Heart rate recovery after the 6-min walk test in people with bronchiectasis

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Abstract

Background The cardiac autonomic response to exercise and during recovery has been poorly explored in bronchiectasis.

Methods A longitudinal study was conducted in adults with bronchiectasis. Sociodemographic and clinical data were collected at baseline and after 12 months of follow-up. The heart rate recovery after the first (HRR_1) and second minute (HRR_2) of recovery in the six-min walk test (6MWT) was estimated in both assessments. Adjusted regression models were used to identify predictors of a delayed HRR_1 ($HRR_1 \leqslant 14$).

Results 104 participants with a mean±SD age of 64±13 years and mostly women (67%) were included. A delayed HRR_1 after the baseline 6MWT was identified in 36% of participants. These participants presented a higher proportion of males, increased body mass index, higher disease severity, more likely to require hospitalisation, more impact on quality of life, lower exercise capacity, lower heart rate at the end of the 6MWT and lower HRR_2. Disease severity (β, 95% CI) (moderate and severe *versus* mild, −0.47 (−0.94 to −0.01)) and distance walked (0.34 (0.11 to 0.56)) were the independent variables associated with HRR_1. Of the 45 participants who completed the entire follow-up period, 24% exhibited delayed HRR_1. The presence of at least two exacerbations during the follow-up period (OR 16.89, 95% CI 1.44 to 197.48) was the only predictor of a delayed HRR_1 in the assessment completed at the end of the study.

Conclusion HRR_1 is related to disease severity and is mainly affected by having severe exacerbations in people with bronchiectasis.

Introduction

Bronchiectasis is a chronic respiratory disease characterised by permanent abnormal dilation of bronchi leading to chronic airway infection and inflammation and an impaired mucociliary clearance system [1]. Patients with bronchiectasis frequently present with respiratory symptoms such as chronic cough and daily sputum expectoration [2] and dyspnoea [3]. These symptoms markedly impair health-related quality of life [4] and contribute to a higher risk of exacerbations and hospitalisations [5].

While respiratory symptoms dominate the clinical presentation of bronchiectasis, it is considered a complex multicomponent disease [6] and the presence of extrapulmonary clinical manifestations such as lower exercise capacity [7] and psychological symptoms [8] as well as lifestyle manifestations such as reduced physical activity [9], are also common in this population. Indeed, the risk of mortality in people with bronchiectasis increases with the number of coexisting comorbidities (*e.g.* cardiovascular disorders,

connective tissue diseases and inflammatory bowel disease) [6]. Furthermore, multimorbidity (defined as the coexistence of at least two chronic conditions) is also associated with higher rates of exacerbation and hospitalisation in this population [10].

An increased systemic inflammation has been proposed as one of potential mechanism in the development of these comorbidities in bronchiectasis, particularly for cardiovascular diseases [11]. Previous studies have reported that people with bronchiectasis have a greater cardiovascular risk compared with the general population [12, 13] and this increased risk seems to be related to disease severity [14, 15] and exacerbations [16], particularly if hospitalisation is required [17].

The presence of cardiac autonomic dysfunction (an imbalance between sympathetic and parasympathetic nervous system activity) is globally considered an independent predictor of cardiovascular events and mortality [18]. Heart rate recovery (HRR), the reduction in heart rate (HR) during the recovery phase after a laboratory- or field-based maximal or submaximal exercise test, is considered a marker of cardiac autonomic function [19]. In people with COPD and other chronic respiratory diseases, a delayed HRR during the recovery phase has been associated with lower exercise capacity [20, 21] and reduced time spent engaged with vigorous physical activity [22] and has been identified as a predictor of future exacerbations [23] and mortality [24, 25].

HRR assessment, though rarely explored in people with bronchiectasis, offers a practical and easily interpretable tool for real-world clinical practice. If a delayed HRR is indeed associated with worse clinical outcomes in bronchiectasis, this biomarker could prove valuable in predicting the prognosis of bronchiectasis and identifying suitable candidates for specific treatments aimed at improving cardiac autonomic function, such as exercise training [26] or physical activity promotion [22].

Therefore, the objectives of this prospective longitudinal study were to 1) describe the HRR of people with bronchiectasis after completing a submaximal exercise test; 2) identify potential clinical determinants for a delayed HRR in this population; and 3) determine what changes in clinical features over a 12-month follow-up period predict a delay in HRR in people with bronchiectasis.

