Respiratory Medicine 119 (2016) 109–114

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Factors associated with pulmonary hypertension and long-term survival in bronchiectasis subjects

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ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form
24 August 2016
Accepted 29 August 2016
Available online 30 August 2016

Keywords:
Bronchiectasis
Pulmonary hypertension
Dyspnea
Survival
Endothelin-1
Hypoxemia

ABSTRACT

Background: The development of pulmonary hypertension (PH) and its effect on long-term survival in bronchiectasis subjects has not been explored. The present study aims to analyze the factors associated with PH and its effect on long-term survival in bronchiectasis subjects.
Methods: We prospectively evaluated 23 bronchiectasis subjects without PH and 16 with PH, as well as 20 healthy volunteers.
Results: Bronchiectasis subjects with PH were more hypoxemic and had a greater number of involved lobes in high resolution computed tomography (HRCT) than did the bronchiectasis subjects without PH ($P < 0.001$ and $P < 0.001$, respectively). At three years, the survival rate was 95.7% for bronchiectasis subjects without PH and 56.3% for bronchiectasis with PH, and at 5 years, these rates were 95.7% and 62.5%, respectively ($P = 0.002$). Multivariate Cox regression analysis revealed that only the Medical Research Council (MRC) dyspnea score was independently related to poor survival in all bronchiectasis subjects (hazard ratio: 6.98; 95% CI: 2.41–20.23; $P < 0.00001$).
Conclusions: Subjects with PH are more hypoxemic and have a greater number of involvements in the lobes of the lungs. Bronchiectasis subjects with PH have worse survival than do bronchiectasis subjects without PH. MRC dyspnea score is an independent predictor of long-term survival.

Contents

Abbreviations: PH, pulmonary hypertension; HRCT, high resolution computed tomography; MRC, Medical Research Council; COPD, chronic obstructive pulmonary disease; ET-1, endothelin-1; BMI, body mass index; LV, Left ventricular; LVEF, Left ventricular ejection fraction; RV, right ventricular; RVEF, right ventricular ejection fraction; RVE, right ventricular early diastolic velocity; RVA, right ventricular late diastolic velocity; RVS, right ventricular systolic velocity; RVIVV, right ventricular velocity during isovolumic contraction; RVIVA, right ventricular acceleration during isovolumic contraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure.

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http://dx.doi.org/10.1016/j.rmed.2016.08.027
0954-6111/

1. Introduction

Until recently, many believed that bronchiectasis was only a problem of developing countries. However, two new studies describe the burden of bronchiectasis in developed countries. An epidemiological study of bronchiectasis-associated hospitalizations in the United States reported that the rate of hospitalization due to bronchiectasis increased from 1993 to 2006, especially among those aged ≥60 years [1]. Similarly, mortality trends were analyzed to obtain data regarding the burden of bronchiectasis in England and Wales, and it was found that there was an increase in bronchiectasis associated mortality of approximately 3% per year between 2001 and 2007 [2].

Subjects with bronchiectasis can also have cardiac dysfunction and pulmonary hypertension (PH) [3–6]. PH, associated with chronic obstructive pulmonary disease (COPD), contributes to a poor prognosis in these subjects [7,8]. However, the factors influencing the development and clinical significance of PH on long-term survival in subjects with bronchiectasis are not fully understood. As such, the present study aimed to compare clinical characteristics, extent of bronchiectasis on high-resolution computed tomography (HRCT), Doppler echocardiographic findings, arterial oxygen and endothelin-1 (ET-1) levels in bronchiectasis subjects with and without PH. The secondary aim of this study was to evaluate the long-term outcomes of these subjects and prognostic factors for survival at a 5-year follow-up.

2. Patients and methods

2.1. Study oversight

The study (Trial registration: HEK 09/270-25) was approved by the applicable institutional review board and independent ethics committee, and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Study HEK 09/270-25 was conducted between March 2010 and March 2015 at the Hacettepe University, Ankara, Turkey.

2.2. Study population

This prospective study included consecutive bronchiectasis subjects (confirmed by HRCT) who presented to an outpatient clinic at Hacettepe University. We aimed to include 30 bronchiectasis subjects without PH and 30 with PH, as well as 20 healthy volunteers. Subjects were excluded from the study if they had a history of hypertension, asthma, other unstable systemic diseases, valvular or rheumatic heart disease, ischemic heart disease or cardiomyopathy.

