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Research article

Decreased and slower diaphragmatic motion during forced breathing in severe COPD patients: Time-resolved quantitative analysis using dynamic chest radiography with a flat panel detector system

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ABSTRACT

Objective: To assess the diaphragmatic motion in chronic obstructive pulmonary disease (COPD) patients during forced breathing by time-resolved quantitative analysis using dynamic chest radiography and to demonstrate the characteristics and the difference from that in normal subjects.

Materials and methods: Thirty-one COPD patients and a matched control of 31 normal subjects on age, sex, height, and weight, who underwent chest radiographs during forced breathing using dynamic chest radiography, were included in this study. COPD patients were classified based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 1, n = 3; GOLD 2, n = 12; GOLD 3, n = 13; GOLD 4, n = 3). We measured excursions and peak motion speeds of the diaphragms for each participant. We compared the results among GOLD 1/2, GOLD 3/4 groups and normal subjects and investigated associations between the data, and participants' demographics, or pulmonary function.

Results: The excursions of bilateral diaphragms were significantly decreased in the GOLD 3/4 group relative to normal subjects (right, 39.8 ± 15.3 mm vs. 52.7 ± 15.1 mm, $P = 0.030$; left, 43.7 ± 14.0 mm vs. 56.9 ± 15.5 mm, $P = 0.017$; mean ± standard deviation) and the GOLD 1/2 group (right, 39.8 ± 15.3 mm vs. 54.4 ± 16.7 mm, $P = 0.036$; left, 43.7 ± 14.0 mm vs. 60.5 ± 13.9 mm, $P = 0.008$). The peak motion speeds of the left diaphragm in the inspiratory phase were slower in the GOLD 1/2 group than in normal subjects (24.5 ± 8.0 mm/s vs. 33.6 ± 14.0 mm/s, $P = 0.038$), and in the GOLD 3/4 group than in normal subjects (25.6 ± 6.8 mm/s vs. 33.6 ± 14.0 mm/s, $P = 0.067$). The excursions of the diaphragms showed correlation with VC, %VC, and FEV_1, while the peak motion speeds showed no significant correlation with pulmonary function tests.

Conclusions: Time-resolved quantitative analysis of diaphragms with dynamic chest radiography indicated differences in diaphragmatic motion between COPD groups and normal subjects during forced breathing. The excursions of the diaphragms during forced breathing were significantly lower in the GOLD 3/4 group than those in the GOLD 1/2 group and normal subjects.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the known diseases with dysfunction of the diaphragm characterized by chronic obstruction of airflow in the lungs that interferes with normal breathing. COPD is a leading cause of the most deaths from chronic respiratory diseases in non-communicable diseases [1]. COPD is progressive and not fully reversible, but proper management can relieve its symptoms and reduce the risk of death. Dysfunction of diaphragms is considered one of the important causes of dyspnea in COPD patients.

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Lung hyperinflation, reduced elastic recoil, increased airway resistance and chest wall remodeling in COPD can negatively influence on and decrease the diaphragmatic function with a progression of COPD [2]. Dynamics of the diaphragm in COPD patients have been investigated in some previous reports using fluoroscopy, ultrasonography (US), and magnetic resonance imaging (MRI) [3–6]. The role of diaphragmatic dysfunction in the clinical course of COPD has not been fully described yet, and the understanding of the role may lead to better management and future treatment for COPD.

As one of the recent advances in imaging devices, dynamic chest radiography using a flat panel detector (FPD) with a large field of view was recently introduced for clinical use. Dynamic chest radiography provides objective and quantifiable data of diaphragm kinetics by a simple procedure like conventional chest radiography in a standing position, and as low radiation dose as a total of posteroanterior and lateral projections of conventional chest radiography [7–9]. Using this technique, Yamada et al. quantitatively assessed the diaphragmatic movements of normal volunteers and COPD patients during tidal breathing in a standing position, including excursion, speed, and time of movement [10,11]. They demonstrated that COPD patients showed significantly larger excursions and faster inspiratory peak motion speeds of the bilateral diaphragms than normal subjects during tidal breathing [11]. Conversely, smaller diaphragmatic excursions during forced breathing in COPD patients have been reported using fluoroscopy, US and MRI, which are thought to associate with decreased pulmonary function, but the degrees vary depending on reports [3,5,6]. To the best of our knowledge, the dynamics of the diaphragm during forced breathing in COPD patients have not been investigated by time-resolved quantitative analysis using dynamic chest radiography.

The aim of this study was to assess diaphragmatic motion in COPD patients during forced breathing in a standing position by time-resolved quantitative analysis using dynamic chest radiography and demonstrate its usefulness for analysis of diaphragm dynamics.

2. Materials and methods

2.1. Cohort selection

This prospective study was approved by our institutional review board and all participants gave written informed consent before participation. Forty-three consecutive COPD patients who underwent pulmonary function tests in our institution from June 2009 to August 2011 and met the following inclusion criteria as previously reported [11] were recruited in the study: (1) clinical diagnosis of pure COPD based on clinical course, symptoms and the test results (i.e., radiological imaging and pulmonary function tests with post-bronchodilator inhalation) without other respiratory disease such as acute respiratory infection, bronchiectasis or any type of interstitial lung disease; (3) current or ex-smoker; (3) ≥20 years old adults who gave informed consent, including for additional X-ray exposure by dynamic chest radiography estimated to be as much as that of a couple of conventional chest radiographs (no upper age limit); (4) no status of pregnant, potentially pregnant or lactating; (5) scheduled for conventional chest radiography; (6) ability to follow instructions for forced breathing. Patients with incomplete dynamic chest radiography data sets (n = 4) or technically unevaluable datasets by the analysis software described below (n = 8) were excluded. A total of 31 COPD patients were finally included in the analysis. Based on GOLD classification [12], COPD patients were classified into two composite groups: GOLD 1/2 and GOLD 3/4.