Methods

Study design and participants

Patients with a confirmed diagnosis of bronchiectasis using high-resolution computed tomography and clinically significant symptoms (*e.g.* cough and sputum production most days of the week) were invited to participate in this longitudinal study between October 2015 and November 2019. Participants were recruited from tertiary hospitals in Zaragoza and Barcelona, Spain.

Adult outpatients with bronchiectasis in a clinically stable condition were included in this study. Exclusion criteria were: 1) a diagnosis of cystic fibrosis; 2) smoker or former-smoker of ⩾10 pack-years; 3) presence of a severe or unstable cardiovascular disease (*e.g.* chronic heart failure or atrial fibrillation); 4) cardiac pacemaker; 5) use of drug treatment that affects cardiovascular autonomic function (*e.g.* β-blockers); and 6) any comorbidities potentially affecting the safe administration of the test (*e.g.* neurological or neuromuscular disorders). Patients involved in a pulmonary rehabilitation programme during the previous year were also excluded. If a new treatment was started during the follow-up period that was likely to impact exacerbations (*e.g.* long-term antibiotic treatment, mucoactive drugs, pulmonary rehabilitation programme or airway clearance techniques), participants withdrew.

Written informed consent was obtained from each participant before any data collection and the study was approved by the Research Ethics Committee of Aragón (PI14/00100) and the Hospital Clinic Research Ethics Committee (HCB/2016/0012).

Procedure and data collection

Sociodemographic, anthropometric (height and weight) and clinical data were first collected. The aetiology, comorbidities, radiological and microbiological features, exacerbation frequency and the need of hospital admission over the last year and the pharmacological treatment were obtained from medical records. Disease severity was evaluated using the bronchiectasis severity index (BSI) and the impact of comorbidities on disease prognosis was assessed using the Charlson comorbidity index. Spirometry was performed according to international guidelines [27] to obtain the post-bronchodilation forced expiratory volume in 1 s as percentage of predicted (FEV_1 % pred). Health-related quality of life was assessed using the respiratory domain of the Spanish-validated version of the quality-of-life questionnaire for bronchiectasis (QoL-B) [28].

Initially, participants performed two 6-min walk tests (6MWTs) according to guidelines [29] which were separated by a rest period of 30 min. Both 6MWTs were conducted on a straight, indoor track of 30 m. HR and peripheral oxygen saturation measured by pulse oximetry (S_{pO_2}) were recorded using a pulse oximeter (Nonin Onyx Vantage 9590) at rest before the 6MWT, at the end of the 6MWT and after 1 and 2 min of the completion of the test while the patient remained seated. This time-based measurement protocol was designed to capture the rapid recovery phase, which is closely associated with the activation of the parasympathetic nervous system. The modified Borg scale [30] was also used to evaluate dyspnoea and lower limb fatigue perception during the same time points. Participants with supplemental O_2 prescribed used their own equipment at the same flow rate as their regular prescription for exercise. Data were extracted from the 6MWT using the greatest distance obtained. After 12 months, participants completed a single 6MWT following the same instructions. Over the follow-up period, exacerbation frequency and hospital admissions were prospectively recorded. Additionally, lung function and QoL-B (respiratory domain) were again assessed at the end of the follow-up period.

The cardiac autonomic dysfunction, using the HRR, was defined as the differences between the HR at the end of 6MWT and after the first minute (HRR_1) and second minute (HRR_2) of the recovery phase [23, 24].

Statistical analysis

Descriptive parameters were presented as frequencies for categorical variables, mean±SD for normally distributed continuous variables or median and percentile 25th to 75th (P_{25}–P_{75}) for continuous variables with non-normal distribution. Differences between participants based on the HRR_1 obtained (delayed if $HRR_1 \leqslant 14$ or normal if $HRR_1 > 14$) [23] and classifications according to BSI score (mild, moderate and severe) were analysed using a t-test for independent samples, Mann–Whitney, one-way ANOVA and Kruskal–Wallis tests, as appropriate. The comparability results are described as mean difference (95% CI) for normally distributed variables or median difference (95% CI) [31] for non-normally distributed variables.

