Clinical Interventions in Aging

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ORIGINAL RESEARCH

Impact of beta2-agonists, beta-blockers, and their combination on cardiac function in elderly male patients with chronic obstructive pulmonary disease

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
12 September 2013
Number of times this article has been viewed

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Purpose: This study was undertaken to determine the association between cardiac function and therapy with beta2-adrenoceptor agonists (β_2-agonists), β-blockers, or β-blocker–β_2-agonist combination therapy in elderly male patients with chronic obstructive pulmonary disease (COPD).

Patients and methods: This was a retrospective cohort study of 220 elderly male COPD patients (mean age 84.1 ± 6.9 years). The patients were divided into four groups on the basis of the use of β-blockers and β_2-agonists. N-terminal fragment pro-B-type natriuretic peptide (NT pro-BNP), left ventricular ejection fraction (LVEF), and other relevant parameters were measured and recorded. At follow-up, the primary end point was all-cause mortality.

Results: Multiple linear regression analysis revealed no significant associations between NT pro-BNP and the use of β_2-agonists ($\beta = 35.502$, $P = 0.905$), β-blockers ($\beta = 3.533$, $P = 0.989$), or combination therapy ($\beta = 298.635$, $P = 0.325$). LVEF was not significantly associated with the use of β_2-agonists ($\beta = -0.360$, $P = 0.475$), β-blockers ($\beta = -0.411$, $P = 0.284$), or combination therapy ($\beta = -0.397$, $P = 0.435$). Over the follow-up period, 52 patients died, but there was no significant difference in mortality among the four groups ($P = 0.357$). Kaplan–Meier analysis showed no significant difference among the study groups (log-rank test, $P = 0.362$). After further multivariate adjustment, use of β_2-agonists (hazard ratio [HR] 0.711, 95% confidence interval [CI] 0.287–1.759; $P = 0.460$), β-blockers (HR 0.962, 95% CI 0.405–2.285; $P = 0.930$), or combination therapy (HR 0.638, 95% CI 0.241–1.689; $P < 0.366$) were likewise not correlated with mortality.

Conclusion: There was no association between the use of β_2-agonists, β-blockers, or β-blocker–β_2-agonist combination therapy with cardiac function and all-cause mortality in elderly male COPD patients, which indicated that they may be used safely in this population.

Keywords: β_2-agonists, β-blockers, β-blocker–β_2-agonist combination, elderly COPD patients, cardiac function, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is a global epidemic and is predicted to be the fifth most widespread disease and the third-leading cause of death worldwide by 2020.[1–3] The incidence of COPD increases sharply with age, and is more common in males.[2,3] Most COPD patients often have complications of multiple-organ insufficiency, such as cardiac insufficiency,[4–7] which increases mortality risk and worsens survival, thereby presenting many therapeutic challenges to health-care providers.[6,8,9]

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Beta2-adrenoceptor agonists (β_2-agonists) are typically used for COPD treatment to relieve airflow limitation and improve respiratory disorders. A recent study observed no association between β_2-agonist therapy and mortality in patients with heart failure (HF) after adjusting for B-type natriuretic peptide (BNP).[10] However, for COPD patients with coexisting HF, there is some concern regarding the relationship between β_2-agonist use and mortality in patients with cardiovascular disease. Several studies reported that regular use of β_2-agonists can cause downregulation of myocardial β_2-adrenoceptors, which may play an important role in onset or worsening HF.[11,12] Au et al[13] showed that β_2-agonist use was associated with an increased risk of all-cause mortality in patients with left ventricular systolic dysfunction (LVSD). Thus, the concerns and controversies make physicians reluctant to prescribe β_2-agonists in COPD patients.

It is generally accepted that β-blockers can be used safely in patients with HF to improve LVSD[14] and reduce mortality.[15] Although a few clinical trials had suggested the safety and efficacy of β-blocker therapy in COPD patients,[16,17] the actual use of β-blockers has remained lower than expected.[18,19] In addition, clinicians are cautious of β-blocker use for fear of provoking bronchospasm,[20,21] which may worsen cardiopulmonary function.

