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Journal

Annals of the American Thoracic Society, 18(11)

ISSN

2329-6933

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Publication Date

2021-11-01

DOI

10.1513/annalsats.202008-1085oc

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ORIGINAL RESEARCH

Chronotropic Index and Acute Exacerbations of Chronic Obstructive Pulmonary Disease

A Secondary Analysis of BLOCK COPD

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Abstract

Rationale: The chronotropic index quantifies the proportion of the expected heart rate increase that is attained during exercise. The relationship between the chronotropic index and acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) has not been evaluated.

Objectives: To determine whether a higher chronotropic index during a 6-minute walk (CI-6MW) is associated with lower risk of AECOPD and whether the CI-6MW is a marker of susceptibility to adverse effects of metoprolol in chronic obstructive pulmonary disease (COPD).

Methods: We analyzed data from the BLOCK COPD (Beta-Blockers for the Prevention of AECOPDs) trial. We used Cox proportional hazards models to investigate the relationship between the CI-6MW and the time to AECOPDs. We also tested for interactions between study group assignment (metoprolol vs. placebo) and the CI-6MW on the time to AECOPDs.

Results: Four hundred seventy-seven participants with exacerbation-prone COPD (mean forced expiratory volume in 1 second, 41% of predicted) were included in this analysis. A higher CI-6MW was independently associated with a decreased risk of AECOPDs of any severity (adjusted hazard ratio per 0.1 increase in CI-6MW of 0.88; 95% confidence interval, 0.80–0.96) but was not independently associated with AECOPDs requiring hospitalization (adjusted hazard ratio, 0.94; 95% confidence interval, 0.81–1.05). There was a significant interaction by treatment assignment, and in a stratified analysis, the protective effects of a higher CI-6MW on AECOPDs were negated by metoprolol use.

Conclusions: A higher CI-6MW is associated with a decreased risk of AECOPDs and may be an indicator of susceptibility to the adverse effects of metoprolol.

Keywords: pulmonary disease; chronic obstructive; cardiac chronotropy; disease exacerbation

(Received in original form August 31, 2020; accepted in final form March 26, 2021)

*These authors contributed equally to this work.

A complete list of BLOCK COPD Study Investigators may be found in the online supplement.

The BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial was supported by a grant from the Department of Defense (W81XWH-15-1-0705). D.M.M. was supported by the University of Minnesota T32 Training in Lung Science training grant (2T32HL007741-26A1). This material is also the result of work supported with resources and the use of facilities at the Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota. The views expressed in this article are those of the authors and do not reflect the views of the U.S. Government, the Department of Defense, the Department of Veterans Affairs, or any of the authors' affiliated academic institutions.

Author Contributions: Conceived the study: D.M.M., M.T.D., and K.M.K. Designed the study: D.M.M., E.S.H., S.A., and K.M.K. Obtained funding: M.T.D. Acquired the data: R.C., W.W.S., M.T.D., and K.M.K. Performed the primary statistical analysis: E.S.H. Drafted the manuscript: D.M.M. Critically revised the manuscript for important intellectual content and approved the final version to be published: all authors. Take responsibility for the integrity of the data and the accuracy of the data analysis: all authors.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 18, No 11, pp 1795–1802, Nov 2021
Copyright © 2021 by the American Thoracic Society
DOI: 10.1513/AnnalsATS.202008-1085OC
Internet address: www.atsjournals.org

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide (1). Much of the morbidity, mortality, and economic cost of COPD is driven by acute exacerbations of COPD (AECOPDs), and hospitalizations for AECOPDs are among the most important concerns for people with COPD (2–4). AECOPDs are commonly infectious or inflammatory in origin, but acute worsening of respiratory symptoms in patients with COPD often has a mixed pulmonary and cardiac etiology (5, 6). AECOPDs are associated with risk of atrial tachyarrhythmias, and changes in atrial depolarization may be a risk factor for AECOPDs, but sinus node dysfunction as a risk factor for AECOPDs has been poorly investigated (7–9).