Univariate and multivariate linear regression models were used to identify potential determinants of a HRR_1 delay after the 6MWTs conducted at the baseline. Variables for the regression models were selected based on two criteria: bronchiectasis-specific clinical relevance and established predictors of delayed HRR_1 in other respiratory conditions. At baseline, the independent variables evaluated were disease severity according to BSI classification (moderate and severe *versus* mild), Charlson comorbidity index, respiratory domain of QoL-B, outcomes obtained at the beginning of the 6MWT (HR, S_{pO_2}, dyspnoea and lower limb fatigue perception) and distance walked. Additionally, after confirming that the cut-off of 14 beats for HRR_1 was appropriate for identifying differences in our sample, a logistic regression model was used to identify potential predictors of a delayed HRR_1 ($HRR_1 \leqslant 14$ *versus* $HRR_1 > 14$) at the end of the 12-month follow-up period. The model included as potential predictors the differences after the follow-up period in lung function and respiratory domain of QoL-B, exacerbations and the changes observed between the 6MWTs conducted at baseline and at the end of the follow-up period (including HR, S_{pO_2}, dyspnoea, lower limb fatigue and distance walked).

Globally, if two independent variables were correlated ($r > 0.30$), the variable with the largest variance was excluded from the univariate regression model to avoid collinearity. Only variables that showed a positive result in the univariate regression model ($p < 0.2$) were included in the multivariate regression models, which was adjusted for potential confounders (age, gender and body mass index (BMI)) [19]. Statistical significance was defined as $p < 0.05$ in two-tailed tests and coefficients (B), standardised coefficients (β) and odds ratio (OR) with 95% confidence intervals were calculated and used for interpretation.

Results

The sample comprised 104 participants with bronchiectasis who were clinically stable at the time of recruitment. The baseline and clinical characteristics are outlined in table 1. Participants had a mean±SD age of 64±13 years, were mostly woman (67%) and the most common aetiology of bronchiectasis was post-infection (46%). According to the BSI classification, the distribution of participants was as follows: 27% were classified as mild, 41% as moderate and 32% as severe. Moreover, all participants completed the baseline 6MWT and walked a mean of 508±95 m. They presented mean HR (beats per min) values of 80 [11] at the start and 112 [18] at the end of the test, respectively (table 2). Only four participants used supplementary oxygen therapy during 6MWT.

Relationship between clinical features and cardiac autonomic function

The mean HRR_1 after the baseline 6MWT was 20 [12] beats and the mean HRR_2 was 27 [13] beats considering the entire study sample. 38 participants (36%) were identified with a delayed HRR_1 after the

TABLE 1 Baseline sociodemographic and clinical characteristics of participants (n=104) overall and stratified by HRR_1 after the initial 6MWT

Characteristics and clinical outcomes	All participants (n=104)	$HRR_1 \leqslant 14$ (n=38)	$HRR_1 > 14$ (n=66)	Between-group differences (p-value)
Demographics				
Age, years	64±13	68±12	62±14	0.06
Gender, female	70 (67)	20 (53)	50 (76)	**0.01**
BMI, $kg \cdot m^{-2}$	24.5±4.3	25.8±4.9	23.8±3.8	**0.03**
Charlson comorbidity index	1 (1–2)	1 (1–2)	1 (1–2)	0.5
Aetiology				0.05
Post-infection	48 (46)	15 (39)	33 (50)	
Idiopathic	23 (22)	13 (34)	10 (15)	
Others	33 (32)	10 (27)	23 (5)	
Disease severity (BSI)				
Total score	7 (4–11)	8 (5–12)	6 (4–8)	**0.01**
BSI classification				**0.007**
Mild	28 (27)	6 (16)	22 (33)	
Moderate	43 (41)	13 (34)	30 (46)	
Severe	33 (32)	19 (50)	14 (21)	
Clinical status				
Number of exacerbations in the last year	2 (1–3)	2 (1–4)	2 (1–3)	0.2
At least one hospitalisation in the last year	28 (27)	16 (42)	12 (18)	**0.008**
Quality of life				
Physical function	56.7 (33.3–80)	50.0 (33.3–66.7)	63.3 (33.3–85.0)	0.22
Role function	66.7 (60.0–100)	66.7 (33.3–91.6)	80.0 (33.3–100)	0.05
Vitality	66.7 (33.3–66.7)	66.7 (33.3–66.7)	66.7 (47.2–66.7)	0.19
Emotional function	83.3 (66.7–100)	66.7 (41.7–89.6)	83.3 (41.7–100)	**0.03**
Social function	66.7 (50.0–100)	62.5 (33.0–83.3)	70.8 (52.1–100)	**0.04**
Treatment burden	66.7 (33.3–100)	66.7 (33.0–100)	88.9 (55.6–100)	0.16
Health perception	50.0 (33.3–66.7)	50.0 (33.3–66.7)	50.0 (33.3–66.7)	0.74
Respiratory domain of QoL-B	66.6 (66.6–100)	66.6 (66.6–82.9)	66.6 (66.6–100)	0.5
Lung function				
FEV_1 % pred	71±22	68±24	74±20	0.2
FVC % pred	80±20	75±23	83±18	0.07
Chronic infection				
Pseudomonas aeruginosa	38 (37)	15 (39)	23 (35)	0.6
Long-term antibiotic treatment				
Inhaled	19 (18)	10 (26)	9 (14)	0.1