To date, there have been a considerable number of clinical trials to assess the use of β_2-agonists and β-blockers, yet most of them have been limited by the absence of detailed data on COPD status and high-risk patients, such as the elderly. In such cases, physicians would be extremely prudent to prescribe β_2-agonists for bronchospasm and β-blockers for tachycardia caused by cardiac insufficiency. To the best of our knowledge, COPD is an age-related disease; however, few studies have reported the effectiveness of β-blockers and β_2-agonists in a population with COPD, particularly the elderly. Therefore, we designed the current study to assess the association between the use of β-blockers, β_2-agonists, or a combination therapy and cardiac function, as well as all-cause mortality in elderly male COPD patients.

Methods

Ethical approval of the study protocol

This study complied with the Declaration of Helsinki[22] and was approved by the Scientific and Ethics Review Board of the Department of Geriatrics, Chinese PLA General Hospital, Beijing, People's Republic of China. All patients enrolled in the study submitted written informed consent.

Patient enrollment

A total of 220 male COPD patients (mean age 84.1 ± 6.9 years) were retrospectively enrolled in the present trial between January 2008 and May 2011. All participants were hospitalized in the Department of Geriatrics of the Chinese PLA General Hospital during the aforementioned recruitment period. Patient information was collected and registered with the electronic database of the cardiovascular center in the same hospital. Patient recruitment was carried out by physicians from the Department of Geriatric Cardiology, PLA General Hospital, who received proper instructions from the research team on the study aims and design.

Overall, 63 patients received β_2-agonists (salbutamol, salmeterol, or procaterol) and 112 were administered β-blockers (metoprolol, bisoprolol, or carvedilol). To evaluate the association between the use of β-blockers, β_2-agonists, or a combination of both with cardiac function, the patients were divided into four groups on the basis of the use of β_2-agonists and β-blockers: β_2-agonists, β-blockers, β_2-agonists and β-blockers, or neither (the control group).

Data on demographic variables, medication use, medical history, and current smoking status were collected. The patients' cardiovascular histories and cardiac risk factors were obtained from medical records of current or previous diagnoses and/or therapies, and included incidences of coronary heart disease, previous myocardial infarction, HF, hypertension, dyslipidemia, diabetes mellitus, renal dysfunction, and peripheral arterial occlusive disease.

Laboratory indicators, such as N-terminal fragment (NT) pro-BNP, total cholesterol, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol (LDL-c), triglycerides, serum creatinine, and high-sensitivity C-reactive protein (HS-CRP) levels, were measured and recorded at the same time. Left ventricular ejection fraction (LVEF), left ventricular end-systolic volume, left ventricular end-diastolic volume, and shortening fraction were calculated via standard transthoracic echocardiography performed by trained doctors blinded to group allocation.

Outcomes

The primary end point of the study was all-cause mortality, and eligible patients were followed up until they died (study end point) or the end of the trial duration (December 31, 2012), with a median follow-up of 22.2 months. Survival status was obtained from patient medical records.

Pulmonary function tests

All patients underwent pulmonary function tests. Spirometric evaluations were conducted in accordance with current guidelines using established reference values. A diagnosis of COPD was based on postbronchodilator spirometric data in conjunction with a history of cough, sputum production, and/or dyspnea. COPD, as defined by the Global initiative for chronic Obstructive Lung Disease criteria,[1] was classified into three stages: I = mild COPD (forced expiratory volume in 1 second/forced vital capacity [FEV_1/FVC] < 0.70 and $FEV_1 \geq 80\%$ of the predicted FEV_1), II = moderate COPD ($FEV_1/FVC < 0.70$ and FEV_1 $50\% \leq FEV_1 < 80\%$ of the predicted FEV_1), and III = severe COPD ($FEV_1/FVC < 0.70$ and FEV_1 $30\% \leq FEV_1 < 50\%$ of the predicted FEV_1).

