

Bronchodilator Therapy in Acute Decompensated Heart Failure Patients Without a History of Chronic Obstructive Pulmonary Disease

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Study objective: Inhaled bronchodilators are often used in the emergency department (ED) before a definitive diagnosis is made. We evaluated the association between inhaled bronchodilators and outcomes in acute decompensated heart failure patients without chronic obstructive pulmonary disease.

Methods: We conducted an analysis of the Acute Decompensated Heart Failure National Registry Emergency Module registry of patients with a principal discharge diagnosis of acute decompensated heart failure enrolled at 76 academic or community EDs. Dichotomous outcomes (mortality, ED discharges, ICU admission, ED IV vasodilator use, new dialysis, ED or in patient endotracheal intubation, ED BiPAP, and asymptomatic at discharge) in patients without a history of chronic obstructive pulmonary disease who were given bronchodilators were compared to those who were not given bronchodilators using logistic regression; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated; and propensity score adjustments were made.

Results: Of the 10,978 patients enrolled, 7299 (66.5%) did not have a history of chronic obstructive pulmonary disease. Bronchodilators were administered by the EMS or in the ED to 2317 (21%) patients. Patients without chronic obstructive pulmonary disease given bronchodilators were more likely to receive ED IV vasodilators (28.4% vs. 16.9%; propensity adjusted OR 1.40 [95% CI 1.18-1.67]) and in-patient mechanical ventilation (6.0% vs. 2.4%; propensity adjusted OR 1.69 [95% CI 1.21-2.37]) than patients without chronic obstructive pulmonary disease who were not given bronchodilators. Hospital mortality in patients without chronic obstructive pulmonary disease was similar regardless of bronchodilator treatment (3.4% vs. 2.6%, propensity adjusted OR 1.02 [95% CI 0.67, 1.56]).

Conclusion: Many acute decompensated heart failure patients without a history of chronic obstructive pulmonary disease receive inhaled bronchodilators. Bronchodilator use was associated with a greater need for aggressive interventions and monitoring, and this may reflect an adverse effect of bronchodilators or it may be a marker for patients with more severe disease. [Ann Emerg Med. 2008;51: 25-34.]

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Editor's Capsule Summary*What is already known on this topic*

Dyspneic patients are often treated with inhaled bronchodilators before the cause of the dyspnea is known.

What question this study addressed

This retrospective analysis of a patient registry compared outcomes of 7299 patients with acute decompensated heart failure and no history of chronic obstructive pulmonary disease who were or were not treated with inhaled bronchodilators.

What this study adds to our knowledge

Patients treated with bronchodilators received more medications, required mechanical ventilation more often, and had longer inpatient stays than those who did not. Mortality rates were similar in the 2 groups.

How this might change clinical practice

This study design cannot differentiate whether the group who received bronchodilators had more complicated courses because they were sicker or because the bronchodilator therapy had deleterious effects. A randomized trial will be needed to answer this question.

SEE EDITORIAL, P. 35.**INTRODUCTION****Background**

Dyspnea is a common complaint among patients presenting to the emergency department (ED). Data from the National Hospital Ambulatory Medical Care survey indicate that shortness of breath was the sixth most common principal reason for ED visits. In 2003, 2.9 million ED visits for shortness of breath were reported.¹

The symptom of dyspnea is associated with a wide range of differential diagnoses. Chronic obstructive pulmonary disease and acute decompensated heart failure are among the most common and potentially serious causes of dyspnea. At patients' initial presentation to the clinic, hospital, or ED, it is often difficult to determine whether their symptoms are the result of an acute exacerbation of chronic obstructive pulmonary disease or acute decompensated heart failure. Because these patients are often in clear distress, physicians may respond by treating for both conditions with a "shotgun" approach.