Data are presented as n (%), mean±SD and median (interquartile range). 6MWT: 6-min walk test; HRR_1: heart rate recovery in the first minute after the 6MWT; BMI: body mass index; BSI: bronchiectasis severity index; QoL-B: quality of life of bronchiectasis questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred: % predicted. Statistically significant differences (p<0.05) are in bold.

baseline 6MWT. This group of patients was characterised by a higher proportion of male participants, had higher BMI, more severe disease and were more likely to be hospitalised in the last year. They also reported a more significant impact on their quality of life (emotional and social domains) (table 1). In the baseline 6MWT, participants with a delayed HRR_1 walked a shorter distance (mean difference −80 m, 95% CI −116 to −45) and achieved a lower HR at the end of the test (−15 beats, 95% CI −21 to −8) compared with those with a HRR_1 >14 beats. The HRR_2 after the 6MWT remained lower the HRR_2 after the 6MWT remained lower in the delayed HRR1 group compared with those with a normal HRR_1 (−18 beats, 95% CI −22 to −14) (table 2).

Delayed HRR_1 after the baseline 6MWT was observed in all disease severity classifications, with 16% in participants classified as mild according to BSI score, 34% in moderate and 50% in severe (p=0.007; table 1). Participants with severe or moderate disease severity had lower values of HRR_1 (p=0.004) and HRR_2 (p=0.002) than those classified as mild. Moreover, lower S_{pO_2} at baseline and after the 6MWT test were observed in participants with severe BSI compared with those classified as mild and moderate. The distance walked in the baseline 6MWT demonstrated a decline from participants with mild disease severity to those with moderate and severe severity (table 3). The distance difference between severe and mild participants was −115 (95% CI −159 to −71) m and this difference is greater than the minimal important difference (25 m) reported in the 6MWT in people with bronchiectasis [32].

TABLE 2 Outcomes obtained during the initial 6MWT and stratified according to the HRR_1 obtained during the recovery phase in this test (n=104)

	All participants (n= 104)	$HRR_1 \leqslant 14$ (n=38)	$HRR_1 > 14$ (n=66)	Between-group differences, mean/median difference (95% CI)
HR at baseline, beats per min	80 (11)	80 (11)	79 (11)	1 (−3 to 5)
HR final, beats per min	112 (18)	103 (14)	118 (17)	**−15 (−21 to −8)**
Maximal HR achieved, %	66 (10)	61 (8)	69 (10)	**−8 (−11 to −4)**
HRR_1, beats	20 (12)	7 (7)	27 (8)	**−20 (−23 to −17)**
HRR_2, beats	27 (13)	15 (9)	33 (10)	**−18 (−22 to −14)**
S_{pO_2} (%) basal	96 (95–97)	95 (94–97)	96 (95–97)	−1 (−1 to 0)[#]
S_{pO_2} (%) final	94 (92–96)	94 (91–96)	94 (92–96)	0 (−1 to 0)[#]
Borg scale (dyspnoea) basal	0 (0–2)	0.5 (0–2)	0 (0–2)	0 (0 to 0)[#]
Borg scale (dyspnoea) final	2 (0.5–4)	3 (0.5–4)	2 (0–4)	0 (0 to 0.5)[#]
Borg scale (lower limb fatigue) basal	0 (0–2)	0 (0–2)	0 (0–2)	0 (0 to 0)[#]
Borg scale (lower limb fatigue) final	2 (0–3)	2 (0–3)	2 (0–3)	0 (0 to 0)[#]
Distance walked, m	508 (95)	457 (99)	537 (80)	**−80 (−116 to −45)**

Data are presented as mean±SD and median (interquartile range), except for the mean/median difference column, which indicates 95% confidence interval (CI). 6MWT: 6-min walk test; HRR_1: heart rate recovery in the first minute after the 6MWT; HR: heart rate; HRR_2: heart rate recovery in the second minute after the 6MWT; S_{pO_2}: oxygen saturation measured by pulse oximetry. Statistically significant differences are in bold (p<0.05). [#]: median difference (95% CI).