Statistical analysis

Baseline characteristics among the patient groups were evaluated. Continuous data are presented as means ± standard deviation or median and 25th to 75th percentiles as appropriate, and compared using one-way analysis of variance or the Wilcoxon rank-sum test, depending on the distribution of variables. Categorical variables are expressed as percentages and evaluated using the chi-squared test. Multiple linear regression analysis was used to determine the relationship between the use of β_2-agonists, β-blockers, or a combination of both, and indices of cardiac function (NT pro-BNP and LVEF). In the model, we entered "P-in was 0.1 and P-out was 0.05".We entered β-blocker and β_2-agonist use and factors associated with NT pro-BNP at a P-value < 0.05, using the Enter and Stepwise fashion, included those variables with a P-value < 0.05. The same method was deemed suitable for LVEF. Patient survival was analyzed using the Kaplan–Meier method. The Cox proportional hazard model was used to adjust the variables. Age, body mass index (BMI), blood pressure, heart rate, biochemical markers, echocardiographic parameters, COPD severity, New York Heart Association (NYHA) classification, current smoking status, comorbidities, and prescribed drug use were included in the final model. For all tests, a two-tailed P-value < 0.05 was considered statistically significant. All calculations were performed using SPSS version 16.0 statistical software for Windows (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Patient demographics are provided in Table 1. Data from the 220 enrolled male patients (mean age 84.1 ± 6.9 years) were subjected to statistical analysis. In all, β_2-agonists were prescribed for 32 patients, β-blockers for 81, both β-blockers and β_2-agonists for 31, and neither (the control group) for 76.

The patients administered β_2-agonists had significantly higher predicted FEV_1% values ($P < 0.001$) and had a greater tendency for severe COPD ($P < 0.001$). Patients treated with β-blockers were more likely to have underlying histories of coronary artery disease and myocardial infarction, whereas those receiving combination therapy had poorer cardiac function status, as indicated by a greater incidence of NYHA classification III ($P = 0.030$). Medication use, age, and current smoking status were similar among the four groups (all $P > 0.05$). Univariate analysis showed significant differences in both HS-CRP ($P = 0.030$) and LDL-c levels among all four groups. Patients using a combination therapy had significantly higher LDL-c and total cholesterol levels ($P = 0.006$ and 0.020, respectively) compared with other patients. Patients using β_2-agonists had slightly higher HS-CRP levels ($P = 0.030$) than others (Table 1).

There was a significant difference in NT pro-BNP values among the four groups, with the highest levels detected in β_2-agonist users (385.7 pg/mL, range 142.6–960.1; $P = 0.004$). However, differences in LVEF were not statistically significant among the four groups ($P = 0.108$, Table 1).

Correlation analysis

Multivariate linear regression analysis with NT pro-BNP as the dependent variable showed that use of β_2-agonists ($\beta = 35.502$, $P = 0.905$), β-blockers ($\beta = -3.119$, $P = 0.989$), and β-blocker–β_2-agonist combination therapy ($\beta = 298.635$, $P = 0.325$) were not significantly associated with NT pro-BNP compared to the control group. Serum creatinine ($\beta = 2.954$, $P = 0.017$) and the presence of HF ($\beta = 746.983$, $P = 0.001$) were positively correlated with NT pro-BNP, whereas LDL-c ($\beta = -312.188$, $P = 0.017$) was negatively correlated with NT pro-BNP. In addition, with LVEF as the dependent variable, there were no significant associations between LVEF and the use of β_2-agonists ($\beta = -0.360$, $P = 0.475$), β-blockers ($\beta = -0.411$, $P = 0.284$), or β-blocker–β_2-agonist combination therapy ($\beta = -0.397$, $P = 0.435$). Meanwhile, LVEF was positively associated with shortening fraction ($\beta = 1.138$, $P < 0.001$) and negatively associated with left ventricular end-systolic volume ($\beta = -0.106$, $P < 0.001$; Table 2).

