
### $^{99m}$Tc-MAA SPECT image analysis

A histogram of voxel radioactivity was generated from the maximum intensity projection (MIP) $^{99m}$Tc-MAA SPECT images using a dedicated work station (Synapse Vincent; Fujifilm Medical, Tokyo, Japan) (Fig. 2a). The total uptake volume (TUV) in bilateral lungs was measured as the areas with a radioactivity higher than a cutoff level of 30% of the maximum value on the histogram; the 30% cutoff level was selected as the TUV that most closely approximated the volume of MIP $^{99m}$Tc-MAA SPECT images at that level (Fig. 2b). The absolute value of the difference between the TUV in the right and left lungs was also measured to determine the laterality of the uptake volume. For 3D-FA, the natural logarithms of the volume of voxels with a radioactivity level higher than the cutoff level were plotted in relation to the natural logarithms of the cutoff levels (30, 35, 40, 45, and 50% of the maximum voxel radioactivity) (Fig. 3). The magnitude of the slopes of linear regression was determined as the fractal dimension [12].

### Statistical analysis

Continuous data were expressed as mean ± SD. Paired *t*-tests were used to compare pre-BPA and post-BPA values of TUV, the laterality of uptake volume, and the fractal dimension. Mann – Whitney *U*-tests were used to

**Fig. 1**




Study outline. $^{99m}$Tc-MAA SPECT and right heart catheterization were performed within 1 month of balloon pulmonary angioplasty in 40 chronic thromboembolic pulmonary hypertension patients. Patients were followed up for a minimum of 3 months and $^{99m}$Tc-MAA SPECT and right heart catheterization were then again performed to measure mPAP and assess therapeutic response to balloon pulmonary angioplasty. $^{99m}$Tc-MAA, technetium-99m-macroaggregated albumin. CT, computed tomography; FDG, fluorodeoxyglucose; SPECT, single-photon emission computed tomography.

**Table 1 Baseline characteristics of patients**

| Characteristics | Values |
|---|---|
| Age (years) | |
| Mean ± SD | 61 ± 11 |
| Median/range | 61/42–81 |
| Sex | |
| Men/women | 8/32 |
| Pre-BPA WHO functional class | |
| I/II/III/IV | 0 (0)/10 (25)/27 (67)/3 (8) |
| Post-BPA WHO functional class | |
| I/II/III | 3 (8)/35 (87)/2 (5)/0 (0) |
| 6-min walk distance before BPA (m) | |
| Mean ± SD | 383 ± 93 |
| Median/range | 390/200–570 |
| 6-min walk distance after BPA (m) | |
| Mean ± SD | 461 ± 93* |
| Median/range | 450/245–615 |
| Pre-BPA mPAP (mmHg) | |
| Mean ± SD | 42 ± 9 |
| Median/range | 41/28–60 |
| Post-BPA mPAP (mmHg) | |
| Mean ± SD | 29 ± 6** |
| Median/range | 28/18–47 |
| Treatment area | |
| Right lung: upper/middle/lower | 37 (93)/29 (73)/40 (100) |
| Left lung: upper/lower | 23 (58)/31 (78) |

BPA, balloon pulmonary angioplasty; mPAP, mean pulmonary arterial pressure.
*$P < 0.001$ vs. the 6-min walk distance before BPA.
**$P < 0.001$ vs. pre-BPA mPAP.

compare TUV, the laterality of uptake volume, TUV increase, and fractal dimension between high-mPAP and low-mPAP groups (after BPA). The Spearman correlation test was used to assess correlations between TUV, fractal dimension, and mPAP. The predictability of therapeutic success after BPA (low mPAP after BPA) on the basis of these parameters was determined from receiver operating characteristic analysis. Analyses were carried out using JMP statistical software (version 12.0; SAS Institute Inc., Cary, North Carolina, USA). A $P$ value of less than 0.05 was considered significant.

## Results

### Comparison of pre-BPA and post-BPA $^{99m}$Tc-MAA SPECT parameters

Pre-BPA TUV, laterality of uptake volume, and fractal dimension were 595 ± 204, 238 ± 147 ml, and 2.3 ± 0.5, respectively, in the entire study group ($n = 40$). After BPA, these values were 885 ± 214, 135 ± 131 ml, and 2.2 ± 0.4, respectively. TUV was significantly greater after BPA than before BPA ($P < 0.001$; Table 2), and the laterality of the uptake volume was significantly smaller after BPA than before BPA ($P < 0.001$; Table 2). There was no significant difference between pre-BPA and post-BPA fractal dimension ($P = 0.59$).