Disease severity, resting HR, S_{pO_2} and distance walked in the baseline 6MWT were positively associated with HRR_1 in the univariable linear regression model (p<0.2). In the multivariable linear regression model (adjusted by age, sex and BMI), disease severity (moderate and severe *versus* mild) and distance walked were the independent variables associated with HRR_1 (table 4).

Relationships between changes in clinical features and cardiac autonomic function

A total of 45 participants (43% of the total sample) completed the 6MWT after the follow-up period, all of whom were clinically stable at the time of the assessment. These patients were younger, had fewer exacerbations, were less likely to require hospital admission and to be treated with long-term inhaled antibiotics at baseline than those who did not complete the follow-up period. This group of participants

TABLE 3 Outcomes obtained during the initial 6MWT stratified according to disease severity (n=104)

	Mild (n=28)	Moderate (n=43)	Severe (n=33)	Between-group differences			
				p-value	Mild *versus* moderate, mean/median difference (95% CI)	Mild *versus* severe, mean/median difference (95% CI)	Moderate *versus* severe, mean/median difference (95% CI)
HR basal, beats per min	78±12	78±11	83±11	0.1		NA	
HR final, beats per min	118±21	111±17	108±15	0.1		NA	
Maximal HR achieved, %	66±12	66±9	66±9	0.9		NA	
HRR_1, beats	26±12	19±11	15±13	0.004	**7 (1 to 12)**	**11 (4 to 17)**	4 (−2 to 9)
HRR_2, beats	34±13	26±10	21±14	0.002	**7 (2 to 13)**	**12 (6 to 19)**	5 (−1 to 10)
S_{pO_2} (%) basal	97 (96–97)	96 (95–97)	95 (94–95)	<0.001	1 (0 to 1)[#]	**2 (2 to 2)**[#]	**2 (1 to 2)**[#]
S_{pO_2} (%) final	95 (94–96)	94 (93–95)	92 (89–96)	0.03	1 (0 to 1)[#]	**2 (1 to 3)**[#]	**1 (1 to 2)**[#]
Borg scale (dyspnoea) basal	0 (0–1)	0 (0–2)	1 (0–2)	0.4		NA	
Borg scale (dyspnoea) final	2 (0–4)	2 (0.5–3)	3 (2–5)	0.05		NA	
Borg scale (lower limb fatigue) basal	0 (0–1)	0.5 (0–2)	0.5 (0–2)	0.3		NA	
Borg scale (lower limb fatigue) final	1 (0–3)	2 (0.5–3)	2 (0–3)	0.4		NA	
Distance walked, m	56±64	512±85	452±100	<0.001	**55 (17 to 92)**	**115 (71 to 159)**	**60 (19 to 102)**

Data are presented as mean±SD and median (interquartile range), except for the mean and median difference columns, which indicate 95% confidence interval (CI). 6MWT: 6-min walk test; HR: heart rate; HRR_1: heart rate recovery in the first minute after the 6MWT; HRR_2: heart rate recovery in the second minute after the 6MWT; S_{pO_2}: oxygen saturation measured by pulse oximetry; NA: not available. Statistically significant differences are in bold (p<0.05). [#]: median difference (95% CI).