Clinical events

Although a total of 52 patients died over the follow-up period, there were no statistical differences in mortality

Table 1 Baseline characteristics

Characteristic	β_2-agonists (n = 32)	β-blockers (n = 81)	β-blockers + β_2-agonists (n = 31)	Control (n = 76)	*P*-value
Demographics					
Age (years)	84.8 ± 6.4	84.6 ± 6.2	86.0 ± 4.6	82.6 ± 8.5	0.135
COPD severity					
FEV_1, predicted (%)	58.9 ± 21.6	80.4 ± 19.9	74.7 ± 18.0	81.6 ± 22.7	<0.001
FEV_1/FVC (%)	50.6 ± 11.5	62.7 ± 6.7	56.5 ± 9.6	60.7 ± 8.5	<0.001
Mild, n (%)	3 (9.4)	41 (50.6)	12 (38.7)	44 (57.9)	<0.001
Moderate, n (%)	17 (53.1)	36 (44.4)	17 (54.8)	27 (35.5)	0.192
Severe, n (%)	12 (37.5)	4 (4.9)	2 (6.5)	5 (6.6)	<0.001
Cardiovascular history					
Coronary artery disease, n (%)	21 (65.6)	70 (86.4)	26 (83.9)	48 (69.2)	0.001
Heart failure, n (%)	9 (28.1)	19 (23.5)	9 (29.0)	13 (17.1)	0.616
NYHA functional class, n (%)					
NYHA I	20 (62.5)	55 (67.9)	17 (54.8)	60 (78.9)	0.068
NYHA II	9 (28.1)	19 (23.5)	9 (29.0)	14 (18.4)	0.575
NYHA III	3 (9.4)	7 (8.6)	6 (19.4)	2 (2.6)	0.030
Myocardial infarction	0 (0.0)	11 (13.6)	3 (9.7)	1 (1.3)	0.004
Clinical characteristics					
BMI (kg/m^2)	22.7 ± 3.1	24.7 ± 2.6	23.9 ± 2.9	24.1 ± 3.0	0.009
Systolic BP (mmHg)	130.1 ± 16.7	131.9 ± 16.4	130.4 ± 11.4	129.1 ± 15.1	0.927
Diastolic BP (mmHg)	67.4 ± 8.7	70.1 ± 10.8	66.8 ± 8.7	69.8 ± 9.8	0.292
Heart rate (bpm)	78.2 ± 16.3	72.7 ± 12.4	74.0 ± 7.5	71.3 ± 9.9	0.068
Current smoker, n (%)	9 (28.1)	25 (30.9)	8 (25.8)	29 (38.2)	0.573
Hypertension, n (%)	25 (78.1)	61 (75.3)	25 (80.6)	52 (68.4)	0.544
Diabetes mellitus, n (%)	12 (37.5)	39 (48.1)	16 (51.6)	32 (42.1)	0.611
Dyslipidemia, n (%)	4 (12.5)	17 (21.0)	6 (19.4)	19 (25.0)	0.565
Atrial fibrillation, n (%)	5 (15.6)	15 (18.5)	6 (19.4)	7 (9.2)	0.304