Importance

Inhaled bronchodilator agents are frequently used in the treatment of acute dyspnea. The actual use of bronchodilators in acute decompensated heart failure patients with or without pulmonary disease has not been well described in the literature. Some data suggest that bronchodilators may be harmful in

patients with heart failure or ischemic heart disease.²⁻⁹ A better understanding of the association between inhaled bronchodilator use and clinical outcomes is needed among acute decompensated heart failure patients without chronic obstructive pulmonary disease.

Goals of This Investigation

Our objective was to evaluate the association between bronchodilator use and outcomes in acute decompensated heart failure patients without a history of chronic obstructive pulmonary disease, after adjusting for differences in baseline characteristics, severity of illness, and prognostic markers.

MATERIALS AND METHODS**Study Design**

The Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM) database was used to conduct this analysis. ADHERE-EM was a multicenter, continuous, observational, quality initiative designed to study the management of acute decompensated heart failure patients treated in the ED of hospitals with an acute decompensated heart failure disease management program. ADHERE-EM collected data on the episode of hospital care, beginning with the ED as the point of initial care and ending with the patient's ED or hospital discharge, transfer out of the hospital, death in the ED, or inhospital death, whichever event occurred last. Patients were enrolled between July 2004 and October 2005. ADHERE-EM was conducted as part of the ADHERE program.¹⁰

Setting

A total of 76 hospitals across the country participated in ADHERE-EM. Hospitals of various sizes from all regions were represented. Participating hospitals included both academic and community settings. All hospitals obtained institutional review board or ethics board approval for participation. The data collection system was designed such that patient informed consent was not necessary.¹⁰

Selection of Participants

The target population consisted of all consecutive adult patients treated in the ED for acute decompensated heart failure. Acute decompensated heart failure was defined as either new-onset heart failure with decompensation or chronic heart failure with decompensation. Patient eligibility was based on the presence of a hospital discharge or ED diagnosis of acute decompensated heart failure, and it was not tied to the use of any specific therapeutic agent or regimen. Patients were enrolled if they met the following inclusion criteria: age greater than or equal to 18 years at ED treatment; received or eligible to receive a principal ED or hospital discharge diagnosis of acute decompensated heart failure or acute decompensated heart failure present as determined clinically by the patient care team and as documented in the diagnosis related groups or

ambulatory payment classification codes; and acute decompensated heart failure was the focus of treatment. Patients were not eligible for registry participation if they had decompensated heart failure present as a comorbid condition but not a principal focus of diagnosis or treatment during the ED or hospital episode or if the patient was not treated in the ED.

Data Collection and Processing and Outcome Measures

Demographic, clinical, and outcome data were collected by research coordinators at each site with a standard electronic case report form. Electronic case report forms were completed according to a standardized set of instructions. The data were entered into an electronic data capture system. The information was encrypted and transmitted to a clinical trial server. Automatic query rules checked for data accuracy. Data queries generated from these rules were immediately sent back to the site for resolution. A full audit trail was maintained for any data changes. Left ventricular ejection fraction collected during the current hospitalization was used, if available. Alternatively, the last out-of-hospital left ventricular ejection fraction was used. A quantitative left ventricular ejection fraction measure was available for 79% of the patients. Inhaled bronchodilator administration by emergency medical personnel (emergency medical services [EMS]) or in the ED was recorded. Initial laboratory values and vital signs were the first values obtained in the ED or observation unit. Sites selected one of the following options when recording bronchodilator use in the electronic case report forms: albuterol, ipratropium bromide, pirbuterol, salmeterol, albuterol/ipratropium, salmeterol/fluticasone, not specified, or other. The following clinical outcomes were collected and evaluated for associations with bronchodilator use: inhospital or ED mortality, ED discharges, ICU admissions at any time during the hospitalization, length of stay, need for endotracheal intubation or mechanical ventilation in the ED or during the inpatient stay, need for bilevel positive airway pressure (BiPAP) in the ED, need for intravenous vasodilator medications in the ED or observation unit, new need for dialysis, and the proportion of patients asymptomatic at discharge.