TABLE 4 Linear regression model for HRR_1 (adjusted by age, sex and BMI) after the 6MWT at baseline (n=104)

	Univariable analysis		Adjusted multivariable analysis (R^2=0.32; adjusted R^2=0.26)		
	B (95% CI)	p-value	B (95% CI)	β (95% CI)	p-value
Disease severity (BSI)					
Moderate and severe *versus* mild	−8.64 (−13.80 to −3.48)	0.001	**−5.81 (−11.56 to −0.07)**	**−0.47 (−0.94 to −0.01)**	**0.04**
Charlson index	0.08 (−2.94 to 3.12)	0.95		NA	
QoL-B, respiratory domain score	−0.02 (−0.23 to 0.17)	0.79		NA	
HR (basal)	−0.15 (−0.37 to 0.06)	0.17	−0.20 (−0.40 to 0.00)	−0.17 (−0.35 to 0.00)	0.05
S_{pO_2} (basal)	0.89 (−0.02 to 1.82)	0.05	0.04 (−0.87 to 0.96)	0.01 (−0.18 to 0.20)	0.92
Borg scale (dyspnoea) basal	−0.71 (−2.52 to 1.10)	0.43		NA	
Borg scale (lower limb fatigue) basal	−0.25 (−1.76 to 1.25)	0.74		NA	
Distance walked, m	0.04 (0.02 to 0.07)	< 0.001	**0.04 (0.01 to 0.07)**	**0.34 (0.11 to 0.56)**	**0.004**
F change; p-value				5.55; p<0.001	

HRR_1: heart rate recovery in the first minute after the 6MWT; BMI: body mass index; 6MWT: 6-min walk test; BSI: bronchiectasis severity index; QoL-B: quality of life questionnaire in bronchiectasis; HR: heart rate; S_{pO_2}: oxygen saturation measured by pulse oximetry; NA: not available. Statistically significant results are in bold (p<0.05).

also showed greater exercise capacity and a smaller proportion of participants with a delayed HRR_1 (supplementary table 1). The reasons for withdrawn are described in supplementary figure 1.

During the 12-month follow-up period, 62% of participants who completed the study experienced at least two exacerbations with a global median (interquartile range) frequency of 2 (1–3) exacerbations. The changes observed over the follow-up period in clinical variables and 6MWT outcomes in this subgroup of participants and stratified according to the cardiac autonomic function ($HRR_1 \leqslant 14$ *versus* $HRR_1 > 14$) are described in supplementary table 2 and supplementary figure 2. A delayed HRR_1 after the 6MWT completed at the end of the follow-up was identified in 11 participants (24%). The presence of at least two exacerbations during the follow-up period was the only predictor of a delayed HRR_1 in the logistic regression model (table 5).

Discussion

This study showed that people with bronchiectasis had delayed HRR after a submaximal exercise capacity test, with frequency increasing alongside disease severity. In addition, the disease severity and the distance walked in the baseline 6MWT seem to be the independent predictors of autonomic cardiac dysfunction in people with bronchiectasis. After 1 year of follow-up, the presence of at least two exacerbations predicts a delayed HRR_1 after a submaximal exercise capacity test.

An imbalance between sympathetic and parasympathetic activation after a submaximal exercise capacity test was observed in over one-third of our participants (36%), representing a similar prevalence to other

TABLE 5 Logistic regression model for delayed HRR_1 (adjusted by age, sex and BMI) after the 6MWT at 12 months follow-up (n=45)

	Univariable analysis		Adjusted multivariable analysis (R^2=0.27)		
	B (95% CI)	p-value	B (95% CI)	OR (95% CI)	p-value
Change in lung function, FEV_1 % pred	0.00 (−0.04 to 0.05)	0.96		NA	
Exacerbations ⩾2, yes *versus* no	2.18 (0.02 to 4.35)	0.04	**2.82 (0.37 to 5.28)**	**16.89 (1.44 to 197.48)**	**0.02**
Hospital admission, yes *versus* no	−0.98 (−2.49 to 0.53)	0.20		NA	
Change in QoL-B, respiratory domain score	−0.01 (−0.04 to 0.03)	0.62		NA	
Change in HR (basal)	−0.01 (−0.07 to 0.06)	0.88		NA	
Change in S_{pO_2} % (basal)	0.03 (−0.28 to 0.34)	0.84		NA	
Change in Borg scale (dyspnoea) basal	0.18 (−0.41 to 0.77)	0.54		NA	
Change in Borg scale (lower limb fatigue) basal	0.07 (−0.38 to 0.52)	0.76		NA	
Change in 6MWT, m	0.01 (−0.01 to 0.03)	0.18	0.01 (−0.01 to 0.03)	1.00 (0.99 to 1.03)	0.32
AUC	NA			0.834	

HRR_1: heart rate recovery in the first minute after the 6MWT; BMI: body mass index; 6MWT: 6-min walk test; FEV_1: forced expiratory volume in 1 s; QoL-B: quality of life questionnaire in bronchiectasis; HR: heart rate; S_{pO_2}: oxygen saturation measured by pulse oximetry; AUC: area under the curve. Statistically significant results are in bold (p<0.05).

respiratory diseases such as 38% in idiopathic pulmonary fibrosis [24] and 37% in pulmonary hypertension [33]. Therefore, autonomic cardiac dysfunction is a common disorder that deserves attention in people with bronchiectasis, especially in more advanced stages of the disease.