Clinical data and blood samples were collected upon presentation. Clinical data included patient age, gender, body mass index (BMI), history of cigarette smoking, and signs and duration of dyspnea. The severity of dyspnea was assessed using the Medical Research Council (MRC) grade. Arterial blood gases were measured while the subjects breathed room air, and the pH, $PaCO_2$, PaO_2 and O_2 saturation were recorded.

HRCT was performed with a Tomoscan SR 7000 (Philips, The Netherlands) without i.v administration of contrast material. Sections 1.5 mm thickness were obtained at 10 mm intervals and at 120 kV and 150 mA with a 0.6 or 1 ms acquisition time. Images were reconstructed with a bone algorithm and a 512 × 512 matrix. The lungs were imaged at a 1300–1400 window at (−200)–(−500) level. Bronchiectasis was deemed to be present if there was evidence of brochial dilatation (internal bronchial diameter greater than the diameter of the accompanying pulmonary artery) and a lack of bronchial tapering on sequential slices. The bronchi were evaluated on a lobar basis (the lingual was regarded as a separate lobe).

2.3. Doppler echocardiography

Standard imaging was performed in the left lateral decubitus position using a commercially available system (Vingmed System Five GE ultrasound, Horten, Norway). Images were obtained using a 2.5–3.5-MHz transducer in the parasternal and apical views. Left ventricular (LV) end-diastolic and end-systolic diameters were determined with an M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the recommendations of the American Society of Echocardiography. Left ventricular ejection fraction (LVEF) was calculated from apical four-chamber view, according to the modified Simpson's rule. Right ventricular (RV) dimensions were assessed as described previously from the apical four-chamber view using the diameter of RV mid-cavity [9].

The pulsed-wave tissue Doppler imaging derived systolic indices of RV, peak myocardial velocity during isovolumic contraction (isovolumic velocity [RVIVV], cm/sec), myocardial acceleration during isovolumic contraction (isovolumic acceleration [RVIVA], m/sec2; defined as the ratio of RVIVV divided by the acceleration time), peak velocity during systolic ejection (RV included systolic [RVS], cm/sec), LV posterior and septum wall thickness at the end diastole were measured. To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to the plane of the annulus [10].

To determine tricuspid annular plane systolic excursion (TAPSE), the M-mode cursor was oriented to the junction of the tricuspid valve plane with the RV free wall using the apical four-chamber view. The echoes generated were received and registered as motion of the RV base. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the peak descent during ventricular systole, as measured from the apical four-chamber view. All annular M-mode images were obtained at the end of expiration to minimize changes in the longitudinal movement of the tricuspid plane; to improve reproducibility, several cardiac cycles were evaluated and the best three consecutive ones were analyzed and averaged [10].

Estimated systolic pulmonary artery pressure (sPAP) was determined based on the velocity of the peak tricuspid regurgitation jet using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure. PH was defined as sPAP

≥40 mmHg according to the World Health Organization 1998 Symposium on Primary Pulmonary Hypertension. Left ventricle diastolic dysfunction was assessed by evaluation of mitral inflow, E-wave velocity, A-wave velocity and E/A ratio.

2.4. Blood sampling and hormonal assays

Samples for plasma and urinary ET-1 were obtained during the cardiac evaluation. Following local anesthesia with 2% xylocaine, blood (2 ml) was drawn from the radial artery using an 18-gauge arterial needle and collected into chilled tubes containing EDTA. Plasma samples were separated via centrifugation at 1500×g for 15 min at 4 °C. Plasma samples were promptly transferred to polypropylene freezer tubes and stored at −80 °C until further analysis. Spot urine samples were divided into 4 Eppendorf tubes (1.5 ml) and stored at −80 °C until further analysis. The levels of plasma and urinary ET-1 were measured with a commercially available ELISA (Biomedica Group, Vienna, Austria) according to the manufacturer's instructions.

Information regarding mortality and cause of death (due to bronchiectasis and bronchiectasis-related diseases) was obtained from the subjects or their relatives by telephone or hospital records. Survival time was calculated as the time between hospital admission and death or May 12, 2015.