PAOD, n (%)	3 (9.4)	22 (27.2)	6 (19.4)	12 (15.8)	0.132
Renal dysfunction, n (%)	4 (30.8)	21 (41.2)	4 (20.0)	11 (34.4)	0.417
Concomitant therapy, n (%)					
ACE inhibitors	3 (9.4)	13 (16.0)	4 (12.9)	4 (5.3)	0.167
A2RAs	9 (28.1)	30 (37.0)	11 (35.5)	22 (28.9)	0.666
Calcium-channel blockers	21 (65.6)	49 (60.5)	20 (64.5)	42 (55.3)	0.711
Loop diuretics	11 (34.4)	26 (32.1)	14 (45.2)	19 (25.0)	0.234
Antiplatelet	22 (68.8)	51 (63.0)	19 (61.3)	49 (64.5)	0.929
Statins	15 (46.9)	45 (55.6)	12 (38.7)	37 (48.7)	0.439
Digoxin	5 (15.6)	7 (8.6)	4 (12.9)	6 (7.9)	0.538
Nitrates	22 (68.8)	50 (61.7)	20 (64.5)	44 (57.9)	0.758
Spironolactone	4 (12.5)	9 (11.1)	3 (9.7)	5 (6.6)	0.714
Laboratory parameters					
NT pro-BNP (pg/mL)	385.7 (142.6–960.1)	226.2 (116.3–718.9)	272.1 (113.1–152.6)	112.6 (71.9–379.1)	0.004
Serum creatinine (μmol/L)	97.5 (70.1–127.7)	93.0 (75.3–126.9)	95.0 (74.0–133.0)	88.9 (75.8–113.3)	0.643
Uric acid (mmol/L)	313.7 (253.5–373.0)	331.4 (266.0–381.1)	353.2 (276.2–453.5)	317.5 (260.7–373.4)	0.282
HS-CRP (mg/dL)	0.84 (0.3–2.9)	0.4 (0.1–0.8)	0.7 (0.3–2.3)	0.6 (0.2–1.9)	0.030
Total cholesterol (mmol/L)	3.9 (3.7–4.8)	3.7 (3.3–4.4)	4.5 (4.0–4.9)	4.3 (3.61–4.87)	0.020
Triglyceride (mmol/L)	1.2 (0.8–1.6)	1.3 (0.9–1.7)	1.6 (1.0–1.9)	1.2 (0.9–1.8)	0.319
HDL-c (mmol/L)	1.3 (1.0–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.229
LDL-c (mmol/L)	2.1 (1.8–2.6)	2.1 (1.7–2.7)	2.7 (2.4–3.2)	2.4 (2.0–3.1)	0.006
Serum glucose (mmol/L)	5.7 (4.9–6.2)	5.7 (5.0–6.4)	5.5 (4.7–6.6)	5.6 (5.1–6.1)	0.931
Echocardiographic parameters					
LVESV (mL)	39.7 ± 7.5	46.4 ± 12.6	44.3 ± 8.4	43.1 ± 8.7	0.018
LVEDV (mL)	106.6 ± 16.8	115.5 ± 21.8	113.9 ± 14.7	111.9 ± 16.0	0.131
Shortening fraction (%)	34.2 ± 2.2	32.6 ± 3.2	32.7 ± 3.3	33.2 ± 2.5	0.055