When metabolic demands increase, such as with stressors like exercise or an AECOPD, the heart rate normally increases to meet demands. The chronotropic index measures the proportion of the expected heart rate increase that a person attains during exercise (10). Chronotropic insufficiency has been reported to be common in COPD, with increasing prevalence as lung function declines, but the pathobiology remains unknown (11–14). Chronotropic insufficiency and a lower chronotropic index are associated with increased mortality in patients with cardiovascular disease, in patients with interstitial lung disease, and in the general population (15–18). One study found that a lower chronotropic index was associated with increased mortality in COPD (11).

To our knowledge, no studies have assessed the association between chronotropic responses, such as the chronotropic index, and AECOPD risk. The chronotropic index is typically measured during a cardiopulmonary exercise test (CPET) (10), but CPETs are not commonly performed clinically. Compared with CPETs, 6-minute-walk (6MW) testing is more commonly performed in patients with COPD and can provide data about the heart rate responses to exertion. We used data from the BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of COPD) trial to assess the relationship between the chronotropic index during a 6MW (CI-6MW) and AECOPDs (19).

Portions of these data were published in abstract form at the 2020 American Thoracic Society International Conference, which was held virtually (20).

Methods

Study Design and Participants

BLOCK COPD. The trial protocol and primary results of the BLOCK COPD trial have been previously published (19, 21). BLOCK COPD randomly assigned 532 patients with exacerbation-prone COPD to metoprolol succinate versus placebo for the prevention of AECOPDs. Inclusion criteria included age of 40–85 years, moderate COPD (forced expiratory volume in 1 second [FEV_1]/forced vital capacity ratio < 0.7 and $FEV_1 < 80\%$ of predicted normal value), and at least 10 pack-years of smoking history. All spirometric data are presented as a percentage of predicted values on the basis of reference equations from NHANES III (National Health and Nutrition Examination Survey III) spirometric data (22). Exclusion criteria included tachyarrhythmias and bradyarrhythmias requiring treatment, pacemakers, class I indications for β-blocker use, and use of other medications known to delay atrioventricular node conduction. AECOPD data were collected at study visits or during phone calls every 8 weeks. The primary results showed that metoprolol did not reduce the risk of AECOPDs (hazard ratio [HR] for time to first AECOPD, 1.05; 95% confidence interval, 0.84–1.32) but increased the risk of AECOPDs requiring hospitalization or intubation (HR, 1.91; 95% confidence interval, 1.29–2.83). The 6MW distance was collected as a secondary outcome, and there was no statistically significant difference in the change in the 6MW distance between treatment groups. The trial protocol was approved by the institutional review board at each participating site (*see* Table E1 in the online supplement).

Current Analysis

In this analysis, we included all BLOCK COPD participants who participated in baseline 6MW testing with a walk distance greater than 0 m and with sufficient data to calculate the CI-6MW (age, resting heart rate, and heart rate at completion of the 6MW). In addition, we excluded participants who had a CI-6MW ≤ 0 because of concerns that lower heart rates after a 6MW are physiologically implausible and likely represent erroneous data.

Procedures

The resting heart rate was checked during study visits after participants rested for at least 10 minutes. The 6MW testing in BLOCK COPD was performed according to standard American Thoracic Society guidelines (19, 23). If participants had not used a short-acting bronchodilator within 2 hours, treatment with a short-acting bronchodilator was administered, and the participant rested for at least 20 minutes before the 6MW. All subjects had been resting for at least 10 minutes before starting the 6MW. We calculated the CI-6MW as follows: (heart rate immediately after 6MW − resting heart rate)/(220 − age in yr − resting heart rate) (10).

In BLOCK COPD, AECOPDs were graded as mild (home management, with or without contacting a healthcare provider), moderate (requiring a visit to an emergency department), severe (requiring hospitalization), and very severe (requiring invasive mechanical ventilation). In this analysis, we analyzed AECOPDs of any severity and separately analyzed "severe AECOPDs," which were defined in this analysis as AECOPDs requiring hospitalization, with or without intubation and mechanical ventilation.

Statistical Analysis

We used Cox proportional hazards models to test the association between the CI-6MW and the time to AECOPDs of any severity, and we tested separately for the time to severe AECOPDs. HRs indicate the change in risk for each 0.1 increase in the CI-6MW. In addition to evaluating the association between the baseline CI-6MW and the time to AECOPDs, we also treated the CI-6MW as a time-varying covariate by using data from 6MW testing that was performed at baseline, on Day 112, and on Day 336. This analytic approach accounts for variation in the exposure of interest over time (e.g., the CI-6MW) and incorporates all available exposure data. All individuals with baseline CI-6MW data were included in time-varying analyses; those without complete follow-up data (and who had not had an event) were censored at the last follow-up date.

