Short Communication

Decreased ventilatory efficiency during incremental exercise in bronchiectasis

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Bronchiectasis is characterized by aberrant bronchial dilatation (1). The structural changes have been associated with ventilatory dysfunction, exercise intolerance and ventilatory inhomogeneity (2,3) that may aggravate during exercise. A decreased ventilatory efficiency, reflected by the high carbon dioxide ventilatory equivalent (V_E/VCO_2), has been identified during incremental exercise in patients with COPD, especially when complicated with heart failure (4). At earlier stages of bronchiectasis, exercise intolerance might have become evident before cardiovascular complications developed (5). The mechanisms underlying exercise intolerance in patients with bronchiectasis without heart failure are, however, not entirely clear. By using incremental cycle ergometer, we determined the ventilation-gas exchange abnormalities in patients with bronchiectasis not complicated with physician-diagnosed heart failure.

Participants were enrolled between March 2017 and December 2018. The diagnosis of bronchiectasis was confirmed according to clinical symptoms (including chronic cough and sputum production) and chest high-resolution computed tomography within 12 months. For eligibility of study entry, patients with bronchiectasis were aged 18 years or greater, remained clinically stable, had no antibiotics use for >4 weeks, and had no physician-diagnosed heart failure. Patients with malignancy, heart attack within 6 months, or acute upper respiratory tract infections within 4 weeks were excluded. We also screened for possible right heart failure based on the radiologic signs on chest high-resolution computed tomography and echocardiography (among 23 out of 53 patients who have undergone the measurement). Healthy subjects were aged 18 years or greater, had no significant diseases influencing on exercise testing. Our study was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University. All participants gave written informed consent.

Patients underwent severity assessment with bronchiectasis severity index, impulse oscillometry, multiple-breath nitrogen washout test (which also measured the lung clearance index), spirometry, and cardiopulmonary exercise testing (CPET). All measurements were made with the commercial lung function testing instrument (Jaeger MasterScreen™. Carefusion Co., Ltd.). The methods for determining the etiology of bronchiectasis have been described previously (2). Healthy subjects underwent spirometry and CPET only. A cycle ergometer equipped with real-time gas-analyzer (COSMED Inc., Italy) was applied for CPET, including steady-state rest, 20-W increase in work rate at 1-min intervals until symptom limitation, and recovery. Main parameters comprised breath-by-breath ventilatory volume (V_E), tidal volume (V_T), oxygen consumption (VO_2), carbon dioxide production

(VCO_2), oxygen pulse (HR/VO_2), oxygen ventilatory equivalent (V_E/VO_2), V_E/VCO_2, and end-tidal carbon dioxide partial pressure ($PetCO_2$). Fatigue and dyspnea were graded using a 10-point scale (Borg's scale) at rest and after maximal exercise. We took reference on a published study to define the cut-off value of hypocapnia based on the partial pressure of end-tidal carbon dioxide ($PetCO_2$) at different time points of exercise [4].

Statistical analysis was performed using Graphpad Prism 5.0 (Graphpad Inc., USA). Kolmogorov-Smirnov test was used to assess normality of the continuous variables. Independent *t*-test or Mann-Whitney test was conducted for two-group comparisons, and multiple-group comparisons (among patients with or without exercise-induced hypocapnia and healthy controls, see the definition in the results section below) were conducted with one-way analysis-of-variance or Kruskal-Wallis test, followed by Bonferroni correction. Correlation analysis was done using Spearman's test.