(*Continued*)

Table 1 (*Continued*)

Characteristic	β_2-agonists (n = 32)	β-blockers (n = 81)	β-blockers + β_2-agonists (n = 31)	Control (n = 76)	*P*-value
LVEF (%)	62.6 ± 3.1	60.1 ± 5.9	60.5 ± 4.6	61.6 ± 3.4	0.108
<50%, n (%)	0 (0.0)	4 (4.9)	1 (3.2)	0 (0.0)	
>50%, n (%)	32 (100)	77 (95.1)	30 (96.8)	76 (100.0)	

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association; BMI, body mass index; BP, blood pressure; bpm, beats per minute; PAOD, peripheral arterial occlusive disease; ACE, angiotensin-converting enzyme; A2RA, angiotensin-II receptor antagonist; HS-CRP, high-sensitivity C-reactive protein; LDL-c, low-density-lipoprotein cholesterol; HDL-c, high-density-lipoprotein cholesterol; NT pro BNP, N-terminal pro-hormone brain natriuretic parameters; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

rates among the study groups ($P = 0.357$). NT pro-BNP levels were significantly higher in those patients who died than those who survived (195.7 pg/mL [range 70.5–449.3] versus 707.1 pg/mL [range 194.9–2,393.1], $P < 0.001$), but in contrast, LVEF was statistically lower in those patients who died (59.9% ± 6.2% versus 61.4% ± 4.1%, $P = 0.014$). Kaplan–Meier analysis of all-cause mortality revealed no significant difference among the study groups (log-rank test, $P = 0.362$). When adjusted for age, BMI, blood pressure, heart rate, serum creatinine, LDL-c, NT pro-BNP, HS-CRP, echocardiographic parameters, COPD severity, NYHA class, current smoking status, prescribed drugs, and comorbidities, there was still no significant association observed between the use of β_2-agonists (hazard ratio [HR] 0.711, 95% CI 0.287–1.759; $P = 0.460$), β-blockers (HR 0.962, 95% CI 0.405–2.285; $P = 0.930$), or β-blocker–β_2-agonist combination therapy (HR 0.638, 95% CI 0.241–1.689; $P = 0.366$) and all-cause mortality. In addition, HS-CRP was not associated with mortality ($P = 0.609$) either, whereas NT pro-BNP had a significant effect on mortality (HR 1.612, 95% CI 1.265–2.055; $P < 0.001$). No statistical interaction was observed between β-blockers and β_2-agonists regarding all-cause mortality ($P = 0.428$). Multivariable associations of mortality are presented in Table 3. In addition, among patients receiving beta-blockers, β_2-agonist use (compared with no β_2-agonist use) was associated with lower all-cause mortality [HR 1.134 (0.378–3.403) versus 1.377 (0.485–3.910) in those not receiving a beta-blocker]. No statistical interaction was observed between β_2-agonists and β-blockers regarding all-cause mortality (Table 4).

Discussion

The primary objective of this study was to examine the association between cardiac function, all-cause mortality, and the use of β_2-agonists, β-blockers, or both in elderly male COPD patients. The main findings of the current study indicated that β_2-agonist use may not be associated with either NT pro-BNP or LVEF in elderly male COPD patients, and that β_2-agonist use was not associated either with all-cause mortality in these patients when adjusted for NT pro-BNP, LVEF, and relevant clinical, demographic, and medication variables. Similar results were also found for patients using β-blockers or combination therapy.

Table 2 Linear regression analyses of clinical data, echocardiographic data and NT pro-BNP/LVEF

Characteristic	Model 1			Model 2		
	NT pro-BNP			LVEF		
	β	t	*P*-value	*β*	t	*P*-value
β_2-agonists	35.502	0.120	0.905	–0.360	–0.715	0.475
β-blockers	–3.119	–0.013	0.989	–0.411	–1.074	0.284
β-blockers + β_2-agonists	298.635	0.986	0.325	–0.397	–0.783	0.435
Heart failure	746.983	3.533	0.001	–	–	–
Serum creatinine	2.954	2.407	0.017	–	–	
LDL-c	–312.188	–2.408	0.017	–	–	–
Shortening fraction	–	–	–	1.138	16.148	<0.001
LVESV	–	–	–	–0.106	–5.337	<0.001

Abbreviations: NT pro-BNP, N-terminal pro-hormone brain natriuretic parameters; LVEF, left ventricular ejection fraction; LDL-c, low-density-lipoprotein cholesterol; LVESV, left ventricular end-systolic volume.

Table 3 Associates of all-cause mortality in the total population

Variable	HR (95% CI, *P*-value)
NT pro-BNP	1.612 (1.265–2.055, <0.001)
Myocardial infarction	4.026 (1.229–13.187, 0.021)
Renal dysfunction	2.363 (1.229–4.544, 0.010)
ACE inhibitors	0.155 (0.035–0.689, 0.014)
A2RAs	0.387 (0.181–0.828, 0.014)
Loop diuretic	3.973 (2.004–7.877, <0.001)
β_2-agonists	0.711 (0.287–1.759, 0.460)
β-blockers	0.962 (0.405–2.285, 0.930)
β-blockers + β_2-agonists	0.638 (0.241–1.689, 0.366)

Abbreviations: HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-hormone brain natriuretic parameters; ACE, angiotensin-converting enzyme; A2RA, angiotensin-II receptor antagonist.