As a control, consecutive volunteers who underwent health screening in our institution from May 2013 to February 2014 and met the following inclusion criteria as previously reported [11] were recruited in this study: (1) ≥20 years old adults who gave informed consent, including for additional X-ray exposure by dynamic chest radiography (no upper age limit); (2) scheduled for conventional chest radiography; (3) pulmonary function test results within normal range (i.e., percent vital capacity (%VC) > 80% and FEV_1%, the ratio of forced expiratory volume in one second (FEV_1) to forced VC, > 70%); (4) ability to follow instructions for forced breathing; (5) never smokers; (6) no status of pregnant, potentially pregnant or lactating; (7) no past medical history of respiratory diseases. Volunteers with incomplete dynamic chest radiography datasets or technically unevaluable data sets by the analysis software were excluded. Using propensity score matching to COPD patients with age, sex, height, and weight, 31 healthy control subjects were selected as a matched control group.

All participants underwent pulmonary function tests on the same day of dynamic chest radiography using a pulmonary function instrument with computer processing (DISCOM-21 FX, Chest MI Co, Tokyo, Japan). Parameters of pulmonary function tests were recorded according to the American Thoracic Society guidelines [13]. The heights and weights of the participants were measured, and the body mass index (BMI, weight in kilograms divided by height in meters squared) and the body surface area (BSA, $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$ [Du Bois formula]) were calculated.

2.2. Imaging protocol of dynamic chest radiology

Dynamic chest radiography was performed using a prototype X-ray system (Konica Minolta Inc., Tokyo, Japan), composed of an FPD (PaxScan 4030CB, Varian Medical Systems Inc., Salt Lake City, UT, USA) and a pulsed X-ray generator (DHF-155HII with Cineradiography option, Hitachi Medical Corporation, Tokyo, Japan), in posteroanterior projection in a standing position. Subjects were instructed to inhale and exhale as fully as possible after tidal breathing. The X-ray exposure conditions were as follows: tube voltage, 100 kV; tube current, 50 mA; pulse duration of pulsed X-ray, 1.6–3.2 ms; source-to-image distance, 2 m; additional filter, 0.5 mm Al + 0.1 mm Cu for filtering out soft X-rays. The exposure time was approximately 10–15 s. The pixel size was 388 × 388 μm, the matrix size was 1024 × 768, and the overall image area was 40 × 30 cm. The gray-level range of the images was 16,384 (14 bits), and the signal intensity was proportional to the incident exposure of the X-ray detector. The dynamic image data, captured at 7.5 (COPD patients) or 15 (healthy volunteers) frames/s, were synchronized with the pulsed X-ray. The pulsed X-ray prevented excessive radiation exposure to the subjects. The entrance surface dose was approximately 0.3–1.0 mGy.

2.3. Image analysis

Examples of dynamic chest radiography and analysis are shown in Figs. 1–3. (Corresponding video materials are available in Supplementary Videos 1–3).

Diaphragmatic motions on sequential chest radiographs during forced breathing were analyzed using prototype software (Konica Minolta Inc., Tokyo, Japan) installed in an independent workstation (Operating system: Windows 7 Professional 64-bit Service Pack 1; Microsoft, Redmond WA; CPU: Intel® Core™ i5-6500, 3.20 GHz; random access memory, 16 GB). The edges of the diaphragms on each dynamic chest radiograph were automatically determined by edge detection using a Prewitt Filter. The highest points of bilateral diaphragms were automatically tracked by the template-matching technique throughout the respiratory phase, and the vertical excursions of the bilateral diaphragm were calculated. The baseline positions of the diaphragms were defined as the positions at the end of the expiratory phase of tidal breathing just before forced inspiration. Baseline positions, maximal inspiratory positions, and maximal expiratory positions from the top of the images of bilateral diaphragms were recorded. The motion speeds of each diaphragm during forced breathing were calculated based on the position and time by the differential method. The beginnings of inspiratory and expiratory phases were set at the time when the motion speed of the diaphragm changed from negative to positive just before