Although the specific mechanisms involved in this autonomic cardiovascular dysfunction in bronchiectasis have not yet been elucidated, our data suggest that BSI classification and distance walked in the 6MWT were the main predictors of delayed HRR_1 in bronchiectasis. Previous studies conducted in people with COPD [22, 23, 25, 34], idiopathic pulmonary fibrosis [24] and pulmonary hypertension [33] also found a relationship between the presence of cardiac autonomic dysfunction and disease severity, suggesting that a delayed HRR_1 may be a potential biomarker of disease progression and prognosis.

The link between severe exacerbations with the increased risk of cardiovascular events and mortality in bronchiectasis is well recognised [16, 17, 35]. The excessive release of airway and systemic inflammation markers and oxidative stress in response to an exacerbation predisposes to vascular endothelial damage and negatively impacts on pre-existing cardiovascular diseases [11, 36], increasing the risk of cardiovascular events in this population. In our study, a higher percentage of participants who had required hospitalisation was observed in the group with a delayed HRR_1, whereas other potential clinical outcomes associated with increased cardiovascular risk (*e.g.* age, lung function, chronic airway infection and comorbidities) [36] seem to be similar to those with normal autonomic cardiac function. This suggests that exacerbations leading to hospitalisations play an important role in autonomic cardiac dysfunction. The underlying mechanism explaining this relationship is still unknown, but it seems that impaired ventilatory mechanisms (*e.g.* hypoxia and/or hypercapnia and respiratory muscle overload) [37] and increased inflammation during severe exacerbations may lead to sustained sympathetic system overactivation and attenuated parasympathetic activity, which is reflected in a delayed HRR_1 after a 6MWT. Future longitudinal studies emphasising the role of airway and systemic inflammation on the cardiac autonomic function in bronchiectasis are desirable.

The distance walked in the baseline 6MWT for our sample (508 m) was in the range previously described (from 434 to 547 m) in people with bronchiectasis from different geographical areas [38–40]; although comparison between studies are difficult because the definition of disease severity was not consistent. Our findings clearly suggest a decline in the exercise capacity in participants with higher BSI scores, with a greater difference in walking distance than the minimal clinically important difference for bronchiectasis (25 m) between participants classified as mild and severe. Indeed, the distance walked in the 6MWT was a predictor of HRR_1 delayed at baseline. Thus, the functional exercise capacity in people with bronchiectasis may be considered as a valuable prognostic outcome.

Although the HR at rest was similar between the participants who showed normal or delayed HRR_1, the HR achieved at the end of the baseline 6MWT and the distance walked were lower for the group of participants with a delayed HRR_1. It is likely that this group of participants also presented an inability to increase appropriately the HR during exercise, which negatively impacts on exercise capacity [18]. Additionally, the intensity of dyspnoea and lower limb fatigue after the baseline 6MWT was similar in both groups; thus, it is unlikely that a lower HR at the end of the test was due to a lower effort level in our participants with a delayed HRR_1. Moreover, participants with delayed HRR_1 ($\leqslant$14 beats) also presented lower values of HRR_2, and this finding was associated with disease severity. These two parameters (HRR_1 and HRR_2) provide insights into the rapid phase of HRR post-exercise. Our findings suggest that measuring HRR_1 alone is likely sufficient for routine clinical practice, as its results are comparable to those from HRR_2. This is consistent with HRR_1 being one of the parameters commonly used for evaluating the autonomic nervous system in other similar diseases.

In this context, sympathetic overactivity has been hypothesised to be the mechanism responsible for the abnormal HR response to exercise and recovery observed in patients with COPD [21, 37]. This increased sympathetic drive in chronic respiratory diseases may be related not only to sustained inflammation, but also to impaired ventilatory mechanisms (*e.g.* reduced inspiratory capacity to total lung capacity ratio) and pulmonary vascular volume during exercise and at rest [21, 41]. These potential relationships need further investigation.