2.5. Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS v.20.0) for Windows (IBM Corp., Armonk, NY) software. Data were determined as being normally distributed or not via visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test). Descriptive data are presented as means ± SD or medians (IQR). Numeric parameters were analyzed using Spearman's correlation test, while the Kruskal-Wallis test was used to compare groups. The Mann-Whitney *U* test was performed to determine the significance of pairwise differences, and the Bonferroni correction was used to adjust for multiple comparisons. The chi-square test and Fisher's exact test were used when appropriate to determine. The level of significance was accepted as $P < 0.05$. Survival curves were constructed via the Kaplan Meier method and compared with a log-rank test. Independent continuous variables were analyzed with a Cox regression analysis, and possible risk factors were identified using a Univariate analysis. Variables having a significant effect on survival via Univariate analysis were included in the multiple Cox regression analysis.

3. Results

This study included 23 steady state bronchiectasis subjects without PH and 16 with PH. The mean age of the subjects was 45 ± 18 years. The control group included 20 age-matched healthy volunteers. The identified etiologies were; post-infection 24 (40.7%), post-tuberculosis 6 (10.2%), primary ciliary dyskinesia 3 (5.1%), cysytic fibrosis and common variable immune deficiency with a single case in each, idiopathic 4 (6.8%). The clinical baseline characteristics, arterial oxygen and ET-1 levels of this cohort are summarized in Table 1. Sixty-nine percent of bronchiectasis subjects without PH and 100% of those with PH experienced dyspnea. Among the bronchiectasis subjects without PH, 18% had mild dyspnea (MRC grade 1), 44% had moderate dyspnea (MRC grade 2), and 9% had severe dyspnea (MRC grades 3). Of the bronchiectasis subjects with PH, 6% had mild dyspnea (MRC grade 1), 25% had moderate dyspnea (MRC grade 2), and 69% had severe dyspnea (MRC grades 3, 4 and 5). Bronchiectasis subjects with and without PH had significantly lower arterial PaO_2 than did the controls. However, subjects with PH had significantly lower arterial PaO_2 and O_2 saturation, but had higher arterial $PaCO_2$, than did those without PH (Table 1).

The median plasma and urinary ET-1, respectively, in the 3 groups were as follows: controls (n = 20): 0.77 fmol ml^{-1} and 0.36 fmol ml^{-1}; bronchiectasis subjects without PH (n = 30): 0.82 fmol ml^{-1} and 0.36 fmol ml^{-1}; bronchiectasis subjects with PH (n = 26): 0.85 fmol ml^{-1} and 0.37 fmol ml^{-1}. There were no significant differences in median plasma or urinary ET-1 levels between the 3 groups ($P = 0.86$ and $P = 0.96$, respectively).

The echocardiographic findings from this study are summarized in Table 2. LVEF and LV end-diastolic diameter were normal in all 3 groups. The RV diastolic dimension was significantly higher in the bronchiectasis subjects with and without PH than in the control group ($P < 0.01$). The following parameters differed significantly between the three groups: Median right ventricular early diastolic velocity (RVE) and right ventricular late diastolic velocity (RVA) as right ventricular diastolic parameters, right ventricular systolic velocity (RVS), TAPSE and right ventricular acceleration during isovolumic contraction (RVIVA) as right ventricular systolic parameters. Peak aortic and pulmonary velocity were higher, and aortic diameter was lower in subjects with and without PH than in the control group ($P < 0.001$, $P < 0.001$, and $P = 0.015$). Both the left and right atrial diameters differed significantly between the 3 groups ($P < 0.001$ and $P < 0.001$, respectively). Diastolic dysfunction was present in 12 (52.2%) bronchiectasis subjects without PH and in 6 (46.2%) bronchiectasis subjects with PH ($P = 0.001$).

The mean follow-up was 49 months. The survival rate was 95.7% for bronchiectasis subjects without PH and 56.3% for bronchiectasis with PH group at 3 years; these values were 95.7% and 62.5% at 5 years ($P = 0.002$) (Fig. 1). Univariate analysis revealed that prognostic factors for long-term survival included the MRC dyspnea scale, the number of involved lobes in HRCT, pH, $PaCO_2$, PaO_2 and O_2, sPAP, right atrium diameter, RV diameter, AX, TAPSE, and peak pulmonary velocity (cm/s) (Table 3). Multivariate Cox regression analysis revealed that only the MRC dyspnea scale was independently related to poor survival in all bronchiectasis subjects (hazard ratio: 6.98; 95% CI: 2.41–20.23; $P < 0.0001$).