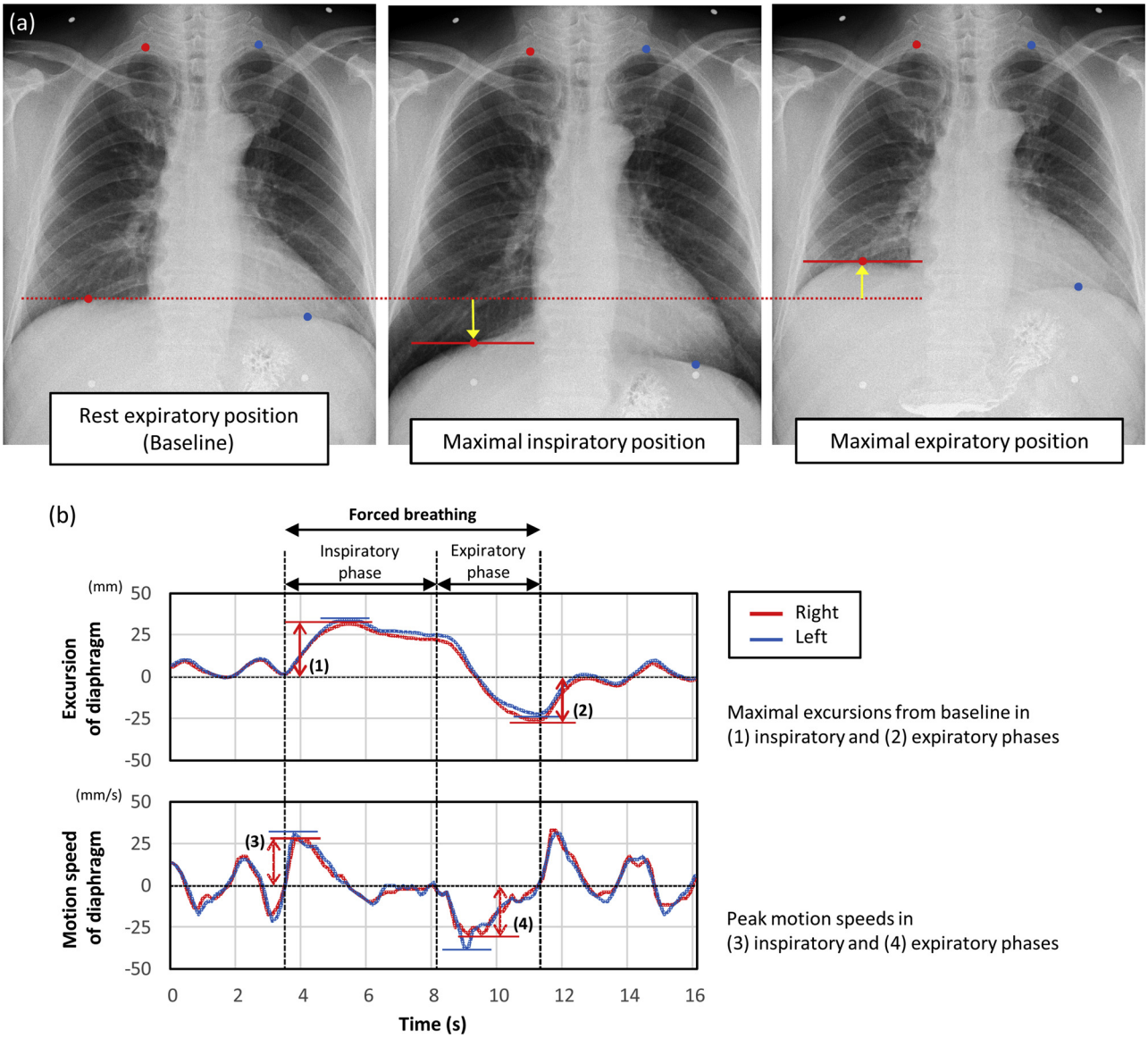

Fig. 1. An example of analysis of dynamic chest radiography in a 58-year-old male with normal pulmonary function. (a) Chest radiographs in rest expiratory (left), maximal inspiratory (center) and maximal expiratory (right) positions obtained using dynamic chest radiography. The highest points of the diaphragms and the apex points were automatically set and tracked using the template-matching technique throughout the respiratory phase (right, red dots; left, blue dots) (Supplementary video 1). The positions of the diaphragms in the rest expiratory phase were defined as the baseline positions (red dot line, right side). Excursions of the diaphragms were evaluated based on the baseline positions (yellow arrows) (b) Graphs of excursions (top) and motion speeds (bottom) of the diaphragms. The motion speeds of the diaphragms were calculated by the differential method.

the peak motion speed of inspiration, and from positive to negative just before the peak motion speed of expiration, respectively.

2.4. Statistical analysis

Demographics and parameters of diaphragmatic motion were analyzed using one-way analysis of variance with the Tukey post hoc test to compare among GOLD 1/2 and 3/4 groups and normal subjects for continuous variables and using Fisher's exact test for comparison of nominal variables. Continuous variables were height, weight, BMI, BSA, tidal volume (TV), vital capacity (VC, %VC), forced expiratory volume (FEV_1, FEV_1%, and %FEV_1), and nominal variables were gender and smoking history. The correlation among parameters of diaphragmatic motion, demographics and pulmonary function tests was analyzed using Spearman's rank correlation test. Statistical analyses were performed using R version 3.4.0 software (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided and $P <$ 0.05 was considered statistically significant.

3. Results

3.1. Demographic characteristics

The demographic characteristics of the participants are summarized in Table 1. Fifteen out of 31 COPD patients were classified as GOLD 1/2 and 16 were classified as GOLD 3/4 according to the results of pulmonary function tests. Among the three groups of GOLD 1/2, GOLD 3/4, and normal subjects, there was a significant difference in age between GOLD 1/2 and normal subjects and in smoking history among the three groups (both $P < 0.001$), but there were no significant differences in sex, height, weight, BMI, and BSA. FEV_1, FEV_1%, and %FEV_1 decreased significantly sequentially from GOLD 3/4, GOLD 1/2, to normal subjects (all $P < 0.001$). VC and %VC were significantly smaller in GOLD 3/4 than in normal subjects (both $P < 0.001$) and