Seventy-nine participants underwent screening, of whom 53 patients with bronchiectasis and 16 controls were analyzed. Reasons for the exclusion of bronchiectasis patients included joint deformity (n=2), FEV_1 <30% predicted (n=5), recent trauma (n=2) and heart failure (n=1). Fifty-eight point five percent of participants were middle-aged females who never smoked. The baseline characteristics are displayed in *Table 1*. Bronchiectasis severity was mostly graded as mild-to-moderate. Idiopathic (45.2%) and post-infection (35.8%) constituted the most common etiologies. None of the eligible participants had documented cardiovascular disorders except for grade II hypertension in one bronchiectasis patient. Sixty-seven-point nine percent of the bronchiectasis patients had restrictive/obstructive/mixed ventilatory dysfunction, and the mean FEV_1 was 72% predicted among 53 patients. Twenty-one (40%) patients with bronchiectasis had an increased ratio of residual volume to total lung capacity. None of the patients with bronchiectasis had radiologic signs of clinically evident heart failure. Three patients had mild pulmonary hypertension (*Table S1*). *Table S2* demonstrates the lung function characteristics of patients with bronchiectasis and healthy controls at rest. Overall, bronchiectasis patients yielded significantly lower levels of FVC and FEV_1 predicted% than healthy controls (both P<0.05).

V_E/VCO_2 was significantly higher in patients with bronchiectasis than in healthy controls throughout exercise (all P<0.01). However, there was no remarkable difference in V_E/VCO_2 between healthy controls and bronchiectasis patients without hypocapnia at anaerobic threshold or maximal intensity exercise. V_E/VCO_2 correlated strongly with $PetCO_2$ at maximal exercise (*Figure 1*), but not resting residual volumes or bronchiectasis severity. V_E/VCO_2 nadir correlated significantly with the simultaneously measured $PetCO_2$ (P<0.01). We next stratified bronchiectasis patients based on $PetCO_2$ because it explained substantially for exertional ventilatory responses. Patients with consistently low $PetCO_2$ throughout exercise (<35 mmHg, hypocapnia group) did not differ from their counterparts regarding resting ventilatory function, diffusing capacity, lung volumes and airway resistance (all P>0.05, *Table S2*) (*Table 1*).

Patients with hypocapnia yielded markedly lower peak work rate and shorter inspiratory time, but higher V_E/VO_2 and V_E/VCO_2, at anaerobic threshold than patients without (all P<0.05). At submaximal exercise, patients with hypocapnia yielded systematically higher V_E, V_E/VO_2 and V_E/VCO_2 but lower $PetCO_2$ than those without (all P<0.05, *Table 2*). Higher V_E was associated with consistently higher respiratory rate and shorter expiratory time at different time points of exercise in patients with hypocapnia as compared with those without hypocapnia. The higher V_E was, however, not associated with significant differences in V_T, the ratio of respiratory rate to inspiratory time, and the ratio of inspiratory to total respiratory time between patients with and without hypocapnia (*Figure 1*). Moreover, the disease severity (i.e., bronchiectasis severity index) did not correlate with most of the lung function parameters at different time points during exercise (data not shown).

There was no substantial difference in dyspnea or fatigue ratings at baseline between patients with and without hypocapnia. At maximal exercise, the increase was similar for dyspnea ratings although appearing greater for fatigue ratings in patients with hypocapnia.

Efficient ventilation is crucial to the exercise tolerability. In adults with cystic fibrosis, the ventilatory efficiency correlated significantly with the imaging severity of bronchiectasis that affects ventilatory inhomogeneity (6). First, our study has reaffirmed the ventilatory inefficiency (high V_E/VCO_2 levels) throughout incremental exercise in bronchiectasis. The high V_E/VCO_2 has previously been attributed to excessive ventilation in COPD-heart failure overlap (4), but the mechanisms in patients without clinically overt heart failure are less clear. The V_E/VCO_2 was recorded at fixed work rate but might get close to the V_E/VCO_2 nadir at anaerobic threshold or maximal exercise. By stratification based on $PetCO_2$ (which mirrored arterial