4. Discussion

To our knowledge, this study is the first to analyze the factors associated with PH in bronchiectasis subjects and long-term survival. Results suggest that bronchiectasis subjects with PH are more hypoxemic and have a greater number of involved lobes in HRCT, but their levels of plasma and urinary ET-1 are not higher. The main finding of the present study is that PH is associated with worse survival in bronchiectasis subjects. Interestingly, subjects with bronchiectasis without PH also had RV systolic and diastolic dysfunction. Multivariate Cox regression indicated that an increased MRC dyspnea score is associated with increased mortality in all bronchiectasis subjects, and it is an independent predictor of long-term survival.

The mechanism of development of PH in subjects with bronchiectasis has not been fully elucidated. It has been hypothesized that hypoxic pulmonary vasoconstriction or destruction of parenchymal lung with the vascular bed are possible causes, but there is no evidence. Our current observations strongly support the hypothesis that bronchiectasis subjects with PH are more hypoxemic and have a greater number of involved lobes in HRCT.

In the current study, we found that mild arterial hypoxemia commonly occurs in subjects with bronchiectasis. In addition, we demonstrated that bronchiectasis subjects with PH are significantly more hypoxic than those without PH. Previous animal studies demonstrated that exposure to mild hypoxemia induces PH [11,12].

Table 1
Clinical characteristics and ET-1 levels of the study groups.

Variables	Control group	Bronchiectasis group	Bronchiectasis + PH group	p-value
	n = 20	n = 23	n = 16	
Age (years)	37 (26–54)	42 (23–56)	48 (40–62)	0.401
Gender (female)	9 (45)	11 (48)	9 (56)	0.848
BMI (kg/m^2)	27 (23–30)	24 (22–26)	24 (19–28)	0.142
Dyspnea (%)	1 (5)	16 (69)	16 (100)	<0.001*
MRC dyspnea scale	0 (0–0)	2 (1–2)§	3 (2–5)§‡	<0.001*
Duration of dyspnea (months)	0 (0–0)	54 (13–108)	150 (42–351)	0.056
Smoker (%)	9 (45)	7 (30)	4 (25)	0.422
Duration of smoking (pack-years)	13 (9–36)	3 (2–8)§	35 (23–85)§‡	0.011*
Number of involved lobes in HRCT	0 (0–0)	2 (1–2)§	3 (2–5)§‡	<0.001*
pH	7.40 (7.38–7.42)	7.43 (7.43–7.44)§	7.36 (7.34–7.39)§‡	0.003*
pO_2 (mmHg)	84 (77–88)	79 (70–83)§	66 (55–73)§‡	<0.001*
pCO_2 (mmHg)	39 (39–42)	38 (37–41)	42 (39–47)§‡	0.005*
O_2 saturation (%)	96 (94–98)	96 (94–97)	92 (89–93)§‡	<0.001*
ET-1 plasma (fmol/ml)	0.77 (0.69–0.90)	0.82 (0.70–1.10)	0.85 (0.67–1.8)	0.860
ET-1 urine (fmol/ml)	0.36 (030–0.50)	0.36 (0.32–0.40)	0.37 (0.33–0.40)	0.967

* $P < 0.05$.
Abbreviations: BMI, body mass index; MRC, Medical Research Council; HRCT, High resolution computed tomography; ET-1, endothelin-1.
Data expressed as median (Q25-Q75) and number (%).
§: p < 0,05 vs control group (Mann-Whitney test with Bonferroni correction).
‡: p < 0,05 vs bronchiectasis group (Mann-Whitney test with Bonferroni correction).

Table 2
The echocardiographic parameters of the study groups.