Adjusted models incorporated demographic variables of age, sex, and race. We also adjusted for confounding variables

that have been associated with risk of AECOPDs and may be associated with changes in the heart rate response during exercise: body mass index (BMI), FEV_1 percent predicted, and smoking status (24–26). We also adjusted for the 6MW distance and San Diego Shortness of Breath Questionnaire (SOBQ) scores, which have been associated with an increased risk of AECOPDs and which we hypothesized may be associated with a decreased heart rate response, either due to effort or due to respiratory limitations to exercise (27, 28). Finally, we adjusted for treatment assignment (metoprolol vs. placebo), as is commonly done in secondary analyses of randomized controlled trials, and stratified by study center to account for nonproportional hazards across centers. In adjusted time-varying models, the 6MW distance, SOBQ score, and FEV_1 percent predicted were also measured during follow-up and were allowed to vary over time, together with the CI-6MW.

In addition, we assessed whether the relationship between the CI-6MW and AECOPDs was influenced by treatment assignment by testing for interactions that reflect the ratio of adjusted HRs (aHRs) in those assigned to metoprolol versus placebo. If a significant interaction was present, we also reported HRs for metoprolol and placebo groups separately. Kaplan-Meier curves and associated log rank tests were used to compare the probability of remaining exacerbation-free between groups, which was defined by a baseline CI-6MW above versus below the median and by the treatment assignment.

A linear mixed effects model with patient-specific random intercepts was used to compare between-treatment-group differences in the change in the CI-6MW from baseline to visits 112 and 336. This model was used to determine the within-subject standard deviation in the CI-6MW.

Measurements from participants who ended the study early were analyzed as if they were measured at the next scheduled study visit. We tested the correlation between the baseline 6MW distance and the CI-6MW using the Pearson correlation coefficient.

Our primary analyses accounted for treatment assignment using the intention-to-treat principle, but we also conducted a secondary analysis using a per-protocol approach. For the time-to-event analyses, individuals were censored at the date they formally discontinued the study drug. For the analysis evaluating the change in the CI-6MW over time, if an individual was not adherent to metoprolol treatment at a specific visit, they were considered as being in the placebo group for that time point. Adherence to study drug treatment was classified as a binary variable. Participants were classified as nonadherent if the study drug was discontinued per protocol before the study visit, if no drug was issued at the last study visit, or if no drug had been taken since the last study visit. Statistical analyses were conducted using R version 3.6.0 (https://www.R-project.org/; R Foundation for Statistical Computing).

Results

Participants

Among the 532 participants in BLOCK COPD, 477 (90%) were included in this analysis. Reasons for exclusion included a CI-6MW $\leqslant 0$ ($n = 37$), a lack of baseline 6MW data ($n = 15$), a lack of heart rate data ($n = 2$), and a 6MW distance of 0 m ($n = 1$) (Figure 1). Baseline characteristics of all participants and divided into those above and below the median CI-6MW are shown in Table 1. Characteristics of participants were similar to those of the full randomized trial population. Among the 477 included participants (238 assigned to metoprolol and 239 assigned to placebo), the mean (standard deviation) age was 65.1 (7.8) years, the FEV_1 percent predicted was 40.9% (16.2%), the number of pack-years of smoking was 50.4 (29.6), and the baseline heart rate was 84 (11) beats per minute. Among participants, 71.3% were White, 25.2% were Black, 46.8% were female, and 30.0% were current smokers. In addition, 7.3% had a history of coronary artery disease, 15.3% had a history of diabetes, and 45.7% had a history of hypertension. The median CI-6MW before randomization was 0.25 (interquartile range [IQR], 0.15–0.34). Current smokers had a lower median CI-6MW than former smokers (0.21 [IQR, 0.12–0.29] vs. 0.26 [IQR, 0.16–0.37]; P value by Mann-Whitney test <0.001). There was no significant difference in the CI-6MW by sex (Figure E1).