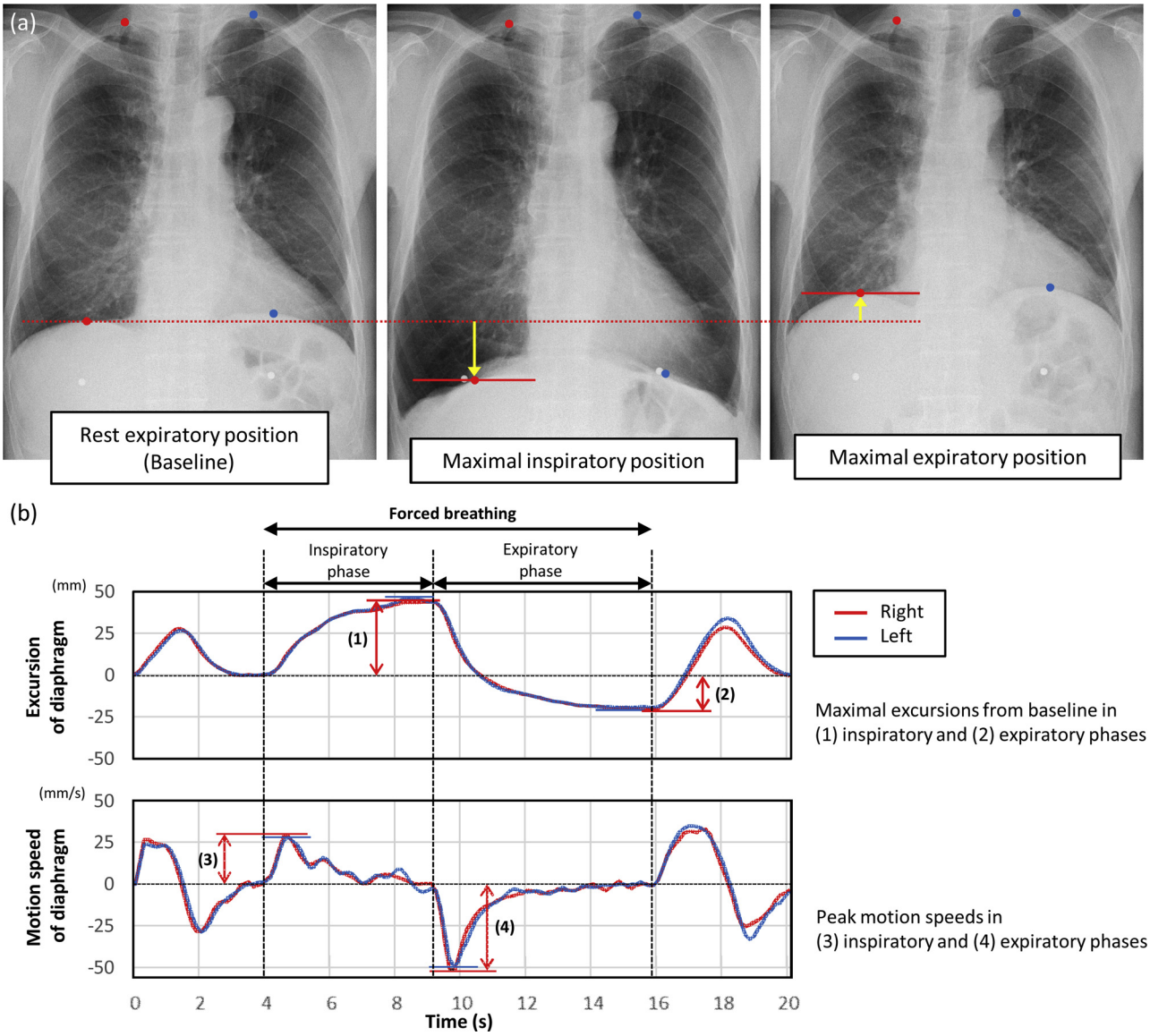

Fig. 2. An example of analysis of dynamic chest radiography in a 79-year-old male with COPD GOLD 2. (a) Chest radiographs in rest expiratory (left), maximal inspiratory (center) and maximal expiratory (right) positions obtained using dynamic chest radiography. The highest points of the diaphragms and the apex points that were automatically set were shown (right, red dots; left, blue dots) (Supplementary video 2). The baseline position of the right diaphragm was shown as a red dot line. Excursions of the diaphragms were evaluated based on the baseline positions (yellow arrows) (b) Graphs of excursions (top) and motion speeds (bottom) of the diaphragms.

GOLD 1/2 (VC, $P = 0.022$; %VC, $P < 0.001$). Tidal volume (TV) was larger in GOLD 1/2 than in normal subjects ($P = 0.043$).

3.2. Comparison of diaphragmatic motion among COPD groups and normal subjects

The measurements of diaphragmatic motion using dynamic chest radiography and the results of comparison among GOLD 1/2, GOLD 3/4, and normal subjects are summarized in Table 2 and in Fig. 4 as bar charts.

The excursions of the diaphragms in GOLD 3/4 patients were significantly decreased compared to those in normal subjects (right, 39.8 ± 15.3 mm vs. 52.7 ± 15.1 mm, $P = 0.030$; left, 43.7 ± 14.0 mm vs. 56.9 ± 15.5 mm, $P = 0.017$) and GOLD 1/2 patients (right, 39.8 ± 15.3 vs. 54.4 ± 16.7 mm, $P = 0.036$; left, 43.7 ± 14.0 mm vs. 60.5 ± 13.9 mm, $P = 0.008$). There were significant differences in maximal expiratory positions from the baseline between GOLD 1/2 and GOLD 3/4 groups (right, 27.6 ± 15.8 mm vs. 16.2 ± 9.0 mm, $P = 0.034$; left, 24.3 ± 14.0 mm vs. 14.7 ± 8.0 mm, $P = 0.036$). The peak distances from apex to diaphragm in GOLD 3/4 patients were significantly greater than those in normal subjects (right, 262.4 ± 15.0 mm vs. 240.1 ± 18.6 mm, $P = 0.004$; left, 279.1 ± 19.1 mm vs. 260.2 ± 20.0 mm, $P = 0.021$). The percentages of excursion to the distance from apex to diaphragm (apex-diaphragm distance) were significantly lower in GOLD 3/4 patients than in normal subjects (right, 16.6 ± 5.8% vs. 23.5 ± 6.7%, $P = 0.004$; left, 17.0 ± 5.1% vs. 23.2 ± 5.9%, $P = 0.003$) and than in GOLD 1/2 patients (right, 16.6 ± 5.8% vs. 23.7 ± 7.1%, $P = 0.013$; left, 17.0 ± 5.1% vs. 24.4 ± 6.1%, $P = 0.003$).