Variables	Control group	Bronchiectasis group	Bronchiectasis + PH group	p-value
	n = 20	n = 23	n = 16	
LVEDD (cm)	4.3 (3.9–5.1)	4.6 (4.4–5.0)	4.7 (4.1–4.9)	0.394
LVESD (cm)	3.5 (2.9–3.9)	3.0 (2.8–3.2)§	2.9 (2.5–3.1)§	0.004*
LVEF (%)	70 (68–78)	64 (63–69)§	66 (60–69)§	0.001*
LV fraction shortening (%)	38 (35–40)	35 (33–39)	38 (35–40)	0.141
Left atrium diameter (cm)	2.5 (2.0–2.8)	3.3 (2.9–3.7)§	3.4 (3.2–3.8)§	<0.001*
Right atrium diameter (cm)	2.9 (2.3–3.7)	3.3 (2.9–3.6)§	4.3 (3.5–5.3)§‡	<0.001*
RV diameter (cm)	2.4 (2.2–2.8)	2.6 (2.5–2.8)	3.1 (2.8–4.4)§‡	<0.001*
RVE (cm/s)	8.5 (7.5–9.6)	14.8 (9.4–17.2)§	10.6 (8.7–12.7)§‡	<0.001*
RVA (cm/s)	11.5 (8.9–12.7)	14.7 (12.7–19.8)§	12.8 (9.1–15.8)‡	<0.001*
RVS (cm/s)	15.6 (13.2–17.1)	13.7 (12.4–15.9)§	9.9 (8.7–14.2)§‡	0.007*
RVIVV (cm/s)	13.8 (11.9–15.8)	17.3 (13.1–22.8)§	11.6 (9.0–15.9)‡	0.028*
RVIVA (m/s^2)	4.0 (3.8–4.2)	3.2 (2.3–3.9)§	1.9 (1.4–3.2)§‡	<0.001*
AX	50 (40–60)	50 (40–60)	65 (50–100)§‡	0.007*
TAPSE (mm)	26 (22–28)	21 (20–22)§	15 (12–22)§‡	<0.001*
Peak aortic velocity (cm/s)	0.9 (0.7–1.2)	1.3 (1.2–1.3)§	1.2 (1.2–1.3)§	<0.001*
Peak pulmonary velocity (cm/s)	0.9 (0.8–1.0)	1.0 (0.8–1.0)	1.1 (0.9–2.0)§‡	<0.001*
sPAP (mmHg)	20 (15–25)	25 (25–30)§	50 (40–65)§‡	<0.001*
Aortic diameter (cm)	2.8 (2.6–3.5)	2.6 (2.4–2.9)§	2.5 (2.4–2.7)§	0.015*
Ascendan aorta (cm)	2.5 (2.1–2.7)	2.6 (2.5–2.9)	2.7 (2.4–2.9)	0.107
LV post wall thickness	0.9 (0.8–0.9)	0.9 (0.8–0.9)	0.9 (0.9–1)§‡	0.013
LV septum wall thickness	0.9 (0.8–0.9)	0.9 (0.8–0.9)	0.9 (0.9–1)§‡	0.013

* $P < 0.05$.
Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RVE, right ventricular early diastolic velocity; RVA, right ventricular late diastolic velocity; RVS, right ventricular systolic velocity; RVIVV, right ventricular velocity during isovolumic contraction; RVIVA, right ventricular acceleration during isovolumic contraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure.
Data expressed as median (Q25-Q75) and number (%).
§: p < 0,05 vs control group (Mann-Whitney test with Bonferroni correction).
‡: p < 0,05 vs Bronchiectasis group (Mann-Whitney test with Bonferroni correction).

Despite the fact that mild hypoxemia is defined as a wide range (60–80 mmHg), it has been reported that endothelial cells sense and respond to oxygen tensions falling below 70 mmHg [13]. In vivo studies have shown that chronic hypoxic exposure may lead to medial hypertrophy and gross adventitial thickening of pulmonary vessels, with a greater effect on pulmonary arteries [14–16]. If hypoxia persists, these structural changes may become irreversible. In addition, there is evidence showing that ET-1 itself is directly released by hypoxia [17].

In the present study, the plasma and urinary ET-1 levels (based on ELISA) did not differ between bronchiectasis subjects and healthy controls. In subjects with bronchiectasis, we showed that plasma and urinary ET-1 levels are unchanged and that there is no relationship between ET-1 and echocardiographic parameters. Soon after the discovery of ET-1, it was reported that plasma ET-1 levels are elevated in subjects with primary PH and PH secondary to systemic sclerosis, mitral stenosis, interstitial lung disease, COPD, and acute respiratory distress syndrome [18–23]. Although ET-1 plays an important role in the pathogenesis of PH, we found no difference between the plasma and urinary levels in subjects and controls in our study. Thus far, there has been only one prior study that assessed circulating ET-1 levels in subjects with