Relationship between CI-6MW and AECOPDs

The baseline CI-6MW was not associated with the time to AECOPDs of any severity in the unadjusted analysis, but after adjustment for important confounders (age, sex, race, smoking status, BMI, FEV_1 percent predicted at baseline, treatment assignment, SOBQ score, 6MW distance, and stratification by study center), a higher baseline CI-6MW was associated with a lower risk of AECOPDs of any severity (aHR, 0.88; 95% CI, 0.80–0.96; $P = 0.005$) (Table 2). There was no significant interaction between assignment to metoprolol and the CI-6MW on the risk of AECOPDs (ratio of metoprolol and placebo aHRs, 1.16; 95% CI, 0.99–1.35; $P = 0.07$) (Table 3). Similarly, there was no significant difference in the probability of remaining exacerbation-free as defined by a baseline CI-6MW above versus below the median and the treatment group assignment ($P = 0.47$) (Figure E2A).

When all available follow-up 6MW heart rate data were used and the CI-6MW was treated as a time-varying covariate, a higher CI-6MW was associated with a lower risk of AECOPDs of any severity (aHR, 0.89; 95% CI, 0.81–0.98; $P = 0.01$) (Table 2). In contrast to the analysis using only baseline CI-6MWs, we did find a significant interaction between assignment to metoprolol and the CI-6MW in the time-varying model ($P = 0.02$) (Table 3). Treating the CI-6MW as a time-varying covariate, the aHR in the metoprolol group was 0.97 (95% CI, 0.86–1.10; $P = 0.69$), and the aHR in the placebo group was 0.82 (95% CI, 0.73–0.93; $P = 0.001$).

A per-protocol sensitivity analysis showed similar results for the relationship between the CI-6MW and the time to AECOPDs of any severity and for the interactions between assignment to metoprolol and the CI-6MW on the time to the first AECOPD of any severity (Tables E2 and E3).

Relationship between CI-6MW and Severe AECOPDs

There was not a significant relationship between the baseline CI-6MW and the time to the first severe AECOPD (aHR, 0.94; 95% CI, 0.81–1.10; $P = 0.46$) (Table 4). In contrast to the analysis of all exacerbations (of any severity), we found a significant interaction between the baseline CI-6MW and assignment to metoprolol on the risk of severe AECOPDs (ratio of aHRs, 1.53; 95% CI, 1.15–2.03; $P = 0.003$) (Table 5), with a higher CI-6MW being associated with a reduced risk of severe AECOPDs in the placebo group (aHR, 0.74; 95% CI, 0.58–0.95;

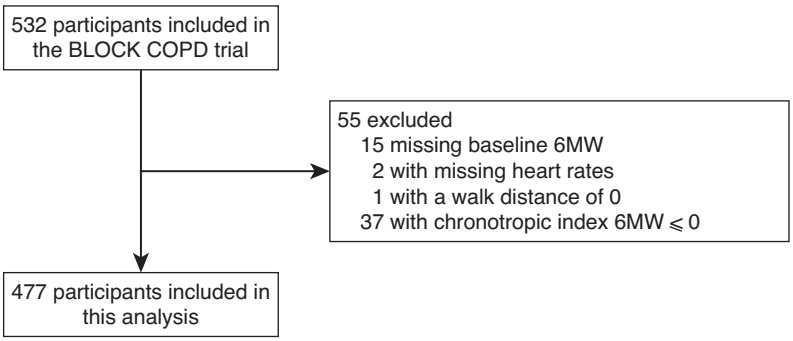

Figure 1. Study participant flow diagram. BLOCK COPD = Beta-Blockers for the Prevention of Acute Exacerbations of COPD; COPD = chronic obstructive pulmonary disease; 6MW = 6-minute-walk.

$P = 0.02$) but not in the metoprolol group (aHR, 1.13; 95% CI, 0.94–1.36; $P = 0.20$). Similarly, there was a significant difference in the probability of remaining exacerbation-free between groups defined by a CI-6MW above or below the median and the treatment group assignment ($P = 0.02$) (Figure E2B).

Findings were similar when the CI-6MW was treated as a time-varying covariate. There was no significant relationship between the CI-6MW and the time to severe AECOPDs (aHR, 0.91; 95% CI, 0.77–1.06; $P = 0.22$) (Table 4). The interaction between assignment to metoprolol and the CI-6MW in the time-varying analysis was similar to that in the baseline analysis (ratio of aHRs, 1.40; 95% CI, 1.05–1.88; $P = 0.02$) (Table 5).