Primary Data Analysis

Patients who received inhaled bronchodilators by EMS or in the ED were compared with those who did not. The primary focus of this analysis is heart failure patients without a history of chronic obstructive pulmonary disease, although descriptive data for patients with a history of chronic obstructive pulmonary disease are also provided.

Categorical variables are presented as percentage of frequency of occurrence and evaluated using the χ^2 statistic. Continuous variables are presented as means and medians, and they were compared using 1-way ANOVA and the Wilcoxon test.

A propensity score was developed for patients without chronic obstructive pulmonary disease to adjust for differences in baseline clinical and demographic characteristics between

patients who did or did not receive a bronchodilator. The propensity score is the conditional probability of assignment to a particular treatment, given observed covariates, and it is used to produce unbiased estimates of the treatment effect in observational studies.¹¹⁻¹³ Thirty-two variables with less than 5% missing were considered for inclusion in the model. Stepwise logistic regression and backward elimination both selected the same set of 10 covariates for the final model, using a significance level of 0.05 for a variable to enter and remain in the model. The variables included in the model are listed in [Figure 1](#).

Multivariable logistic regression was used to adjust group comparisons for treatment propensity and previously identified risk factors in this population: sex, age, initial serum creatinine level, blood urea nitrogen (BUN) level, dyspnea at rest, systolic blood pressure, diastolic blood pressure, and pulse rate.^{14,15} Odds ratios (ORs), 95% confidence intervals (CIs), and *P* values were calculated. No missing data were imputed, so only records with complete data for these variables were included in the model. Median length of stay was compared by bronchodilator use by the Wilcoxon test. Analysis of covariance on rank length of stay, adjusted as described above, was also performed. The analysis was performed using SAS, version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 10,978 patient records were contained in the ADHERE-EM database. There was a history of chronic obstructive pulmonary disease in 3,679 patients, and the remaining 7,299 (66.5%) did not have a history of chronic obstructive pulmonary disease. A bronchodilator was administered by the EMS or in the ED, for a total of 2,317 (21%) patients in the overall cohort. Heart failure patients with a history of chronic obstructive pulmonary disease were more likely to receive a bronchodilator than heart failure patients without chronic obstructive pulmonary disease (34.7% versus 14.3%; difference 20.4% [95% CI 18.6% to 22.1%]). The primary focus of this analysis is heart failure patients without a history of chronic obstructive pulmonary disease who did or did not receive an inhaled bronchodilator.

Baseline characteristics were generally similar between heart failure patients without chronic obstructive pulmonary disease who received a bronchodilator and those who did not ([Table 1](#)). Male sex and a history of heart failure were both less common among bronchodilator-treated patients without chronic obstructive pulmonary disease. More patients without chronic obstructive pulmonary disease who received a bronchodilator had a positive smoking history compared with those who were not treated with a bronchodilator.

Dyspnea, dyspnea at rest, and rales at ED admission were more common among patients without chronic obstructive pulmonary disease who were treated with bronchodilators than nonbronchodilator-treated patients ([Table 2](#)). Blood PCO₂ was measured in a subset of patients, and it was significantly higher in the patients without chronic obstructive pulmonary disease

Demographics
Age
Sex
Race (white, black, other)
Medical history before current episode
Atrial fibrillation
Long-term dialysis*
Diabetes
Heart failure
Any previous heart failure hospitalizations (yes/no)
Hypertension
Ventricular tachycardia/ventricular fibrillation
Baseline clinical characteristics
Dyspnea* (yes/no)
Edema
Fatigue
Congestion or evidence of ADHF on first chest radiograph
Rales*
Chest pain*
Weight gain
Principal admitting diagnosis of heart failure (yes/no)
Systolic BP*
Diastolic BP
Pulse*
ED O ₂ saturation*
Creatinine
BUN
Long-term nonintravenous medication use
ACE/ARB
Diuretics*
Antiarrhythmics
β-Blockers
Calcium-channel blockers
Digoxin*
Warfarin
Other
EMS arrival*