Correlation of β_2-agonist use with cardiac function and mortality

Unlike some studies that demonstrated that β_2-agonist use was associated with increased risk of all-cause mortality,[13,23] the present study found that β_2-agonist use did not influence all-cause mortality in elderly male COPD patients over the follow-up period. Au et al[13] showed a dose–response increase in mortality in patients with LVSD who used β_2-agonists. However, they focused on a population with LVSD and did not include patients with HF and preserved systolic function (HFPSF). Another retrospective analysis of the Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) study examined the effect of bronchodilator use in trial participants. The analysis indicated an increased risk of mortality, cardiovascular death, and major adverse cardiovascular events in bronchodilator users compared to patients not using bronchodilators.[23] Although previous studies focused on patients with LVSD and/or HFPSF, only a portion of the subjects had coexisting COPD. However, our study included only COPD patients with predominantly normal cardiac function or mild-to-moderate cardiac insufficiency. Furthermore, the incidence of COPD sharply increased with age.[1] The mean patient age in the two previous studies was less than 70 years, but average patient age in the current study was 84.8 years, which gives more evidence for β_2-agonist therapy in elderly male COPD patients.

The present study showed that β_2-agonist use was not associated with either NT pro-BNP or LVEF, which was partially consistent with the finding that chronic β_2-agonist treatment did not affect LVEF in mice.[24] In addition, some authors suggested that β_2-agonists may improve pulmonary function in patients with HF.[25] Perhaps a plausible hemodynamic explanation is that COPD patients gradually achieved improved right ventricular function and may have achieved improved left ventricular function as well as NT pro-BNP levels to some degree, with ameliorating pulmonary function mediated by β_2-agonists. Further survival analysis indicated that NT pro-BNP level was an independent risk factor for all-cause mortality. Thus, these data may partly explain why there was no influence of β_2-agonist use on outcome in our study patients. Bermingham et al[10] reported that β_2-agonist therapy in patients with HF showed no relationship with long-time mortality when adjusted for population differences, including BNP levels, which was in accordance with our results. These findings suggested that β_2-agonists may be used safely in elderly male COPD patients.

Correlation of β-blocker use with cardiac function and mortality

The benefit of β-blocker use in cardiovascular disease with heart dysfunction has been widely accepted in recent years.[14] Two randomized clinical trials showed a relationship between β-blocker use and cardiac function.[26,27] One showed that carvedilol administration had no influence on plasma NT pro-BNP levels in patients with HF.[26] In the other study, β-blocker use was associated with increasing LVEF in patients undergoing coronary artery bypass grafting.[27] However, neither reported an association in COPD patients, especially in high-risk patients, such as the elderly or those with multiple comorbidities for whom physicians may be hesitant to prescribe β-blockers. Our analysis examined this particular patient group, and found that β-blocker use had no association with NT pro-BNP, or LVEF. To elucidate this problem, we next assessed the association between β-blocker use and death from any cause among confirmed COPD patients. The adjusted data confirmed that β-blocker use was

Table 4 Association between β_2-agonist use and all-cause mortality according to β-blocker therapy

Outcome, β-blockers	β_2-agonists	No β_2-agonists	HR (95% CI)	*P*-value	*P*-value interaction[a]
β-blockers	31	81	1.134 (0.378–3.403)	0.823	0.428
No β-blockers	32	76	1.377 (0.485–3.910)	0.548	

Note: [a]Interaction between β_2-agonists and β-blockers.
Abbreviations: HR, hazard ratio; CI, confidence interval.

not associated with all-cause mortality in elderly male COPD patients, which was consistent with the results of studies that described the beneficial effects of β-blocker use in COPD patients.[26,27] An observational study suggested that β-blocker use had a tendency to lower mortality risk in patients with combined COPD and hypertension.[28] Also, a recent study produced evidence of the survival benefits of β-blocker use in COPD patients.[29] Despite the shared viewpoint that caution should be exercised when prescribing β-blockers to COPD patients, the present study demonstrated that even in elderly male COPD patients, β-blocker use may not have an impact on all-cause mortality and may not be contraindicated in older male COPD patients. Thus, we should pay more attention to additional tests.