A per-protocol sensitivity analysis showed similar results for the relationship between the CI-6MW and the time to severe AECOPDs (Table E4).

Effect of Metoprolol on CI-6MW

The treatment group assignment was not associated with a significant difference in the change in the CI-6MW over time (P value for interaction = 0.50, Figure E3). The sensitivity analysis accounting for adherence to study drug treatment had comparable results (P value for interaction = 0.57, Figure E4). The within-subject standard deviation in the CI-6MW between visits was 0.12 U.

Relationship between 6MW Distance and CI-6MW

We found no correlation between the baseline 6MW distance and the CI-6MW (Pearson correlation coefficient, 0.02; 95% CI, −0.07 to 0.11; $P = 0.68$) (Figure E5).

Discussion

Among patients with exacerbation-prone COPD, a higher CI-6MW was independently associated with a lower risk of AECOPDs of any severity. We did not find a significant relationship between the CI-6MW and the risk of severe AECOPDs but found that the relationship between CI-6MW and severe AECOPDs was modified by the treatment assignment, with only those assigned to placebo experiencing a lower risk of severe AECOPDs with a higher CI-6MW.

We are aware of no other data on the relationship between the chronotropic response to exercise and AECOPDs. Several small and/or retrospective studies have reported that chronotropic insufficiency, defined as a chronotropic index less than 0.8 during a CPET is common in COPD, ranging from 49% ($n = 47$) to 69% ($n = 39$) prevalence (12, 13). Among 449 patients with severe COPD, those with a chronotropic index in the first (lowest) quartile had an odds ratio of 3.2 for mortality compared with those with a chronotropic index in the fourth quartile (11). Only one study has analyzed changes in the chronotropic index after an intervention in patients with COPD. In 103 patients with COPD who had longitudinal CPET data available, 75 underwent lung volume reduction surgery (LVRS) and had subsequent improvement in the mean chronotropic index obtained during a CPET (0.41 ± 0.17 before LVRS to 0.50 ± 0.18 after LVRS; $P < 0.001$); there was no change in the 28 control patients who had similarly severe COPD but did not undergo LVRS (14). No trials have specifically targeted chronotropy for therapeutic intervention in COPD. We are aware of no other studies that have reported on the CI-6MW in COPD.

The etiology of a low chronotropic index in COPD is unclear. Proposed etiologies include smoking, hypoxia, medications, comorbid cardiovascular disease, impaired baroreflex sensitivity, respiratory limitations to exercise, and hyperinflation (11–14, 29). The heart rate is controlled by the autonomic nervous system through a balance of vagal and sympathetic activity. The proposed etiologies above could cause chronic sympathetic activation, leading to downregulation of cardiac β-receptors and an imbalance between vagal and sympathetic tone. Heart rate recovery measures the rate at which the heart rate returns to normal after exercise and is a measure of the balance between vagal and sympathetic tone (18). In a retrospective study of 101 patients with COPD, impaired heart rate recovery at 1 minute was an independent predictor of AECOPDs (30). Our 6MW protocol did not measure heart rate 1 minute after completion, so we were unable to analyze heart rate recovery. Impaired heart rate recovery and a decreased chronotropic index are both markers of autonomic dysfunction. Although we cannot conclusively determine that our findings are related to autonomic dysfunction, autonomic dysfunction is common in COPD, and it may play a role in the high rates of chronotropic insufficiency observed in COPD (31, 32). We are aware of no other studies on autonomic dysfunction as a risk factor for AECOPDs.