Figure 1. Variables considered in propensity model.* ADHF, Acute decompensated heart failure; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

*Variables included in propensity model.

who received a bronchodilator. The first O₂ saturation (on room air or with supplemental oxygen, according to the hospital's own procedure and individual patient treatment) measured in the ED was lower, and blood pressure and pulse rate were higher in patients without chronic obstructive pulmonary disease who were treated with a bronchodilator than in patients without chronic obstructive pulmonary disease who did not receive a bronchodilator. Chest radiograph congestion was present in a higher proportion of patients without chronic

obstructive pulmonary disease who received a bronchodilator compared with those who did not (80.1% versus 71.9%).

Bronchodilator treatment among heart failure patients without chronic obstructive pulmonary disease in the emergency setting was associated with a greater likelihood of receiving loop diuretics (18.6% versus 9.2%) or nitroglycerin (23.2% versus 16.2%) by EMS personnel before ED arrival compared with nonbronchodilator-treated patients without chronic obstructive pulmonary disease. More patients without chronic obstructive pulmonary disease who were treated with a bronchodilator also received continuous positive airway pressure, BiPAP, or mechanical ventilation in the ED or observation unit compared with those who did not receive a bronchodilator (11.7% versus 4.5%). BiPAP was used in 7.3% of non-chronic obstructive pulmonary disease bronchodilator-treated patients and in 2.9% of non-chronic obstructive pulmonary disease patients who did not receive a bronchodilator.

During the ED stay, intravenous vasodilator use was more common among heart failure patients without chronic obstructive pulmonary disease who received bronchodilators compared with those who did not (28.4% versus 16.9%; propensity-adjusted OR 1.40 [95% CI 1.18 to 1.67]) (Figure 2A; Table 3A, 3B). The median (interquartile range) time to vasodilator initiation was also shorter for patients without chronic obstructive pulmonary disease treated with bronchodilators compared with those not treated with bronchodilators (1.0 hours [0.5 to 2.5 hours] versus 2.1 hours [0.9 to 3.8 hours]). Use of intravenous diuretics and angiotensin-converting enzyme inhibitors in the ED was also higher in patients without chronic obstructive pulmonary disease treated with bronchodilators (77.4% versus 72.5% and 2.4% versus 0.9%, respectively) (Figure 2A).

In contrast to the findings for heart failure patients without chronic obstructive pulmonary disease, intravenous vasodilator and intravenous angiotensin-converting enzyme inhibitor use was not different in heart failure patients with chronic obstructive pulmonary disease according to bronchodilator use. Intravenous diuretics were used more often among heart failure patients with chronic obstructive pulmonary disease who received a bronchodilator (79.4% versus 72.5%), and the median (interquartile range) time to receive diuretic therapy was slightly shorter (1.8 hours [0.8 to 3.2 hours] versus 2.0 hours [1.0 to 3.4 hours]) compared with patients with chronic obstructive pulmonary disease who were not treated with a bronchodilator.

Most patients were admitted to the hospital from the ED regardless of chronic obstructive pulmonary disease status or bronchodilator treatment. The ICU was the first inpatient unit after admission for more patients without chronic obstructive pulmonary disease who received a bronchodilator compared with those who did not receive a bronchodilator (17.2% versus 11.3%).

Table 1. Baseline characteristics.