### Comparison of $^{99m}$Tc-MAA SPECT parameters between low-mPAP and high-mPAP groups

After BPA, 24 of 40 patients had low mPAP and the remaining 16 patients had high mPAP. There were no significant differences in the pre-BPA measures (TUV, laterality of uptake volume, fractal dimension) between the two groups. Similarly, there were no significant differences in post-BPA TUV and post-BPA laterality of uptake volume between the groups. However, the increase in TUV after BPA was significantly greater in the low-mPAP group than in the high-mPAP group (337 ± 209 vs. 219 ± 196 ml, $P = 0.044$; Table 3 and Fig. 4a). The fractal dimension was also significantly lower in the low-mPAP group (2.0 ± 0.3) than in the high-mPAP group (2.5 ± 0.4, $P < 0.001$; Table 3 and Fig. 4b).

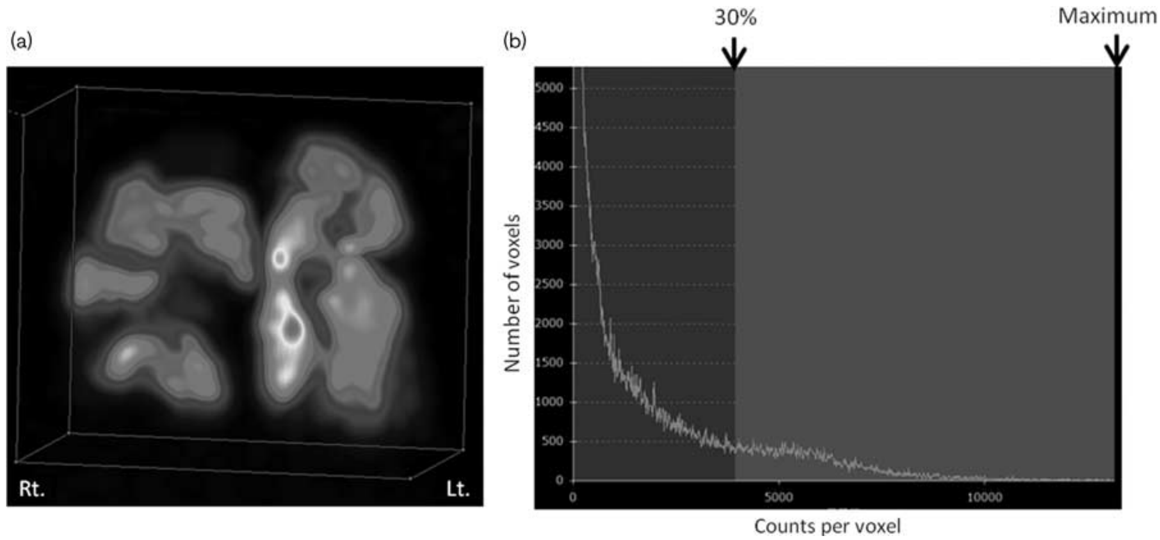
### Correlations between TUV, fractal dimension, and mPAP

There was no significant correlation between TUV and mPAP either before BPA ($P = 0.42$) or after BPA ($P = 0.94$). There was a significant positive linear correlation between pre-BPA fractal dimension and pre-BPA mPAP ($r = 0.39$, $P = 0.013$; Fig. 5a) and between post-BPA fractal dimension and post-BPA mPAP ($r = 0.49$, $P = 0.001$; Fig. 5b). However, there was no significant correlation between pre-BPA fractal dimension and post-BPA mPAP ($P = 0.96$).