Although we are not able to prove causality in this observational study, there are several possible mechanisms for the association between a decreased CI-6MW and AECOPDs. The autonomic nervous system is responsible for responding to changes in physiologic demands. If a lower

Table 1. Baseline characteristics of included participants

Characteristic	CI-6MW below Median (*N = 238*)	CI-6MW above Median (*N = 239*)	Total (*N = 477*)
Age, yr	63.6 ± 7.7	66.5 ± 7.7	65.1 ± 7.8
Race, *n* (%)			
White	161 (67.6)	179 (74.9)	340 (71.3)
Black	70 (29.4)	50 (20.9)	120 (25.2)
Other	7 (2.9)	10 (4.2)	17 (3.6)
Female sex, *n* (%)	110 (46.2)	113 (47.3)	223 (46.8)
FEV_1 after bronchodilator, percentage of predicted value*	41.6 ± 17.3	40.2 ± 15.0	40.9 ± 16.2
FEV_1/FVC ratio	45.0 ± 14.7	42.7 ± 14.4	43.9 ± 14.6
Smoking history, pack-years	51.3 ± 30.0	49.5 ± 29.2	50.4 ± 29.6
Current smoking, *n* (%)	86 (36.1)	57 (23.8)	143 (30.0)
COPD medication, *n* (%)			
Inhaled glucocorticoids, LABA, and LAMA	142 (59.7)	142 (59.4)	284 (59.5)
Inhaled glucocorticoids and LABAs only	42 (17.6)	40 (16.7)	82 (17.2)
LAMAs only	12 (5.0)	19 (7.9)	31 (6.5)
LABAs and LAMAs only	14 (5.9)	10 (4.2)	24 (5.0)
Inhaled glucocorticoids and LAMAs only	6 (2.5)	7 (2.9)	13 (2.7)
Inhaled glucocorticoids only	2 (0.8)	5 (2.1)	7 (1.5)
Other	20 (8.4)	16 (6.7)	36 (7.5)
BMI, kg/m^2	27.0 ± 7.0	27.5 ± 5.8	27.2 ± 6.5
Heart rate, beats per minute	84.9 ± 11.1	83.3 ± 10.9	84.1 ± 11.0
Systolic blood pressure, mm Hg	128.3 ± 16.2	131.5 ± 16.3	129.9 ± 16.3
Diastolic blood pressure, mm Hg	77.1 ± 9.2	77.1 ± 9.0	77.1 ± 9.1
Coronary artery disease, *n* (%)	20 (8.4)	15 (6.3)	35 (7.3)
Diabetes, *n* (%)	38 (16.0)	35 (14.6)	73 (15.3)
Hypertension, *n* (%)	107 (45.0)	111 (46.4)	218 (45.7)
Statin use, *n* (%)	86 (36.1)	88 (36.8)	174 (36.5)
Number of courses of systemic glucocorticoid or antibiotic use within previous 12 mo	2.0 ± 1.7	1.9 ± 1.6	1.9 ± 1.6
Number of hospitalizations within previous year	0.6 ± 1.2	0.6 ± 0.9	0.6 ± 1.1
Baseline COPD assessment test score	21.6 ± 7.4	19.5 ± 7.1	20.5 ± 7.3
COPD exacerbation leading to emergency department visit or hospitalization within previous 12 mo, *n* (%)	141 (59.2)	130 (54.4)	271 (56.8)
Systemic glucocorticoid or antibiotic use within previous 12 mo, *n* (%)	213 (89.5)	214 (89.5)	427 (89.5)
CI-6MW, median (IQR)†	0.15 (0.08–0.20)	0.34 (0.29–0.46)	0.25 (0.15–0.34)
Supplemental oxygen use at baseline visit, *n* (%)	107 (45.0)	126 (52.7)	233 (48.8)
Approx. daily hours of supplemental oxygen use for those on supplemental oxygen, *n* (%)			
⩽6 h	19 (17.8)	18 (14.3)	37 (15.9)
>6 h to ⩽18 h	34 (31.8)	48 (38.1)	82 (35.2)
>18 h to 24 h	53 (49.5)	58 (46.0)	111 (47.6)

Definition of abbreviations: 6MW = 6-minute walk; Approx. = approximate; BMI = body mass index; CI-6MW = chronotropic index during a 6MW; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; LABA = long acting β-agonist; LAMA = long-acting muscarinic antagonist; NHANES III = National Health and Nutrition Examination Survey.

*Based on reference equations from NHANES III data.

†The CI-6MW is defined as (heart rate immediately after 6MW − resting heart rate)/(220 − age in yr − resting heart rate) (10).