Variable	Patients Without COPD		Patients With COPD	
	Bronchodilator, N=1,042	No Bronchodilator, n=6,257	Bronchodilator, n=1,275	No Bronchodilator, n=2,404
Demographics				
Age, mean (SD), y	74.1 (15.1)	73.5 (15.1)	72.4 (13.2)	71.9 (13.5)
Male, No. (%)	456 (43.8)	2,972 (47.5)	612 (48)	1,205 (50.1)
Caucasian, No. (%)	698 (67)	4,343 (69.4)	933 (73.2)	1,742 (72.5)
Comorbidity				
Previous heart failure, No. (%)	736 (70.6)	4,620 (73.8)	1,038 (81.4)	1,977 (82.2)
Heart failure hospitalizations in previous 6 months, No. (%)				
0	0	2/1,454 (0.1)	1/359 (0.3)	2/665 (0.3)
1	172/230 (74.8)	1,016/1,454 (69.9)	247/359 (68.8)	433/665 (65.1)
2	34/230 (14.8)	288/1,454 (19.8)	57/359 (15.9)	123/665 (18.5)
≥3	24/230 (10.4)	148/1,454 (10.2)	54/359 (15)	107/665 (16.1)
Atrial fibrillation, No. (%)	314 (30.1)	1,980 (31.6)	411 (32.2)	843 (35.1)
Long-term dialysis, No. (%)	76 (7.6)	478 (7.9)	87 (7.1)	203 (8.8)
Diabetes, No. (%)	483 (46.4)	2,757 (44.1)	553 (43.4)	1,121 (46.6)
Hypertension, No. (%)	845 (81.1)	4,917 (78.6)	1,014 (79.5)	1,934 (80.4)
Smoker (current), No. (%)	138 (14.5)	714 (12.6)	369 (30.5)	565 (24.9)
Smoker (ever), No. (%)	428 (44.9)	2,334 (41.1)	903 (74.6)	1,538 (67.8)
History of ventricular fibrillation, No. (%)	6 (0.6)	52 (0.8)	13 (1)	21 (0.9)
History of ventricular tachycardia, No. (%)	41 (3.9)	328 (5.2)	60 (4.7)	170 (7.1)

COPD, Chronic obstructive pulmonary disease.

Patterns of intravenous vasoactive drug use at any time during the hospitalization were similar to the patterns observed in the ED (Figure 2B). Intravenous diuretic use was more common among patients with chronic obstructive pulmonary disease who received a bronchodilator (92.2% versus 88.1%), and the median (interquartile range) time to administration was shorter compared with that of patients with chronic obstructive pulmonary disease who were not receiving a bronchodilator (2.1 hours [0.9 to 4.1 hours] versus 2.4 hours [1.2 to 4.7 hours]).

Patients without chronic obstructive pulmonary disease who received a bronchodilator were more likely to require inpatient mechanical ventilation (6.0% versus 2.4%; propensity-adjusted OR 1.69 [95% CI 1.21 to 2.37]). The total median length of stay was longer among patients without chronic obstructive pulmonary disease who were prescribed a bronchodilator compared with those who were not. Fewer patients without chronic obstructive pulmonary disease who were treated with a bronchodilator were asymptomatic at hospital discharge compared with those who did not receive a bronchodilator (55.5% versus 60.1%; propensity-adjusted OR 0.84 [95% CI 0.71 to 0.99]). Outcomes among heart failure patients with chronic obstructive pulmonary disease were analyzed for descriptive purposes, and no differences were observed, with the exception of ED use of BiPAP (Table 3B).

Mortality was not different in either patients with or without chronic obstructive pulmonary disease who received a bronchodilator or those who did not (Table 3A, B). After adjusting for sex, age, serum creatinine level, BUN level, dyspnea at rest, systolic blood pressure, diastolic blood pressure, pulse rate, and the propensity score, bronchodilator use in heart

failure patients without chronic obstructive pulmonary disease was not associated with increased mortality (OR 1.02; 95% CI 0.67 to 1.56).

LIMITATIONS

These data should be interpreted in the context of several limitations. First, these data were generated from an observational database and not from a randomized controlled trial. Because of the observational nature of the study, only associations can be detected between bronchodilator use, treatment patterns, and outcomes. Causality cannot be determined from these data. Although rigorous statistical methodology was applied to adjust for differences in severity of illness and other confounders, unrecognized factors not accounted for in the data set or statistical analysis could have been present that influenced the outcome. The statistical methods applied control for illness severity and other differences to some extent, but it cannot completely control for treatment allocation. It is possible that sicker patients who needed a greater intensity of treatment were selected for bronchodilator therapy. In addition, the exact time of bronchodilator administration in the ED was not collected. It is possible that intravenous vasoactive agents were given before or with bronchodilators in the ED. The presence of chronic obstructive pulmonary disease was based on medical history alone rather than on formal pulmonary function testing. Thus, some patients categorized as not having chronic obstructive pulmonary disease may have actually had chronic obstructive pulmonary disease. This limitation could have resulted in overestimation of the association between

Table 2. ED admission characteristics.