### Value of increase in TUV and fractal dimension for predicting therapeutic success after BPA

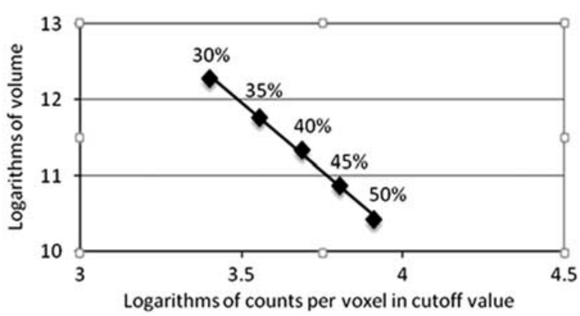
Receiver operating characteristic analysis showed that cutoff values of a TUV increase of 112 ml and a post-BPA fractal dimension of 2.4 were optimal for differentiating between the low-mPAP and the high-mPAP groups, with 44% (7/16) and 75% (12/16) sensitivity, 96% (23/24) and 79% (19/24) specificity, 75% (30/40) and 78% (31/40) accuracy, and areas under the curve of 0.69 and 0.85, respectively. Representative pulmonary perfusion scintigraphy images in patients with a good therapeutic response after BPA are presented in Fig. 6.

**Fig. 2**




The region of interest was placed to include the bilateral lung on maximum intensity projection $^{99m}$Tc-MAA SPECT images (a). Total uptake volume in the bilateral lungs was measured as the areas with a radioactivity higher than the cutoff level of 30% of the maximum value on a histogram of radioactivity voxels generated from maximum intensity projection $^{99m}$Tc-MAA SPECT images (b). $^{99m}$Tc-MAA, technetium-99m-macroaggregated albumin; SPECT, single-photon emission computed tomography.

**Fig. 3**




The natural logarithms of the volume of voxels with a radioactivity higher than the cutoff level were plotted in relation to the natural logarithms of the cutoff levels at 30, 35, 40, 45, and 50% of the maximum radioactivity voxels. The slopes of linear regression were determined as the goodness-of-fit ($R^2$) values. The magnitude of the slopes of linear regression was determined as the fractal dimension.

**Table 2 Comparison of $^{99m}$Tc-MAA SPECT parameters before and after BPA**

| | Before BPA | After BPA | *P* value |
|---|---|---|---|
| TUV (ml) | 595 ± 204 | 885 ± 214 | < 0.001 |
| Laterality of uptake volume (ml) | 238 ± 147 | 135 ± 131 | < 0.001 |
| Fractal dimension | 2.3 ± 0.5 | 2.2 ± 0.4 | 0.59 |

$^{99m}$Tc-MAA, technetium-99m-macroaggregated albumin; BPA, balloon pulmonary angioplasty; SPECT, single-photon emission computed tomography; TUV, total uptake volume.

## Discussion

This study aimed to develop a new quantitative index of pulmonary perfusion scintigraphy using fractal analysis to predict therapeutic success after BPA in CTEPH patients. BPA significantly improved TUV and reduced laterality of the uptake volume in our case series, showing that recanalization of pulmonary artery stenosis by BPA improved pulmonary perfusion and increased pulmonary perfusion volume. Moreover, we show that $^{99m}$Tc-MAA SPECT is a useful modality for quantifying the therapeutic effect of BPA visually and objectively.

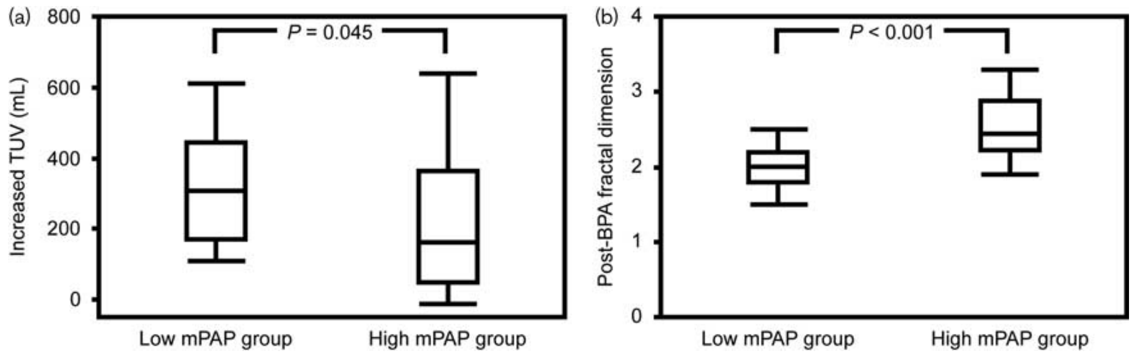
**Table 3 Comparison of $^{99m}$Tc-MAA SPECT parameters after BPA**