Table 1 Baseline characteristics of study participants

Parameters	Bronchiectasis patients		Healthy subjects (n=16)	P value*	P value**	P value#
	Hypocapnia (n=34)	No hypocapnia (n=19)				
Anthropometry						
Age (years)	45.0±15.2	54.0 (18.0)	36.6±15.1	0.022	0.197	0.008
Height (cm)	160.6±8.2	162.2±5.9	162.2±8.1	0.700	0.458	0.895
Body-mass index (kg/m^2)	19.4±2.4	21.9±3.8	22.7±2.5	<0.001	0.035	0.354
Females, n (%)	22 (64.7)	9 (47.4)	9 (56.3)	0.467	0.219	0.601
Never-smokers, n (%)	33 (97.1)	19 (100.0)	14 (87.5)	0.167	0.450	0.113
Disease characteristics						
No. of exacerbations in 2 years	1.0 (4.0)	1.0 (3.0)	NA	ND	0.541	ND
No. of bronchiectatic lobes	3.2±1.3	4.0 (2.0)	NA	ND	0.092	ND
HRCT total score	8.1±3.5	5.0 (5.0)	NA	ND	0.044	ND
Bronchiectasis severity index category, n (%)						
Mild	13 (38.2)	11 (57.9)	NA	ND	0.168	ND
Moderate	12 (35.3)	5 (26.3)	NA	ND	0.502	ND
Severe	9 (26.5)	2 (10.5)	NA	ND	0.170	ND
Bronchiectasis etiology, n (%)						
Idiopathic	15 (44.1)	7 (36.8)	NA	ND	0.606	ND
Post-infectious	10 (29.4)	9 (47.4)	NA	ND	0.191	ND
Other known etiologies	9 (26.5)	3 (15.8)	NA	ND	0.373	ND
Sputum bacteriology, n (%)						
Pseudomonas aeruginosa	13 (38.2)	6 (31.6)	NA	ND	0.628	ND
Other PPMs	13 (38.2)	5 (26.3)	NA	ND	0.380	ND
Commensals	8 (23.5)	8 (42.1)	NA	ND	0.158	ND
Medications used within 6 months, n (%)						
Mucolytics	21 (61.8)	10 (52.6)	NA	ND	0.518	ND
Macrolides	3 (8.8)	0	NA	ND	0.545	ND
Muscarinic receptor antagonist	7 (20.6)	0	NA	ND	0.041	ND

Mean ± standard deviation or otherwise median (interquartile range) were presented for numerical data depending on the normality, and categorical data were expressed as number (percentage) if appropriate. The threshold for statistical significance was 0.015 (after Bonferroni correction). Data in bold indicated the statistical analysis with significance. *, P value denoted the comparison among the three groups; **, P value for the comparison between bronchiectasis patients with and without hypocapnia; #, P value for the comparison between healthy controls and bronchiectasis patients without hypocapnia. PPMs, potentially pathogenic microorganisms, including *Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella Catarrhalis, Haemophilus parainfluenzae, Staphylococcus aureus, Staphylococcus epidermis, Sphingomonas paucimobilis, Rothia mucilaginosa*). NA, not applicable; ND, not done.

Table 2 CPET parameters at anaerobic threshold and maximal exercise intensity in bronchiectasis patients and healthy subjects