Variable	Patients Without COPD		Patients With COPD	
	Bronchodilator, N=1,042	No Bronchodilator, n=6,257	Bronchodilator, n=1,275	No Bronchodilator, n=2,404
Signs and symptoms				
Chest pain, No. (%)	209 (20.1)	1,655 (26.5)	279 (21.9)	690 (28.7)
Dyspnea, No. (%)	1,010 (96.9)	5,680 (90.8)	1,241 (97.3)	2,254 (93.8)
Dyspnea at rest, No. (%)	480 (46.1)	2,013 (32.2)	579 (45.4)	807 (33.6)
Edema, No. (%)	636 (61)	3,973 (63.5)	789 (61.9)	1,555 (64.7)
Elevated jugular venous pressure, No. (%)	202 (33.6)	1,281 (34.8)	214 (29.2)	423 (31.1)
Fatigue, No. (%)	259 (24.9)	1,667 (26.6)	317 (24.9)	696 (29)
Rales, No. (%)	723 (69.4)	3,712 (59.3)	855 (67.1)	1,495 (62.2)
Weight gain, No. (%)	75 (7.2)	622 (9.9)	96 (7.5)	240 (10)
Laboratory data and vital signs				
LVEF, mean (SD)	39.4 (16.7)	38 (17)	40.2 (16.9)	38.6 (17.2)
Chest radiograph congestion, No. (%)	822 (80.1)	4,340 (71.9)	938 (75.2)	1,741 (74.5)
*BUN (mg/dL), mean (SD)	29.7 (18.6)	30.6 (19.4)	27.6 (17.5)	30.6 (19.9)
Serum creatinine (mg/dL), mean (SD) [†]	1.8 (1.6)	1.8 (1.7)	1.7 (1.4)	1.7 (1.4)
Serum creatinine (mg/dL), median (Q1, Q3) [†]	1.4 (1.1, 1.9)	1.3 (1.1, 1.9)	1.2 (1.1, 1.7)	1.3 (1.1, 1.9)
BNP (pg/mL), median (Q1, Q3)	n=706, 875 (464, 1,610)	n=4,256, 896 (451, 1,688)	n=820, 769 (375, 1,511)	n=1,657, 806 (410, 1,500)
Pro-BNP (pg/mL), mean (SD), median (Q1, Q3)	n=246, 8,502 (9,280), 4,508 (2,179, 10,408)	n=1226, 8,189 (8,795), 4,820 (1,916, 11,178)	n=330, 6,760 (7,814), 3,833 (1,518, 9,041)	n=450, 8,618 (9,268), 4,815 (1,964, 12,219)
Troponin I (ng/mL), mean (SD), median (Q1, Q3)	n=624, 0.2 (0.4), 0.1 (0, 0.1)	n=3,469, 0.3 (4.2), 0.1 (0, 0.1)	n=678, 0.6 (9.5), 0.1 (0, 0.1)	n=1,319, 0.3 (2.1), 0.1 (0, 0.1)
Blood PO ₂ (mm Hg), mean (SD)	n=323, 97.2 (68.6)	n=992, 94.7 (65.8)	n=490, 90.9 (70.1)	n=550, 97.4 (76.1)
Blood PCO ₂ (mm Hg), mean (SD)	n=326, 45.4 (13.8)	n=995, 41.4 (11.5)	n=494, 50.4 (23.8)	n=558, 47.5 (27.7)
First ED O ₂ sat, mean (SD)	92.6 (7.7)	94.7 (5.3)	93 (6.9)	93.8 (6.2)
Systolic blood pressure (mm Hg), mean (SD)	155.2 (34.6)	146.6 (33.5)	148.4 (32.9)	142.8 (33.2)
Diastolic blood pressure (mm Hg), mean (SD)	83 (23.1)	79.2 (20.6)	78.6 (20.8)	77 (20.6)
Pulse rate (bpm), mean (SD)	94.6 (22)	87.6 (21.8)	94.5 (22.1)	89.4 (22.2)