Table 2. Relationship between CI-6MW and time to first acute exacerbation of COPD of any severity

	Crude HR	95% CI	*P* Value	Adjusted HR*	95% CI	*P* Value
Baseline CI-6MW	0.95	0.89–1.03	0.21	0.88	0.80–0.96	0.005
Time-varying CI-6MW	0.93	0.86–1.00	0.05	0.89	0.81–0.97	0.009

Definition of abbreviations: 6MW = 6-minute walk; BMI = body mass index; CI = confidence interval; CI-6MW = chronotropic index during a 6MW; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio.
HRs represent the change in risk for a 0.1 increase in the CI-6MW.
*Adjusted HRs are adjusted for age, sex, race, current smoking status, BMI, baseline FEV_1 percent predicted, study group assignment, San Diego Shortness of Breath Questionnaire score, and 6MW distance and are stratified by study center.

CI-6MW is a marker of autonomic dysfunction, it may indicate a decreased ability to respond to even small changes in physiologic stress, leading to the clinical presentation of events that would otherwise remain undetected. Alternatively, and more directly, a lower CI-6MW may indicate an inability to raise the heart rate, and thus cardiac output, leading to cardiac dysfunction and perhaps explaining some of the findings of increased cardiac enzymes during AECOPDs (6).

One of our goals in this analysis was to investigate the safety signal seen in BLOCK COPD, in which patients assigned to metoprolol had a similar risk of AECOPDs of any severity but had a higher risk of severe AECOPDs (19). One way to interpret these primary outcome results is that metoprolol did not alter the risk of AECOPDs, but when AECOPDs occurred, those assigned to metoprolol were more likely to be hospitalized or require invasive mechanical ventilation for AECOPDs. In this secondary analysis, a higher baseline CI-6MW was strongly associated with a decreased risk of severe AECOPDs among those assigned to placebo, whereas for those assigned to metoprolol, this relationship was absent. These results suggest that metoprolol may be particularly harmful to those who are more heart rate–dependent in their responses to stressors like exercise or AECOPDs, as indicated by a higher CI-6MW before metoprolol exposure. Those with a low CI-6MW may cope with AECOPD stressors through other compensatory mechanisms that are less susceptible to adverse effects of metoprolol. The interaction between the CI-6MW and assignment to metoprolol on the risk of AECOPDs of any severity was not as strong. We did not find a significant interaction using only baseline data, but when we incorporated all available data in the more robust time-varying analysis, we found an increased risk of AECOPDs of any severity in those with a higher CI-6MW who were assigned to metoprolol compared with those who were assigned to placebo. This relationship may be weaker because less severe AECOPDs may not impose the same degree of metabolic demand, and blocking compensatory mechanisms with metoprolol might therefore have less deleterious effects in less severe AECOPD events.

We were surprised to not find an effect of metoprolol on the CI-6MW, which might argue against reductions in the chronotropic response being responsible for the safety signal in BLOCK COPD. However, we had follow-up measures at only two time points and in a relatively small sample because of early termination of the BLOCK COPD trial, resulting in only 125 participants receiving metoprolol having CI-6MW values recorded on both Day 112 and Day 336 study visits. Therefore, our analysis of metoprolol's effects on the CI-6MW may have had low power. It is also possible that BLOCK COPD participants who experienced significant decreases in the CI-6MW from metoprolol may have been more likely to discontinue metoprolol. We did not see evidence of this in secondary analyses incorporating adherence data, but we used a conservative measure of adherence, relying on pill counts at study visits rather than on more technical methods such as electronic pill vial recorders. Lastly, we did not have access to heart rates at the time of AECOPDs, and the effects of metoprolol on the heart rate during AECOPDs may differ from the data we collected from 6MW testing during routine, scheduled study visits.

Strengths and Limitations

Our study was limited by its use of the CI-6MW as opposed to the gold standard of the CPET. As opposed to the CPET, the 6MW test is not a maximal test and has no measure of exercise intensity, and we were unable to determine whether cardiac, pulmonary, effort, or other limitations were responsible for decreased chronotropic responses. Although published data suggest little difference in the heart rates achieved

Table 3. Interactions between CI-6MW and treatment assignment on time to first acute exacerbation of COPD of any severity

	Interaction Term	95% CI	*P* Value
Interaction between baseline CI-6MW and metoprolol assignment	1.16	0.99–1.35	0.07
Interaction between time-varying CI-6MW and metoprolol assignment	1.19	1.01–1.40	0.04

Definition of abbreviations: 6MW = 6-minute walk; BMI = body mass index; CI = confidence interval; CI-6MW = chronotropic index during a 6MW; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio.
Interaction terms represent the ratio of adjusted HRs in the metoprolol group compared with the placebo group. Adjusted HRs are adjusted for age, sex, race, current smoking status, BMI, baseline FEV_1 percent predicted, San Diego Shortness of Breath Questionnaire score, and 6MW distance and were stratified by study center.