Parameters	Time point	Healthy subjects (n=16)	No hypocapnia (n=19)	Hypocapnia (n=34)	P value*	P value**	P value#
Peak work rate	–	174.1±50.4	134.7±47.2	110.0 (48.8)	<0.001	<0.001	0.023
V_E	AT	45.2±17.5	34.6±9.5	38.0±10.7	0.229	0.361	0.033
	MI	58.0±19.2	48.7±15.2	48.2±14.2	0.220	0.718	0.185
V_T	AT	1.6±0.6	1.3±0.5	1.1 (0.3)	0.027	0.266	0.166
	MI	1.6±0.5	1.5±0.5	1.2 (0.5)	0.020	0.121	0.300
VO_2 (L/min)	AT	1,707±717	1,258±399	1,231±406	0.040	0.795	0.029
	MI	1,859±662	1,526±413	1,432±424	0.027	0.239	0.079
VCO_2 (L/min)	AT	1,713±731	1,265±403	1,242±412	0.051	0.825	0.032
	MI	2,088±688	1,771±573	1,530±439	0.010	0.140	0.147
HR (bpm)	AT	142.1±18.4	129.1±12.7	131.6±19.2	0.087	0.624	0.021
	MI	166.5 (19.3)	151.3±12.0	146.3±16.3	0.005	0.164	0.020
VO_2/HR	AT	11.8±4.0	9.7±2.4	8.5 (3.3)	0.078	0.483	0.066
	MI	9.8 (5.2)	10.0±2.3	8.7 (3.8)	0.224	0.409	0.363
RR	AT	29.4±6.1	27.2±6.9	32.8±5.9	0.009	0.006	0.346
	MI	36.1±6.4	34.2±8.0	39.5±8.4	0.080	0.039	0.449
V_E/VO_2	AT	26.8±2.0	27.8±2.6	31.5±3.2	<0.001	<0.001	0.240
	MI	31.9±6.6	31.5±5.1	34.0±5.1	0.151	0.140	0.835
V_E/VCO_2	AT	26.8±2.1	27.2±3.6	31.1±3.4	<0.001	<0.001	0.696
	MI	27.9±3.1	27.4±3.2	31.7±3.0	<0.001	<0.001	0.662
Ti	AT	1.0±0.2	1.0 (0.4)	0.9±0.1	0.005	0.003	0.260
	MI	0.8±0.1	0.8±0.2	0.7±0.2	0.137	0.055	0.328
Te	AT	1.2±0.3	1.1 (0.3)	1.1 (0.3)	0.572	0.782	0.407
	MI	1.0±0.2	1.0±0.3	0.9±0.2	0.064	0.031	0.443

Mean ± standard deviation or otherwise median (interquartile range) were presented for numerical data, and categorical data were expressed as number (percentage) if appropriate. The threshold for statistical significance was 0.015 (after Bonferroni correction). Data in bold indicated the statistical analysis with significance. *, P value denoted the comparison among the three groups; **, P value for the comparison between bronchiectasis patients with and without hypocapnia; #, P value for the comparison between healthy controls and bronchiectasis patients without hypocapnia. CPET, cardiopulmonary exercise testing; AT, anaerobic threshold, MI, maximal intensity of exercise; V_E, ventilatory volume; V_T, tidal volume; RR, respiratory rate; SpO_2, pulse oximetry; VO_2, oxygen consumption; VCO_2, carbon dioxide production; VO_2/HR, oxygen pulse, which is the ratio of heart rate and oxygen consumption; V_E/VO_2, oxygen ventilatory equivalent, which is the ratio of ventilatory volume and oxygen consumption; V_E/VCO_2, carbon dioxide ventilatory equivalent, which is the ratio of ventilatory volume and carbon dioxide production; $PetCO_2$, end-tidal carbon dioxide pressure; Ti, inspiratory duration; Te, expiratory duration.