| | Low-mPAP group (*n* = 24) | High-mPAP group (*n* = 16) | *P* value |
|---|---|---|---|
| Pre-BPA uptake volume (ml) | | | |
| TUV | 563 ± 219 | 644 ± 175 | 0.12 |
| Laterality | 271 ± 158 | 188 ± 116 | 0.08 |
| Pre-BPA fractal dimension | 2.2 ± 0.5 | 2.3 ± 0.6 | 0.61 |
| Post-BPA uptake volume (ml) | | | |
| TUV | 899 ± 227 | 862 ± 197 | 0.64 |
| Laterality | 151 ± 138 | 112 ± 122 | 0.19 |
| Increased TUV after BPA (ml) | 337 ± 209 | 219 ± 196 | 0.045 |
| Post-BPA fractal dimension | 2.0 ± 0.3 | 2.5 ± 0.4 | < 0.001 |

$^{99m}$Tc-MAA, technetium-99m-macroaggregated albumin; BPA, balloon pulmonary angioplasty; mPAP, mean pulmonary arterial pressure SPECT, single-photon emission computed tomography; TUV, total uptake volume.

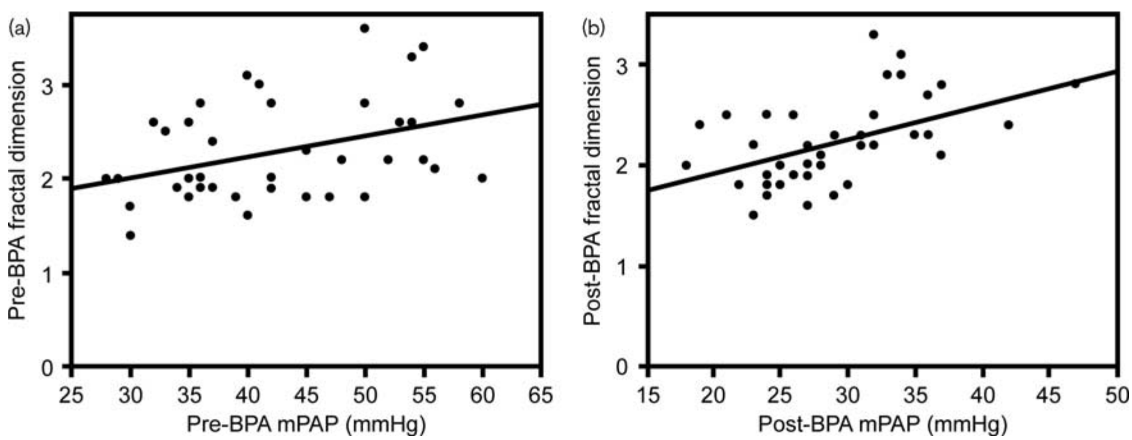
A significant correlation was observed between fractal dimension and mPAP values, both before BPA and after BPA, suggesting that the image heterogeneity of pulmonary perfusion scintigraphy correlates with mPAP in CTEPH patients. Image heterogeneity of pulmonary perfusion scintigraphy probably represents the imbalance

**Fig. 4**




Box-and-whisker plots of the increase in the total uptake volume (TUV) increase and postballoon pulmonary angioplasty fractal dimension in the low-mean pulmonary arterial pressure (mPAP) and high-mPAP groups. The boxes, bisecting lines, and the horizontal bars represent the interquartile range, the median value, and the 10−90% range, respectively. The TUV increase was significantly lower in the high-mPAP group than in the low-mPAP group ($P = 0.044$) (a). The postballoon pulmonary angioplasty fractal dimension was significantly higher in the high-mPAP group than in the low-mPAP group ($P < 0.001$) (b).