The peak motion speeds of the left diaphragm in the inspiratory phase were significantly slower in the GOLD 1/2 group than in the normal subjects (24.5 ± 8.0 mm/s vs. 33.6 ± 14.0 mm/s, $P = 0.038$), and tended to be slower in the GOLD 3/4 group compared to the normal subjects (25.6 ± 6.8 mm/s vs. 33.6 ± 14.0 mm/s, $P = 0.067$). The average motion speeds up to the maximal excursion in the expiratory phase were significantly smaller in GOLD 3/4 patients than in normal

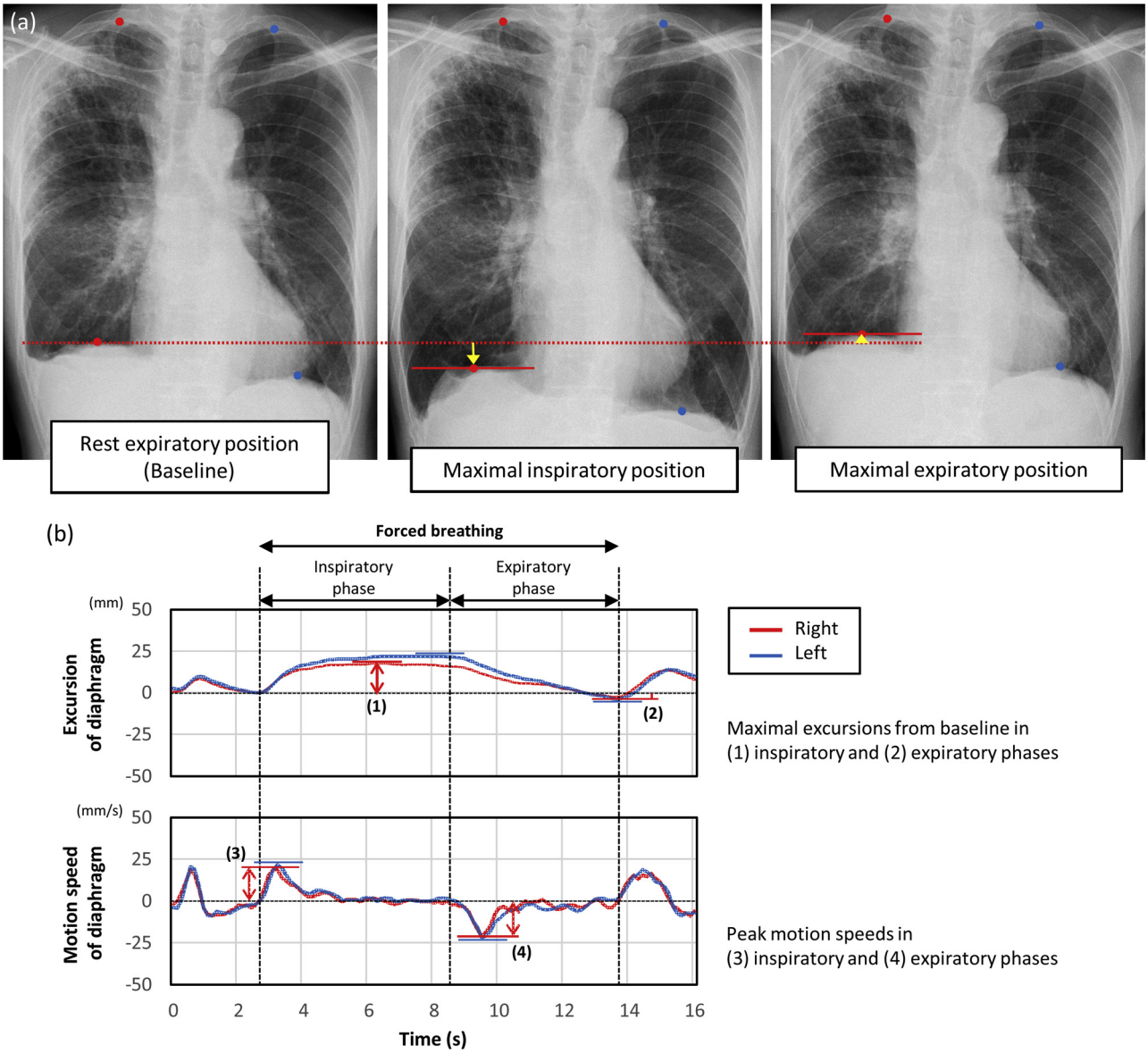

Fig. 3. An example of analysis of dynamic chest radiography in an 81-year-old male with COPD GOLD 3. (a) Chest radiographs in rest expiratory (left), maximal inspiratory (center) and maximal expiratory (right) positions obtained using dynamic chest radiography. The highest points of the diaphragms and the apex points that were automatically set were shown (right, red dots; left, blue dots) (Supplementary video 3). The baseline position of the right diaphragm was shown as a red dot line. Excursions of the diaphragms were evaluated based on the baseline positions (yellow arrows) (b) Graphs of excursions (top) and motion speeds (bottom) of the diaphragms.

subjects (right, 6.8 ± 2.7 mm/s vs. 10.4 ± 4.0 mm/s, $P = 0.009$; left, 7.4 ± 2.3 mm/s vs. 10.7 ± 4.2 mm/s, $P = 0.015$). The other measurements of the motion speed of the diaphragms showed no significant difference among the three groups.

3.3. Correlation between the diaphragmatic motion and pulmonary function

The whole excursions of the diaphragms showed a positive correlation with VC (right, r = 0.43; left, r = 0.50), %VC (right, r = 0.40; left, r = 0.41) and FEV_1 (right, r = 0.36; left, r = 0.39). The maximal expiratory positions of the diaphragms showed a positive correlation with VC (right, r = 0.34; left, r = 0.33) and %VC (right, r = 0.39; left, r = 0.35). The maximal inspiratory positions of the left diaphragm showed a positive correlation with FEV_1 (r = 0.33), $\%FEV_1$ (r = 0.32) and VC (r = 0.32). Percentages of excursion to apex-diaphragm distance showed a positive correlation with VC (right, r = 0.37; left, r = 0.41), %VC (right, r = 0.41; left, r = 0.38) and FEV_1 (right, r = 0.38; left, r = 0.39). The peak distance from apex to diaphragm showed a negative correlation with $FEV_1\%$ (right, r = −0.42; left, r = −0.36) and $\%FEV_1$ (right, r = −0.42; left, r = −0.35).