Table 4. Relationship between CI-6MW and time to first severe acute exacerbation of COPD (requiring hospitalization with or without mechanical ventilation)

	Crude HR	95% CI	*P* Value	Adjusted HR*	95% CI	*P* Value
Baseline CI-6MW	0.91	0.80–1.03	0.13	0.94	0.81–1.10	0.46
Time-varying CI-6MW	0.88	0.78–1.01	0.07	0.91	0.77–1.06	0.22

Definition of abbreviations: 6MW = 6-minute walk; BMI = body mass index; CI = confidence interval; CI-6MW = chronotropic index during a 6MW; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio.
HRs represent the change in risk for a 0.1 increase in CI-6MW.
*Adjusted HRs are adjusted for age, sex, race, current smoking status, BMI, baseline FEV_1 percent predicted, study group assignment, San Diego Shortness of Breath Questionnaire score, and 6MW distance and were stratified by study center.

Table 5. Interactions between CI-6MW and treatment assignment on time to first severe acute exacerbation of COPD (requiring hospitalization with or without mechanical ventilation)

	Interaction Term	95% CI	*P* Value
Interaction between baseline CI-6MW and metoprolol assignment	1.53	1.15–2.03	0.003
Interaction between time-varying CI-6MW and metoprolol assignment	1.40	1.05–1.88	0.02

Definition of abbreviations: 6MW = 6-minute walk; BMI = body mass index; CI = confidence interval; CI-6MW = chronotropic index during a 6MW; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio.
Interaction terms represent the ratio of adjusted HRs in the metoprolol group compared with the placebo group. Adjusted HRs are adjusted for age, sex, race, current smoking status, BMI, baseline FEV_1 percent predicted, San Diego Shortness of Breath Questionnaire score, and 6MW distance and were stratified by study center.

during the 6MW and the CPET, these studies have been small and have generally performed 6MW testing in a focused exercise physiology laboratory environment rather than in the context of a secondary assessment in an epidemiologic study or complex clinical trial such as BLOCK COPD (33). For example, in BLOCK COPD, the heart rate after the 6MW was collected as part of a series of many secondary outcomes, so testing procedures may have been less stringent and more variable than those in studies focused specifically on exercise or cardiac physiologic outcomes. BLOCK COPD also enrolled participants who had exacerbation-prone COPD, had at least moderate COPD, and did not have other indications for β-blockers; it remains to be seen whether these data are generalizable to people with COPD less prone to exacerbation, people who have mild COPD, or people who have indications for β-blocker use. Lastly, the effect of long- and short-acting β-agonists and supplemental oxygen on the CI-6MW is unknown and should be investigated in future studies. Despite these limitations, the 6MW is commonly used in clinical practice, and after controlling for known confounders, including baseline dyspnea and the 6MW distance, we found that the CI-6MW was an independent predictor of AECOPDs of any severity. Our data suggest that the CI-6MW may help identify those with COPD who are at increased risk of AECOPDs and adverse effects from metoprolol.

Our study has several strengths. We used data from a randomized controlled trial with AECOPDs as the primary outcome, so AECOPD events were carefully collected and recorded in a prospective fashion. The performance of baseline and sequential 6MW tests allowed us to conduct complementary analyses using both baseline and time-varying CI-6MW values that led to very similar conclusions. In addition, participants were randomized to metoprolol or placebo, which provides a unique opportunity to evaluate the interaction between metoprolol and the CI-6MW with a low risk of bias.

Conclusions

In conclusion, a higher CI-6MW is independently associated with a decreased risk of AECOPDs. Our study also suggests that metoprolol may be particularly risky among patients with COPD with a higher CI-6MW before metoprolol initiation. Further study is needed to validate these findings and to determine whether clinical trials targeting chronotropic insufficiency in COPD are warranted. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the participants in the BLOCK COPD trial.

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