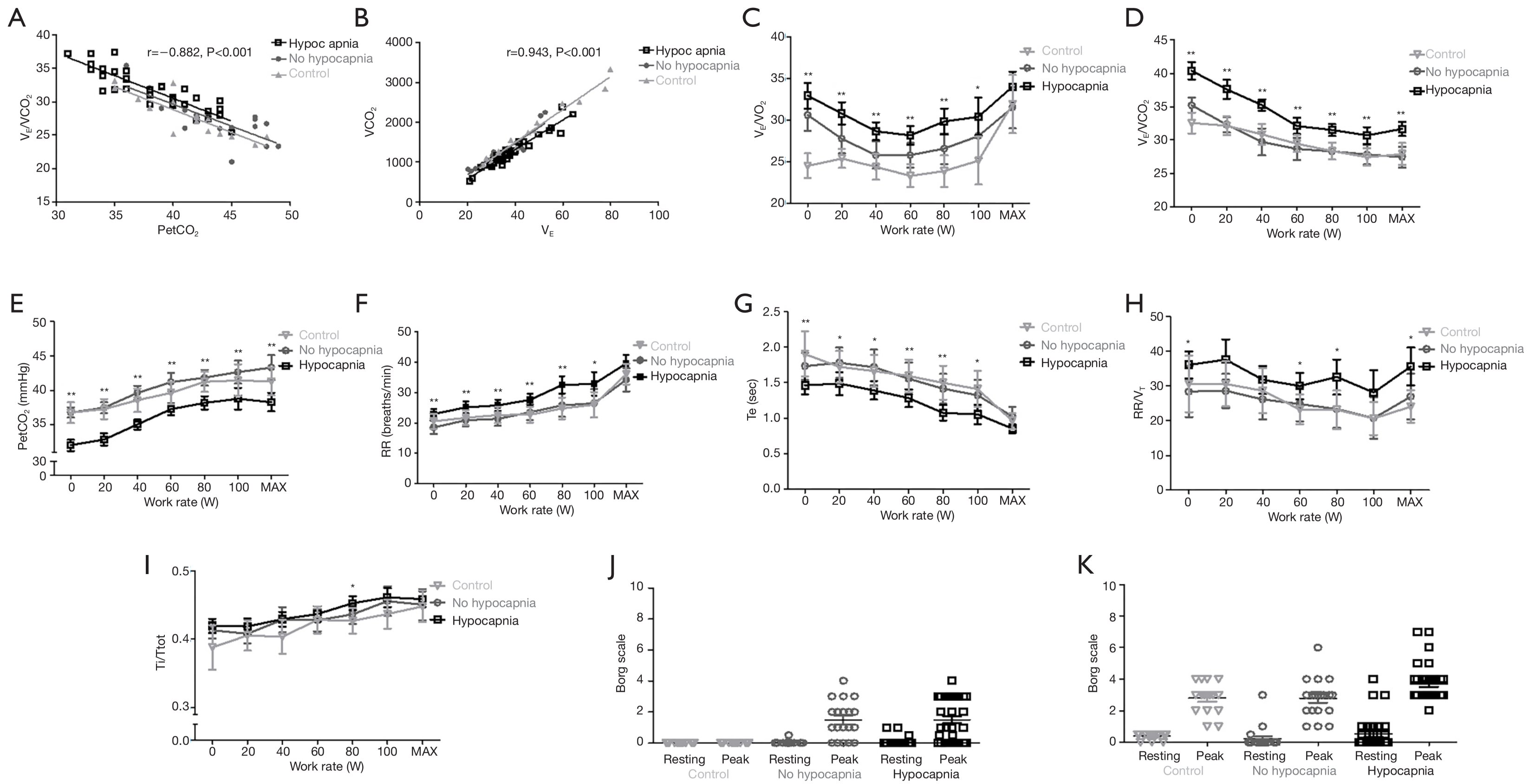

Figure 1 Ventilatory, gas exchange, and parameters reflecting on breathing and lung volume during incremental cycle exercise in bronchiectasis patients and healthy subjects. (A) The correlation between V_E/VCO_2 and $PetCO_2$ at peak exercise; (B) the correlation between V_E and VCO_2 at anaerobic threshold; (C) V_E/VO_2; (D) V_E/VCO_2; (E) $PetCO_2$; (F) RR; (G) Te; (H) RR/V_T; (I) Ti/Ttot; (J) changes in dyspnea scale at resting and maximal exercise; (K) changes in fatigue scale at resting and maximal exercise. Mean ± standard deviation were presented for all the values demonstrated in the figure. *, P<0.05 for the comparison among bronchiectasis patients with and without hypocapnia and healthy subjects at individual time points; **, P<0.01 for the comparison among bronchiectasis patients with and without hypocapnia and healthy subjects at individual time points. V_E, ventilatory volume; V_T, tidal volume; VO_2, oxygen consumption; VCO_2, carbon dioxide production; VO_2/HR, oxygen pulse, which is the ratio of heart rate and oxygen consumption; V_E/VO_2, oxygen ventilatory equivalent, which is the ratio of ventilatory volume and oxygen consumption; V_E/VCO_2, carbon dioxide ventilatory equivalent, which is the ratio of ventilatory volume and carbon dioxide production; $PetCO_2$, end-tidal carbon dioxide pressure; Te, expiratory time; Ti, inspiratory time; Ttot, total respiratory time per breath cycle; RR, respiratory rate; RR/V_T, the ratio of respiratory rate to tidal volume.