The peak motion speeds of the diaphragms showed no association with pulmonary function tests. The average motion speeds of the diaphragms showed correlation with VC (right, r = 0.37; left, r = 0.31), FEV_1 (right, r = 0.42; left, r = 0.36) with both sides, and $FEV_1\%$ with left side (r = 0.36).

4. Discussion

This is the first report to demonstrate decreased and slower diaphragmatic motion during forced breathing in a standing position in severe COPD patients grouped by GOLD classification using time-resolved quantitative analysis of the diaphragms with dynamic chest radiography. Dysfunction of the diaphragm can be caused by various diseases and cause respiratory difficulties. Objective and quantitative

Table 1
Demographics and pulmonary function of the study population.

	GOLD 1/2 (n = 15)	GOLD 3/4 (n = 16)	Normal subjects (n = 31)
	Mean ± SD [range] or n		
Age (years)	74.3 ± 9.7[a] [48–85]	69.6 ± 9.2 [54–85]	64.2 ± 5.1 [56–74]
Sex, Male/Female	13 / 2	14 / 2	20 / 11
Height (cm)	162.6 ± 5.2 [150.0–171.0]	163.0 ± 6.3 [150.0–174.0]	162.2 ± 8.6 [145.5–176.7]
Weight (kg)	58.5 ± 6.7 [46.0–73.0]	56.6 ± 14.2 [42.0–94.0]	58.1 ± 12.1 [39.8–78.3]
BMI (kg/m^2)	22.2 ± 2.7 [16.3–26.8]	21.2 ± 4.5 [16.6–34.5]	22.2 ± 2.6 [16.7–28.1]
BSA (m^2)	1.62 ± 0.09 [1.44–1.80]	1.59 ± 0.19 [1.36–2.01]	1.61 ± 0.20 [1.18–1.89]
Smoking history			
Current or former	15	16	0
Never	0	0	31
GOLD classification, 1/2/3/4	3 / 12 / 13 / 3		–
Pulmonary function test			
TV (L)	1.06 ± 0.43 [0.39–2.30]	0.81 ± 0.20 [0.54–1.22]	0.77 ± 0.38 [0.22–1.76]
VC (L)	3.11 ± 0.57[b] [2.35–4.34]	2.44 ± 0.56[c] [1.64–3.86]	3.25 ± 0.74 [2.11–5.69]
%VC (%)	103.1 ± 17.6[b] [78.2–140.0]	77.8 ± 15.0[c] [46.9–102.7]	106.8 ± 13.0 [87.1–159.6]
FEV_1 (L)	1.72 ± 0.33[a,b] [1.08–2.41]	0.97 ± 0.26[c] [0.52–1.60]	2.57 ± 0.64 [1.68–4.72]
FEV_1% (%)	57.6 ± 6.2[a,b] [45.8–68.9]	41.6 ± 4.4[c] [34.6–48.3]	80.8 ± 4.9 [71.0–91.1]
%FEV_1 (%)	69.7 ± 12.4[a,b] [52.4–97.9]	36.5 ± 8.1[c] [16.3–47.1]	110.1 ± 15.7 [85.3–163.9]

Significant differences were seen between [a] GOLD 1/2 group and normal subjects, [b] GOLD 1/2 and GOLD 3/4 groups, and [c] GOLD 3/4 and normal subjects. BMI, body mass index; BSA, body surface area; FEV, forced expiratory volume; SD, standard deviation; TV, tidal volume; VC, vital capacity.

Table 2
Parameters of diaphragmatic motion in COPD groups and normal subjects.

		GOLD 1/2 (n = 15)	GOLD 3/4 (n = 16)	Normal subjects (n = 31)
		Mean ± SD [range]		
Excursion of the diaphragm (mm)	Right	54.4 ± 16.7[b] [18.0–83.2]	39.8 ± 15.3[c] [12.9–62.2]	52.7 ± 15.1 [24.8–80.6]
	Left	60.5 ± 13.9[b] [34.6–85.2]	43.7 ± 14.0[c] [23.8–65.6]	56.9 ± 15.5 [21.7–85.6]
Maximal inspiratory position from baseline (mm)	Right	26.8 ± 11.3 [5.0–43.9]	23.6 ± 13.3 [1.5–53.4]	29.0 ± 11.4 [11.5–55.0]
	Left	36.2 ± 12.0 [14.6–55.7]	29.0 ± 12.8[c] [12.0–50.2]	39.8 ± 12.7 [12.2–63.4]
Maximal expiratory position from baseline (mm)	Right	27.6 ± 15.8[b] [3.2–62.6]	16.2 ± 9.0 [2.6–34.8]	24.1 ± 11.3 [6.6–50.4]
	Left	24.3 ± 14.0[b] [9.0–59.6]	14.7 ± 8.0 [3.5–31.5]	17.6 ± 9.3 [1.2–38.8]
Ratio of left/right excursion		0.89 ± 0.21 [0.52–1.24]	0.90 ± 0.21 [0.47–1.32]	0.93 ± 0.14 [0.64–1.35]
Peak distance of apex-diaphragm (mm)	Right	253.9 ± 30.0 [179.1–294.0]	262.4 ± 15.0[c] [236.7–288.0]	240.1 ± 18.6 [202.3–283.8]
	Left	274.8 ± 27.3 [216.6–320.9]	279.1 ± 19.1[c] [246.6–305.1]	260.2 ± 20.0 [219.6–297.2]
Percentage of excursion/apex-diaphragm distance (%)	Right	23.7 ± 7.1[b] [7.1–33.8]	16.6 ± 5.8[c] [5.8–26.3]	23.5 ± 6.7 [10.9–38.6]
	Left	24.4 ± 6.1[b] [12.0–35.6]	17.0 ± 5.1[c] [9.5–25.4]	23.2 ± 5.9 [11.0–37.7]
Peak motion speed in inspiratory phase (mm/s)	Right	21.1 ± 9.3 [6.3–37.8]	23.1 ± 10.1 [3.4–40.7]	25.4 ± 10.4 [11.6–50.4]
	Left	24.5 ± 8.0[a] [11.2–38.8]	25.6 ± 6.8 [13.1–36.9]	33.6 ± 14.0 [15.5–73.7]
Peak motion speed in expiratory phase (mm/s)	Right	25.0 ± 12.8 [6.8–53.4]	20.2 ± 9.5 [4.9–35.9]	23.2 ± 9.0 [7.8–44.6]
	Left	31.4 ± 12.9 [14.1–56.7]	24.8 ± 9.1 [9.2–40.7]	27.8 ± 11.7 [9.7–66.0]
Average motion speed up to maximal excursion in expiratory phase (mm/s)	Right	9.3 ± 3.9 [3.9–16.8]	6.8 ± 2.7[c] [1.4–11.8]	10.4 ± 4.0 [3.9–20.4]
	Left	10.2 ± 3.8 [5.1–18.9]	7.4 ± 2.3[c] [3.6–10.5]	10.7 ± 4.2 [4.1–21.3]