LVEF, Left ventricular ejection fraction; Q, quartile.

*To convert BUN from mg/dL to SI units (mmol/L), multiply by 0.357.

[†]To convert serum creatinine from mg/dL to SI units (μmol/L), multiply by 88.4.

bronchodilators and poor outcomes in those without chronic obstructive pulmonary disease. Finally, data describing the bronchodilator dose and the method of administration (nebulizer versus metered dose inhaler) were not available in this data set.

DISCUSSION

These data from the ADHERE-EM registry demonstrate that 14% of patients who present with dyspnea are treated for chronic obstructive pulmonary disease when in fact chronic obstructive pulmonary disease is absent and acute decompensated heart failure is the cause of dyspnea. Inhaled bronchodilator use in these heart failure patients without chronic obstructive pulmonary disease appeared to be associated with worse outcome. Because of the observational nature of these data, we cannot determine whether these patients' outcomes were worse because they were more severely ill or because of a directly harmful effect of the inhaled bronchodilator. However, this association persisted after adjustment for propensity score and standard risk factors for mortality. This finding suggests that inhaled bronchodilators may have contributed to the poorer

outcomes observed in heart failure patients without chronic obstructive pulmonary disease who were treated with bronchodilators.

Patients without a history of chronic obstructive pulmonary disease who received a bronchodilator were also more likely than nonbronchodilator-treated patients to receive other therapies, including intravenous vasodilators in the ED and in patient mechanical ventilation. In contrast, the use of these therapies did not differ according to bronchodilator treatment among patients with a history of chronic obstructive pulmonary disease. This analysis cannot determine whether bronchodilator use in heart failure patients without chronic obstructive pulmonary disease is simply a marker of more aggressive disease and therapy overall or if bronchodilator use caused an increased need for aggressive treatments.

Dyspnea is a common but nonspecific symptom among patients presenting with acute decompensated heart failure. Primary care physicians, internists, hospitalists, intensivists, cardiologists, and emergency physicians encounter these patients daily. Physicians may attempt multiple interventions aimed at several possible diagnoses in an effort to improve patient symptoms rapidly. Our findings suggest that this broad,