Correlation of combination therapy with cardiac function and mortality

The present study is the first to demonstrate that combined use of β-blockers and β_2-agonists is not associated with NT pro-BNP levels or LVEF in elderly COPD male patients compared to a control group.

Perhaps the most reasonable explanation for this observation is that there was a potential reciprocity between β-blocker and β_2-agonist use. Some authors have found that β_2-agonist use may increase cardiac sympathetic outflow and augment ventricular contractility.[30–32] Beta-blocker use, however, may have a partial antagonistic effect on the inotropic and cardiac sympathetic results of β_2-agonist use and increased susceptibility to the effects of β_2-inotropic properties.[33–35] Newton et al[11] also observed a significantly less inotropic response to salbutamol in patients treated with β-blockers compared to those not using β-blockers. Together, these studies suggested a pathophysiological and pharmacological plausibility that there may be no influence on cardiac function in elderly COPD patients administered β-blocker and β_2-agonist combination therapy. Further analysis showed that combination therapy had no influence on all-cause mortality in the fully adjusted model. The results presented here are in line with a large-scale study, which also reported no increased risk of mortality in patients with HF taking both β-blockers and β_2-agonists.[10] Two studies that demonstrated that NT pro-BNP was associated with mortality[36,37] were also consistent with our results. However, unlike the previous large-scale study study, we focused on COPD patients who were almost 10 years older. This new information may provide important evidence and background information for further prospective studies.

Our results showed that β_2-agonist users had a higher incidence of severe COPD and higher HS-CRP levels, which was consistent with an observation that COPD severity was correlated with CRP.[38] However, after full adjustment, there was no significant association between HS-CRP and mortality. Therefore, this finding suggested that β_2-agonist use may have no influence on mortality in elderly male COPD patients.

To our knowledge, different drugs have different chemical formulas, which could cause a potential discrepancy in the mode of action. In the current study, no significant difference was observed in medication use at baseline, such as loop diuretics and calcium-channel blockers. However, our results may not reflect the discrepancy on different kinds of β-blockers/β_2-agonists. Thus, further prospective studies on the issue are needed to validate these early findings.

There were some limitations to the present study. First, all patients were male and the study population was relatively small. Further large-scale studies (including female patients) are required to verify the findings of the present study. Second, the specific type, administration route, dose, frequency, and duration of therapy were not recorded. It was also difficult to adjust adequately for measurement of patient adherence. Third, this was an observational, retrospective, cohort study and not a large-scale, prospective, randomized trial; therefore, the lack of association we observed cannot be assessed definitively. However, the information regarding β-blocker use was based on prescription records and clinic data, all of the included patients were carefully examined, data were obtained on lung-function measurements and demographic information, and sophisticated statistical modeling was performed. Given that the prevalence of COPD increases with age and most of the patients were male,[2,3] the present study may at least give some implications for COPD management and timely initiation of disease-modifying therapy in elderly male patients.

Conclusion

In summary, the present study showed no significant association between the administration of β_2-agonists, β-blockers, or a β-blocker–β_2-agonist combination therapy and cardiac function as well as all-cause mortality in elderly male COPD patients, thus these medications may be used safely in elderly male COPD patients. Our results may be helpful to assess the clinical effectiveness of β_2-agonist and β-blocker use in such patients; however, additional prospective studies are required to validate our findings.

Disclosure

The authors report no conflicts of interest in this work.

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