Significant differences were seen between [a] GOLD 1/2 group and normal subjects, [b] GOLD 1/2 and GOLD 3/4 groups, and [c] GOLD 3/4 and normal subjects. SD, standard deviation.

evaluation of diaphragmatic movement can be useful for management and treatment of several respiratory diseases, including COPD and interstitial lung diseases, postoperative conditions for lung diseases, and respiratory rehabilitation. By using dynamic chest radiography, Yamada et al. revealed greater diaphragmatic motion in COPD patients than in normal subjects during tidal breathing [11]. This compensatory motion of the diaphragm is thought to be one of the characteristic features of tidal breathing in COPD, and to be related to respiratory fatigue in patients' daily living. On the other hand, using the same technique, we found that the maximal diaphragmatic motion in severe COPD patients during forced breathing was smaller than in normal subjects, which indicates a limitation of motility of the diaphragm in COPD. These results and the difference between tidal and forced breathing may be important to understand the role of the diaphragm in COPD patients for pathogenesis and personalized management.

Our study demonstrated that overall diaphragmatic excursion during forced breathing was significantly decreased in the GOLD 3/4 group compared to both normal subjects and the GOLD 1/2 group. Moreover, in the GOLD 1/2 group, diaphragmatic excursions in expiration tended to be higher, while excursions in inspiration tended to be smaller than in GOLD 1/2. Previous studies have reported that the diaphragmatic motility in COPD patients decreased as GOLD stages progressed [5,14]. While those results are consistent with ours regarding the GOLD 3/4 group, they differ from ours when describing the GOLD 1/2 group. Although there may be a difference resulting from cohorts, our result suggests that diaphragm motion in the GOLD 1/2 group may be relatively reserved or shows compensatory larger movement in expiration. As in other findings regarding excursion, the peak distance from apex to diaphragm was significantly larger in the COPD groups than in normal subjects, which may be due to the difference of the thoracic cavity size between the two. We also demonstrated that the average and peak motion speeds of the diaphragms in expiration tended to be smaller in the GOLD 3/4 group than the other groups, whereas in inspiration, the peak motion speeds were decreased in both GOLD 1/2 and 3/4 groups. This decreasing of motion speeds of the diaphragms in the expiratory phase may relate to the progression of outward airflow limitation in severe COPD patients resulting from chronic bronchitis and destruction of the alveolar walls due to emphysema. Our findings indicate that the difference is not only between COPD patients and normal subjects but also between mild and severe COPD groups. These differences of diaphragmatic excursion and motion speed can be an indicator of COPD severity and may be useful in monitoring COPD patients.

The correlation between the excursion of the diaphragm and pulmonary function tests has been reported in several studies. Unal et al. demonstrated the correlation between diaphragmatic movement and FEV_1 using MR fluoroscopy [6]. With ultrasonography, Scheibe et al. reported the correlation with FEV_1, residual volume (RV) and VC [5], and Dos Santos Yamaguti et al. showed the correlation with pulmonary