**Fig. 5**



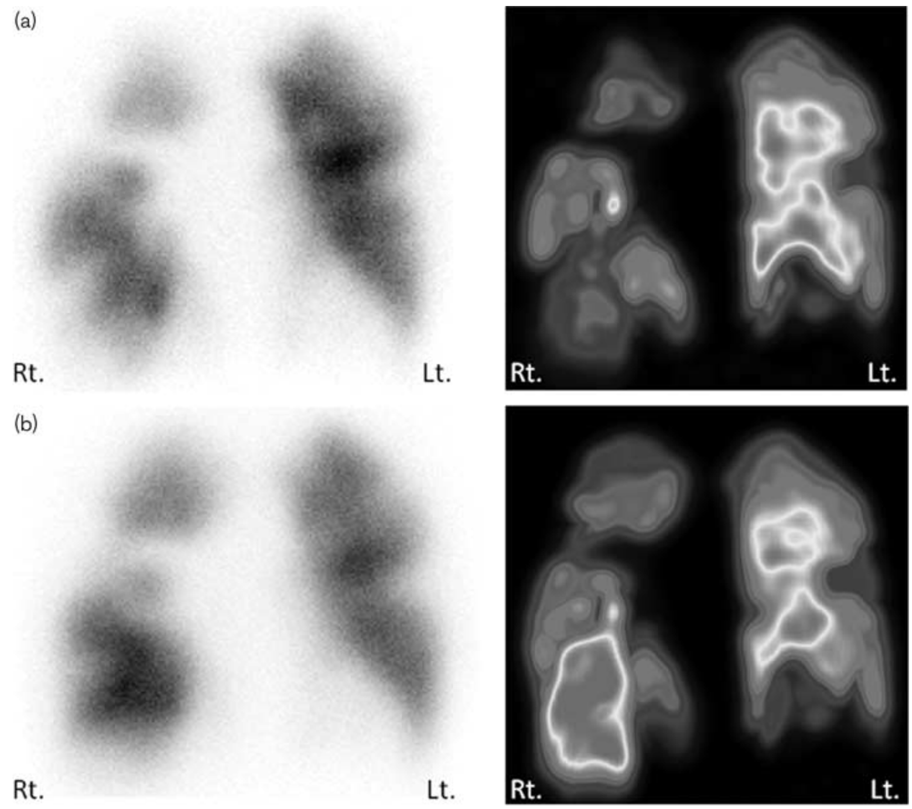

Correlation between fractal dimension and mean pulmonary arterial pressure (mPAP), preballoon pulmonary angioplasty (BPA; $r = 0.39$, $P = 0.013$) (a) and after BPA ($r = 0.49$, $P = 0.001$) (b).

in pulmonary perfusion in CTEPH patients, which can increase pulmonary vascular resistance and increase mPAP. A recent study has reported that a decline in pulmonary vascular resistance after BPA correlated significantly with reduced right ventricular volume [18]. Thus, fractal dimension can be valuable for assessing disease progression in CTEPH and for monitoring the efficacy of BPA in CTEPH patients. However, there was no significant correlation between pre-BPA fractal dimension and post-BPA mPAP, indicating that pre-BPA fractal dimension is not predictive of the therapeutic effect of BPA.

Patients with a poor therapeutic response to BPA (high-mPAP group) showed a significantly smaller TUV increase and a significantly greater post-BPA fractal dimension than those in the low-mPAP group. This suggests that a smaller TUV increase and persistent image heterogeneity on $^{99m}$Tc-MAA SPECT after BPA may indicate the need for additional treatment after BPA. Specifically, a cutoff of post-BPA fractal dimension of 2.4 could optimally distinguish between sufficient and insufficient response after BPA with 75% sensitivity, 79% specificity, 78% accuracy, and an area under the curve of 0.85, suggesting that post-BPA fractal dimension could be used as an outcome metric in the clinical management of CTEPH after BPA.

The study had several limitations. First, the cutoff level of 30% of the maximum radioactivity value in $^{99m}$Tc-MAA SPECT image analysis for estimating TUV was based on visual observation of a close match between TUV and total lung volume in MIP images. However, the adequacy of this selected cutoff level has not been