On the other hand, we lost 57% of the sample during the 12-month follow-up period, mainly because they had received a new intervention likely to reduce exacerbations (*e.g.* inhaled antibiotic or airway clearance management) and/or improve functional capacity and cardiac function (*e.g.* pulmonary rehabilitation). These participants were older, more likely to need hospital admissions and were treated with inhaled antibiotics. This finding suggests that these participants already had a greater impairment of the autonomic

cardiac function during exercise, which was confirmed by showing lower exercise capacity and a higher rate of participants with delayed HRR_1 in the drop-out group.

Although the likelihood of exacerbations and hospital admissions was lower in participants who completed the study, 62% of them had at least two exacerbations during the follow-up period, with 22% requiring hospitalisation, while maintaining stable lung function and similar scores of quality of life to baseline. Indeed, the only clinical outcome that predicts a delayed HRR_1 in the 6MWT conducted at the conclusion of the study was exacerbation frequency ($\geqslant$2 exacerbations per year), confirming again the negative impact of exacerbations in the autonomic cardiac function in people with bronchiectasis.

Given this relationship, treatments to prevent exacerbations (*e.g.* inhaled antibiotics treatments and airway clearance management) [42, 43] should be a priority for people with bronchiectasis at increased risk of exacerbations and autonomic cardiac dysfunction. In fact, the role of new anti-inflammatory treatments, such as dipeptidyl peptidase-1 inhibition [44], as a strategy to control the effect of inflammation on sympathetic overactivation, may be promising. Additionally, facilitate the accessibility to pulmonary rehabilitation and physical activity promotion programmes is essential to improve the HR response to exercise in people with bronchiectasis with a sustained delayed HRR_1 after an exercise test [37].

The strengths of our study include the assessment of autonomic cardiac function using parameters easily monitored in clinical practice and showing that HRR_1 may be a promising biomarker of autonomic cardiac dysfunction in bronchiectasis, and that it is related to disease severity. Additionally, the longitudinal data confirm the negative impact of exacerbations, particularly those leading to hospitalisation, in the autonomic cardiac function in this population even with sustained clinical outcomes (lung function and quality of life) and exercise capacity after 12 months of follow-up.

Limitations of this study can be summarised in the cut-off selected for a delayed HRR_1, which was based on people with COPD [23]. As it is still unknown whether another cut-off of HRR_1 is more adapted to people with bronchiectasis, the HRR_1 criterion was selected from one of the respiratory diseases where autonomic cardiac function during exercise has been most explored. Additionally, the same submaximal field test was used to determine this specific cut-off and was previously evaluated for its potential role in detecting future exacerbations, which aligned with our secondary objective. This approach demonstrates methodological consistency and enhances the comparability of our results with existing literature. Future research including larger and more diverse cohorts representing the full spectrum of bronchiectasis severity is desirable.

Our longitudinal findings should also be taken with caution, as the rate of losses during the follow-up was considerable and the group of participants who completed the assessment at the end of follow-up differed from those who did not; however, by excluding participants who started a new treatment during the follow-up period, we were able to better confirm the relationship between exacerbations and autonomic cardiac dysfunction. Furthermore, HRR has been linked to exercise and physical activity levels in patients with respiratory diseases [22, 26]. While our study excluded participants who had completed a pulmonary rehabilitation program in the year prior to recruitment and withdrew those who entered such a program during the follow-up period, the levels of physical activity or exercise were not monitored during the follow-up period. This oversight means that we cannot discount the potential impact of changes in these factors on our results. Indeed, the risk of misclassification in the assessment of the autonomic cardiac dysfunction by using the HRR during a submaximal test also should be considered. Finally, this study was not designed to identify the underlying mechanisms of how exacerbations impair the HRR response to exercise in bronchiectasis; thus, future work evaluating the impact of airway and systemic inflammation, as well as ventilatory mechanisms on the autonomic cardiac function in people with bronchiectasis with clinical stability and during exacerbations are needed.

In summary, HRR_1 after a submaximal exercise test is related to disease severity and is mainly impaired by having severe exacerbations in people with bronchiectasis. Therefore, HRR_1 seems to be a promising biomarker of autonomic cardiac dysfunction in this population.

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