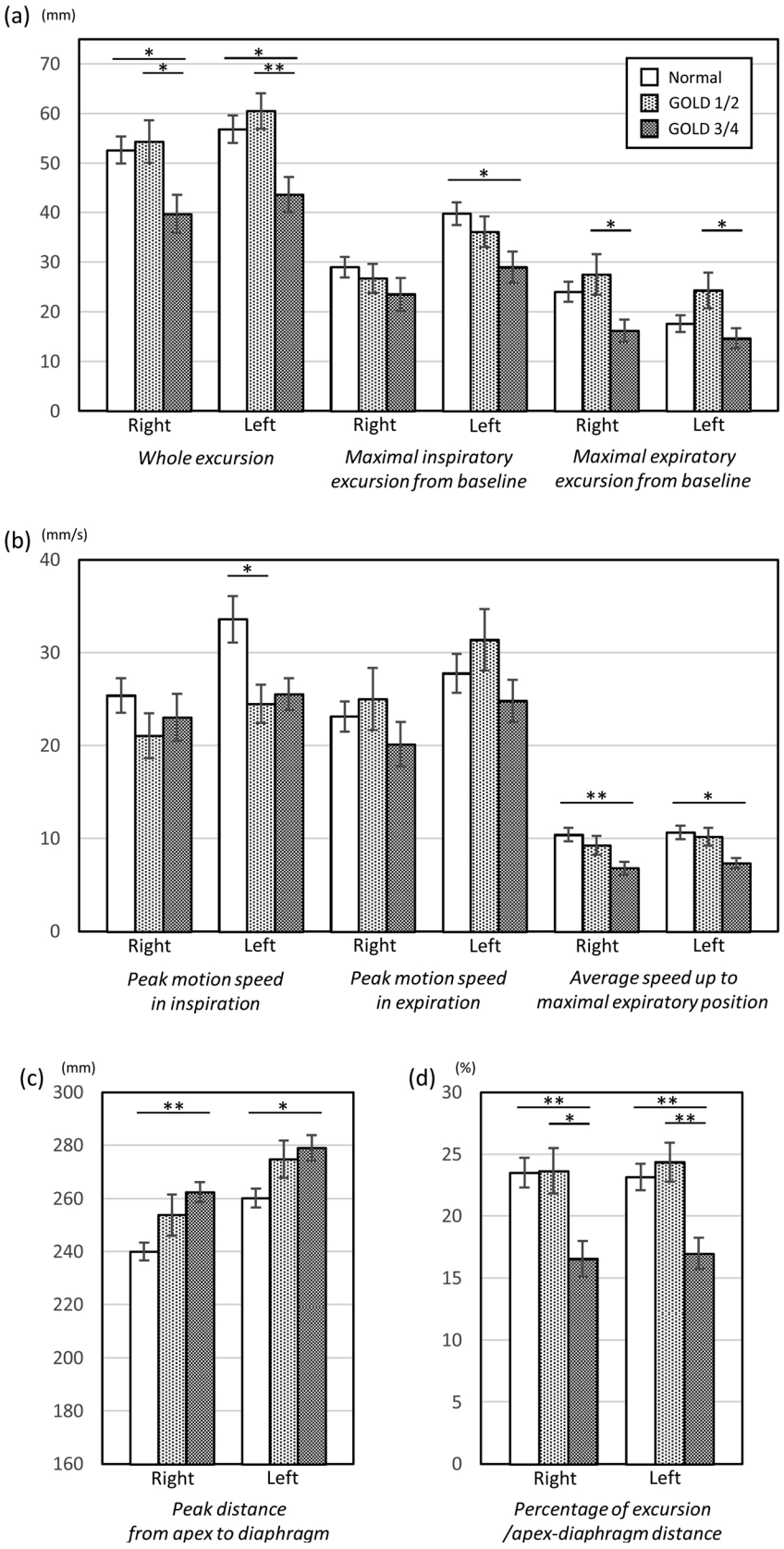

Fig. 4. Comparison of the measurements among the groups of GOLD 1/2, GOLD 3/4 and normal subjects. Bar charts show mean of (a) the excursion of the diaphragm, (b) the motion speed of the diaphragm, (c) the peak distance from apex to diaphragm, and (d) the percentage of excursion to apex-diaphragm distance. Error bars show the standard error of each parameter. * indicates $P < 0.05$; **, $P < 0.01$.

function parameters that quantify air trapping of residual volume (RV) and airway obstruction of FEV_1 in COPD patients [14]. In this study using dynamic chest radiography, the excursion of the diaphragm in COPD patients showed a correlation with VC and FEV_1. This result is compatible with the previous reports and indicates adequacy of our evaluation for diaphragmatic motion using dynamic chest radiography. However, the correlation is relatively mild in comparison to the previous reports. In addition to the difference in subjects, the differences in the respiration method and instructions may also result in the difference of degree of the correlation. On the other hand, although we also investigated the motion speed of the diaphragm, there were no significant associations with the pulmonary function tests. Evaluation of the motion speed of the diaphragm may provide another new indicator for diaphragmatic and respiratory function, but further investigation is needed to clarify the significance in COPD.

For evaluation of diaphragmatic movement in this study, we used dynamic chest radiography, a new modality for chest imaging, and confirmed it to be useful for analysis of diaphragmatic kinesis. Dynamic chest radiography can provide reproducible data owing to the simple procedure like conventional chest radiography and can be performed repeatedly because of as low radiation dose as conventional chest radiography [8,9]. Besides diaphragmatic kinetics, it can simultaneously provide other data such as pulmonary ventilation and circulation, cardiovascular function, as well as conventional chest radiograph information [7]. To date, quantitative assessment of diaphragm kinetics has been performed using various imaging modalities, including conventional chest radiography, fluoroscopy, US, CT, and MRI [3,15–19], and may be useful for evaluation and management of respiratory diseases, postoperative conditions for respiratory organs, and respiratory rehabilitation. Dynamic chest radiography can be used as one of these useful modalities in the future.

There are several limitations in this study. First, this study included only 31 COPD patients and 31 matched normal subjects. Larger cohorts are needed to confirm the preliminary findings of this study. Second, we evaluated the motion of the top of the diaphragm in posteroanterior view only. The function of the diaphragm is thought to be due to its three-dimensional structure and movement. We believe this analysis of the top of the diaphragm is a simple, practical, and easily applicable method in a clinical setting, but we must note that it does not necessarily represent the whole function of the diaphragm. In addition, the influence of the paradoxical motion of the diaphragm cannot be described in this study. Third, the analysis in this study was based on one cycle of forced breathing in each participant. We confirmed the condition of each participants' respiration was proper for the study, but assessment with multicycle forced breathing or repeated examinations of each participant is desired to exclude the possibility of improper respiration.

In conclusion, time-resolved quantitative analysis of the diaphragms with dynamic chest radiography indicated the different characteristics of diaphragmatic motion among normal subjects and COPD groups classified with the GOLD classification during forced breathing in a standing position. The excursions of diaphragms during forced breathing were significantly decreased in the GOLD 3/4 group than those in normal subjects and the GOLD 1/2 group. Quantitative assessment of diaphragm kinetics using dynamic chest radiography may provide an easy way and an added value in monitoring of patients with COPD.

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Conflicts of interest

The other authors (Tomoyuki Hida, Yoshitake Yamada, Masako Ueyama, Tetsuro Araki, Mizuki Nishino, Atsuko Kurosaki, Masahiro Jinzaki, Hiroshi Honda, and Shoji Kudoh) have no conflicts of interest to be disclosed related to this article.

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Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejrad.2018.12.023.

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