**Fig. 6**




A 63-year-old woman with chronic thromboembolic pulmonary hypertension who underwent balloon pulmonary angioplasty (BPA). (a) Planar image and maximum intensity projection SPECT of pulmonary perfusion scintigraphy before BPA show multiple perfusion defects in the bilateral lung. The patient's pre-BPA mean pulmonary arterial pressure (mPAP), pre-BPA TUV, and pre-BPA fractal dimension were 35 mmHg, 672 ml, and 2.6, respectively. (b) Planar image and maximum intensity projection SPECT of pulmonary perfusion scintigraphy 10 months after BPA show improvements of $^{99m}$Tc-MAA uptake in the right lung. The patient's post-BPA mPAP, post-BPA TUV, and post-BPA fractal dimension were 26 mmHg, 862 ml, and 2.2, respectively. $^{99m}$Tc-MAA, technetium-99m-macroaggregated albumin; SPECT, single-photon emission computed tomography.

tested or validated. Second, the number of CTEPH patients analyzed in the present study was relatively small and from a single center. Further studies are needed to confirm our findings by evaluating the outcomes of CTEPH patients during long-term follow-up in multicenter studies.

## Conclusion

CTEPH patients with a low mPAP after BPA showed greater increases in TUV and less heterogeneity on $^{99m}$Tc-MAA SPECT than those with higher mPAP. 3D-FA is a feasible and noninvasive technique for evaluating response to BPA in CTEPH patients.


## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.


## References


1 Lang I. Chronic thromboembolic pulmonary hypertension: a distinct disease entity. *Eur Respir Rev* 2015; **24**:246–252.
2 Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest* 1982; **81**:151–158.
3 Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, *et al.* Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest* 2001; **119**:818–823.
4 Kim NH. Assessment of operability in chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc* 2006; **3**:584–588.
5 Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, *et al.* Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; **124**:1973–1981.
6 Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. *Circulation* 2014; **130**:508–518.
7 Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, *et al.* Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2013; **62** (Suppl):D92–D99.
8 Ogawa A, Matsubara H. Balloon pulmonary angioplasty: a treatment option for inoperable patients with chronic thromboembolic pulmonary hypertension. *Front Cardiovasc Med* 2015; **2**:4.
9 Van Velden FH, Cheebsumon P, Yaqub M, Smit EF, Hoekstra OS, Lammertsma AA, *et al.* Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. *Eur J Nucl Med Mol Imaging* 2011; **38**:1636–1647.
10 Miwa K, Inubushi M, Wagatsuma K, Nagao M, Murata T, Koyama M, *et al.* FDG uptake heterogeneity evaluated by fractal analysis improves the differential diagnosis of pulmonary nodules. *Eur J Radiol* 2014; **83**:715–719.
11 Tixier F, Le Rest CC, Hatt M, Albarghach N, Pradier O, Metges JP, Corcos L. Intratumor heterogeneity characterized by textural features on baseline

$^{18}$F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. *J Nucl Med* 2011; **52**:369–378.
12 Nagao M, Murase K, Kikuchi T, Ikeda M, Nebu A, Fukuhara R, *et al*. Fractal analysis of cerebral blood flow distribution in Alzheimer's disease. *J Nucl Med* 2001; **42**:1446–1450.
13 Nagao M, Murase K, Yasuhara Y, Ikezoe J. Quantitative analysis of pulmonary emphysema: three-dimensional fractal analysis of single-photon emission computed tomography images obtained with a carbon particle radioaerosol. *Am J Roentgenol* 1998; **171**:1657–1663.
14 Grgic A, Miodek F, Schäfers HJ, Held M, Kaiser R, Khreish F, *et al*. Assessment of operability by means of CTPA and perfusion SPECT in patients with chronic thromboembolic pulmonary hypertension. *Acta Radiol* 2016; **57**:33–40.
15 Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. *Radiology* 1992; **182**:393–398.
16 Hosokawa K, Abe K, Oi K, Mukai Y, Hirooka Y, Sunagawa K. Negative acute hemodynamic response to balloon pulmonary angioplasty does not predicate the long-term outcome in patients with chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2015; **188**:81–83.
17 Fukui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki K, *et al*. Right ventricular reverse remodelling after balloon pulmonary angioplasty. *Eur Respir J* 2014; **43**:1394–1402.
18 Tsugu T, Murata M, Kawakami T, Yasuda R, Tokuda H, Minakata Y, *et al*. Significance of echocardiographic assessment for right ventricular function after balloon pulmonary angioplasty in patients with chronic thromboembolic induced pulmonary hypertension. *Am J Cardiol* 2015; **115**:256–261.