or capillary carbon dioxide partial pressure), we have identified patients with hypocapnia at different time points during exercise. Because $PetCO_2$ might not invariably be a reliable surrogate of $PaCO_2$, caution should be exercised in interpreting some of our findings. The reduced exercise tolerance might have also resulted from the dead space ventilation (7), because airflow limitation (47% among 53 patients) and increased residual volumes (~30.2%) were present at resting.

Second, patients with hypocapnia had more prominent airflow limitation, and consistently higher respiratory rate and a trend towards shorter expiratory time during exercise. Hence, the inspiratory constraint could also be due to the greater V_E. In COPD, although the high V_E/VCO_2 could be partially compensated by the inspiratory constraint and hypercapnia, V_E/VCO_2 may remain high because of the exaggerated dead space ventilation and greater respiratory drive, particularly when complicated with heart failure (4). We cannot preclude subclinical pulmonary hypertension or heart failure, particularly in those with bilateral bronchiectasis (8). This might help partially explain for the lack of significant difference in dyspnea scale between patients with and without hypocapnia.

Despite efforts to identify possible signs of right heart failure, echocardiography was not performed in every individual, and therefore we might have included some patients with early-stage right heart insufficiency. Catheterization was not performed before incremental exercise testing, thus pulmonary hypertension which is a crucial indicator of right heart failure could have been under-diagnosed. However, the invasiveness and requirement of medical expertise have limited the applicability of catheterization as a routine measurement in our clinical setting.

In summary, the greater ventilatory demand might have contributed to inspiratory constraint, partly explaining for the decreased ventilatory efficiency on exertion in patients with bronchiectasis without physician-diagnosed heart failure. Further studies are needed to determine whether interventions (i.e., pulmonary rehabilitation) could help improve the outcomes of bronchiectasis by increasing the ventilatory efficiency.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at 10.21037/jtd.2020.03.113). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Radiologic signs among bronchiectasis patients

Patient no.	Age (yrs)	Sex	Signs of right heart failure on HRCT	Echocardiographic findings
1	35	Female	Unremarkable	ND
2	62	Female	Unremarkable	Mild tricuspid valve regurgitation
3	54	Female	Unremarkable	ND
4	28	Male	Unremarkable	ND
5	51	Male	Unremarkable	ND
6	51	Female	Unremarkable	Normal right heart function
7	56	Male	Unremarkable	Normal right heart function
8	41	Male	Unremarkable	ND
9	29	Female	Unremarkable	Normal right heart function
10	52	Female	Unremarkable	ND
11	63	Male	Unremarkable	Normal right heart function
12	65	Male	Unremarkable	ND
13	51	Male	Unremarkable	ND
14	39	Male	Unremarkable	ND
15	59	Female	Unremarkable	ND
16	54	Female	Unremarkable	ND
17	55	Female	Unremarkable	ND
18	58	Male	Unremarkable	ND
19	69	Male	Unremarkable	ND
20	38	Female	Unremarkable	ND
21	65	Male	Unremarkable	Mild pulmonary hypertension
22	56	Female	Unremarkable	Mild tricuspid valve regurgitation
23	37	Female	Unremarkable	Normal right heart function
24	55	Male	Unremarkable	ND
25	54	Female	Unremarkable	Normal right heart function
26	23	Female	Unremarkable	ND
27	70	Female	Unremarkable	Mild tricuspid valve regurgitation
28	46	Male	Unremarkable	ND
29	59	Male	Unremarkable	ND
30	40	Male	Unremarkable	Mild tricuspid valve regurgitation
31	30	Male	Unremarkable	Normal right heart function
32	47	Female	Unremarkable	ND
33	38	Female	Unremarkable	ND
34	26	Male	Unremarkable	ND
35	51	Female	Unremarkable	Normal right heart function
36	21	Female	Unremarkable	Normal right heart function
37	66	Female	Unremarkable	ND
38	25	Male	Unremarkable	ND
39	37	Female	Unremarkable	Normal right heart function
40	57	Male	Unremarkable	Normal right heart function
41	24	Female	Unremarkable	Mild pulmonary hypertension
42	27	Female	Unremarkable	ND
43	61	Male	Unremarkable	ND
44	46	Male	Unremarkable	ND
45	56	Female	Unremarkable	Mild tricuspid valve regurgitation
46	49	Female	Unremarkable	ND
47	65	Female	Unremarkable	Mild tricuspid valve regurgitation; mild pulmonary hypertension
48	63	Female	Unremarkable	ND
49	29	Female	Unremarkable	Mild tricuspid valve regurgitation
50	51	Male	Unremarkable	ND
51	24	Female	Unremarkable	Normal right heart function
52	31	Female	Unremarkable	Normal right heart function
53	63	Female	Unremarkable	Normal right heart function