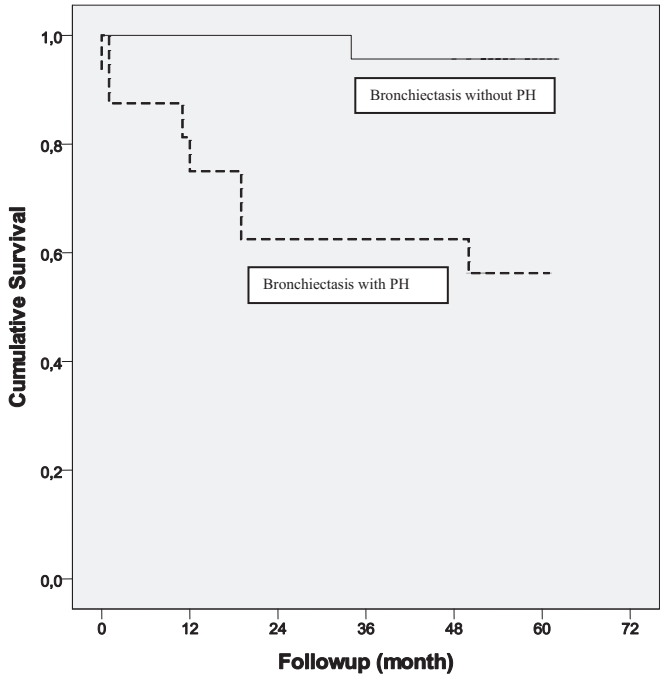

Fig. 1. Survival curve (Kaplan-Meier) for bronchiectasis patients according to PH (P = 0.002).

bronchiectasis; they found that ET-1 was significantly higher in *P. aeruginosa* infected subjects with bronchiectasis. However, they evaluated only subjects with bronchiectasis, and did not discern whether they had PH or not [24].

ET-1 is a vasoactive peptide with potent vasoconstrictor properties. The lung has the highest levels of ET-1, which are secreted by the endothelium, smooth muscle, airway epithelium, and a variety of other cells. Additionally, ET-1 has a short plasma half-life (~4–7 min), so we evaluated its urinary excretion [25]. However, ET-1 plasma and urinary levels were unchanged in bronchiectasis subjects with and without PH. It may be difficult to establish the role of ET-1 in the development of PH in these subjects, because most of the ET-1 synthesized in the lungs is released abluminal. Therefore, locally increased production of ET-1 in the lung may not necessarily result in increased plasma levels. Clearly, further studies are needed in this area, especially regarding its pulmonary excretion in bronchiectasis subjects.

PH is the major cardiovascular complication of chronic lung diseases. A recent study reported that the prevalence of PH subjects with bronchiectasis is 33% as evaluated by echocardiography [6]. PH is a known factor of poor prognosis in COPD subjects, but the clinical significance of this condition in bronchiectasis subjects is uncertain. A retrospective study reported that diagnosing PH with CT is an independent predictor of mortality in subjects with bronchiectasis [26]. In our current study, the mean follow-up duration of 49 months allowed for an adequate evaluation of survival; the survival rate was 95.7% for bronchiectasis subjects without PH and 56.3% for bronchiectasis subjects with PH at 3 years, and these values were 95.7% and 62.5% at 5 years (P = 0.002). A prior study reported that age was an independent prognostic factor for mortality, but the subjects in that study were much older than those in ours. In addition, PH was not analyzed in their study [27].

Even the mildest forms of lung diseases are known to effect heart functions. We observed right ventricular (RV) dysfunction, both systolic and diastolic, in subjects with bronchiectasis without

Table 3
Correlations between both plasma and urinary ET-1 and others data.

Variables	Plasma ET-1		Urinary ET-1	
	r	p	r	p
Plasma ET-1 (fmol/ml)	–	–	−0.010	0.950
Urinary ET-1 (fmol/ml)	−0.010	0.950	–	–
Age (years)	0.373	0.019*	−0.169	0.303
BMI (kg/m^2)	0.025	0.880	−0.063	0.704
MRC dyspnea scale	0.179	0.328	0.193	0.289
Dyspnea duration (months)	0.153	0.404	0.059	0.750
Smoker duration (packs/year)	−0.062	0.708	−0.042	0.799
Number of involved lobes in HRCT	0.281	0.083	0.035	0.834
pH	−0.141	0.392	−0.315	0.051*
pO_2	−0.107	0.515	−0.038	0.816
pCO_2	0.403	0.011*	−0.007	0.965
O_2sat	−0.163	0.321	−0.133	0.420
LVEDD (cm)	−0.018	0.914	0.048	0.773
LVESD (cm)	−0.040	0.809	−0.167	0.310
LVEF (%)	−0.075	0.649	0.515	0.001*
LV fraction shortening (%)	0.065	0.696	0.291	0.072
RV diameter (cm)	0.057	0.730	−0.179	0.276
RVE (cm/s)	−0.059	0.720	0.367	0.022*
RVA (cm/s)	0.220	0.179	−0.238	0.145
RVS (cm/s)	−0.215	0.189	−0.060	0.717
RVIVV (cm/s)	0.141	0.393	−0.060	0.717
RVIVA (m/s^2)	0.034	0.838	−0.117	0.479
AX	−0.064	0.700	−0.105	0.525
TAPSE (cm)	−0.153	0.352	−0.120	0.467
Peak aortic velocity (cm/s)	−0.153	0.352	0.146	0.375
Peak pulmonary velocity (cm/s)	0.079	0.633	−0.008	0.961
sPAP (mmHg)	0.006	0.972	−0.099	0.550
Aortic diameter (cm)	0.079	0.632	0.023	0.892
Ascendan aorta (cm)	0.003	0.988	−0.208	0.205
Left atrium diameter (cm)	−0.010	0.953	−0.305	0.059
Right atrium diameter (cm)	0.022	0.896	−0.106	0.520

* P < 0.05.

Abbreviations: BMI, body mass index; MRC, Medical Research Council; HRCT, High resolution computed tomography; ET-1, endothelin-1, LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RVE, right ventricular early diastolic velocity; RVA, right ventricular late diastolic velocity; RVS, right ventricular systolic velocity; RVIVV, right ventricular velocity during isovolumic contraction; RVIVA, right ventricular acceleration during isovolumic contraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure.

echocardiography indices for PH when compared to healthy individuals. It is important to note that RV function may be affected by impaired left ventricular (LV) function. Hence, LV function was analyzed in both the patient and control groups in our study, and was found to be within normal range and did not differ between groups. In addition, Koelling et al. demonstrated LV diastolic dysfunction by evaluating radionuclide ventriculography in subjects with cystic fibrosis; LV diastolic dysfunction was preserved in a small number of these subjects who had bronchiectasis, which is similar to our current results [28]. Numerous studies have shown that subjects with cystic fibrosis have RV and LV dysfunction [29–32]. Unfortunately, our results cannot be compared to those results in subjects with cystic fibrosis because subjects with that disease have myocardial involvement.

Dyspnea is the most prominent and disabling symptom in subjects with lung diseases. The MRC chronic dyspnea scale estimates dyspnea; it is simple to administer and has been used for many years to grade the effects of breathlessness on daily activities. This scale has been particularly used in subjects with COPD; it has been proven to be useful and is complementary to the forced expiratory volume in 1 s in the classification of disease. In the present study, dyspnea was common in all of the bronchiectasis subjects. In addition, all of the subjects with PH sensed dyspnea, and the majority of them had severe dyspnea. In a recent review by *Onen*, the level of dyspnea (as measured by the MRC chronic

dyspnea scale) was an important independent risk factor for mortality in bronchiectasis subjects, which is similar to the finding of our cohort [27]. The present study suggests that the level of dyspnea as evaluated by the MRC dyspnea scale may be similarly useful in the prediction of survival.

The present study has some limitations. In this study we aimed to recruit 30 consecutive patients for each group but we could not reach the target number of patients during the study period. Duration of dyspnea for patients with PH was on average 8 years longer than those without PH. This is not a matched-controlled study according to duration of dyspnea. However, it can be considered to be hypothesis generating so that further prospective controlled studies can be undertaken to explore the effect of symptom duration.

5. Conclusion

PH subjects are more hypoxemic and have a greater number of involvements in the lobes of the lungs. Right ventricle dysfunction can develop in bronchiectasis subjects without PH. Survival is worse in bronchiectasis subjects with PH than in those without PH, and MRC dyspnea score is an independent predictor of long-term survival.

Author's contributions

SÖ participated in the design of study and acquisition of data, and drafted the manuscript. OP participated in the design of the study and analyzed of samples for plasma and urinary ET-1. AÖ performed echocardiography and analyzed of data. AUD performed the statistical analysis and manuscript preparation. AT participated in the design and conception of the study and analysis of data. LÇ conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

Conflict of interest statement

This study was performed at Hacettepe University. None of the authors have any involvement –financial or otherwise- with the material mentioned in the manuscript which might lead to conflict of interest.

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