ND, not done.

Table S2 Resting lung function parameters in bronchiectasis patients and healthy subjects

Parameter	Healthy subjects (n=16)	No hypocapnia (n=19)	Hypocapnia (n=34)	P value*	P value**
FVC (L)	3.30±0.94	2.71±0.82	2.57±0.85	0.057	0.578
FVC pred%	90.3±5.1	80.5±17.5	77.1±17.5	0.014	0.442
FEV_1 (L)	2.78±0.83	2.03±0.77	1.77±0.68	<0.001	0.282
FEV_1 pred%	90.1±6.1	76.1 (42.8)	63.2±19.2	<0.001	0.109
TLC (L)	ND	4.89±0.88	4.36±1.13	NA	0.070
TLC pred%	ND	88.6±9.8	85.8±14.6	NA	0.325
RV (L)	ND	2.10±0.54	1.84±0.63	NA	0.101
RV pred%	ND	109.3±28.6	110.1±24.0	NA	0.907
RV/TLC	ND	43.2±9.9	42.2±9.4	NA	0.944
RV/TLC pred%	ND	128.4±27.9	130.0±20.8	NA	0.900
D_LCO (mL/min/mmHg)	ND	20.7 (7.0)	22.2±4.7	NA	0.656
D_LCO pred%	ND	86.4±11.2	85.7±15.6	NA	0.836
D_LCO/V_A (mL/min/mmHg/L)	ND	5.09±0.62	5.20±0.74	NA	0.686
D_LCO/V_A pred%	ND	107.8±14.7	103.4±15.8	NA	0.305
Z_5	ND	0.36 (0.19)	0.47±0.22	NA	0.685
R_5	ND	0.35 (0.16)	0.44±0.21	NA	0.901
R_{20}	ND	0.30 (0.06)	0.34±0.11	NA	0.361
X_5	ND	–0.10 (0.08)	–0.14 (0.13)	NA	0.115
Fres	ND	15.6±8.0	15.1±7.9	NA	0.653
AX	ND	0.25 (0.58)	0.47 (0.85)	NA	0.521

Mean ± standard deviation or otherwise median (interquartile range) were presented for numerical data, and categorical data were expressed as number (percentage) if appropriate. *, P value denoted the comparison on individual clinical parameters among the three groups; **, P values for the comparison between bronchiectasis patients with and without hypocapnia. FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; TLC, total lung capacity; RV, residual volume; D_LCO, diffusing capacity for carbon monoxide; D_LCO/V_A, diffusing capacity for carbon monoxide corrected with the alveolar volume; Z_5, total respiratory impedance; R_5, airway resistance at 5 Hz; R_{20}, airway resistance at 20 Hz; X_5, elastance at 5Hz; Fres, resonant frequency; AX, the area of the resonance frequency.