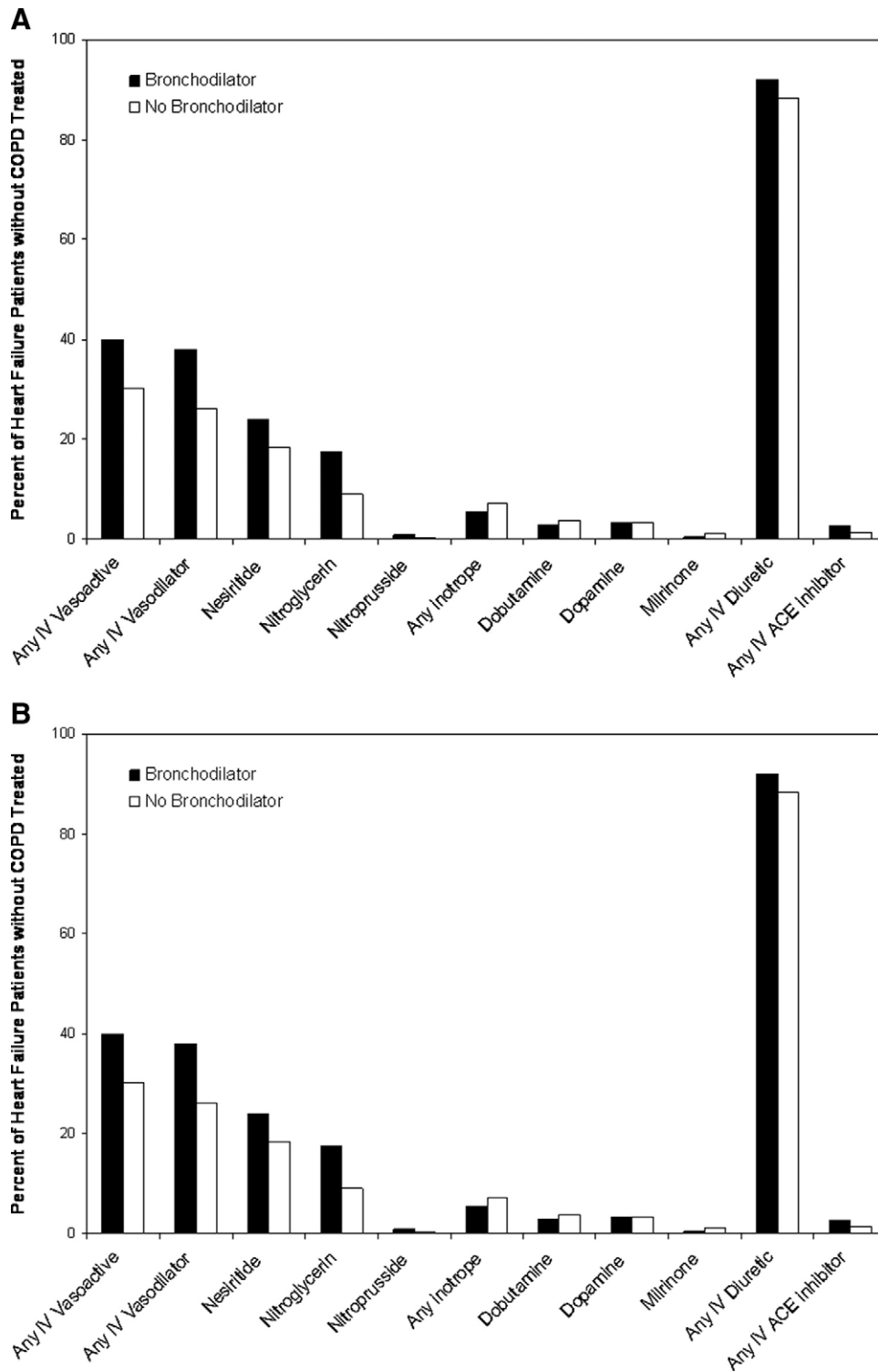


Figure 2. A, Intravenous vasoactive medication use during the ED or observation unit stay, in patients without COPD (chronic obstructive pulmonary disease). N=1,042 Patients without COPD who received a bronchodilator. N=6,257 For patients without COPD who did not receive a bronchodilator. B, Intravenous vasoactive medication use at any time during hospitalization, in patients without COPD (chronic obstructive pulmonary disease). N=1,042 Patients without COPD who received a bronchodilator. N=6,257 For patients without COPD who did not receive a bronchodilator.

Table 3A. Clinical outcomes in patients without a history of COPD,

Outcome	Bronchodilator, N=1,042	No Bronchodilator, N=6,257	OR (95% CI) Unadjusted, Adjusted*	
			Unadjusted	Adjusted With Propensity Score
Mortality, No. (%)	35 (3.4)	165 (2.6)	1.28 (0.89–1.86)	1.35 (0.91–2.00)
Discharged alive from ED, No. (%)	48 (4.6)	443 (7.1)	1.02 (0.67–1.56)	0.63 (0.47–0.86)
ICU admission, No. (%)	198 (19)	826 (13.2)	0.82 (0.59, 1.13)	1.01 (0.72–1.41)
ED intravenous vasodilators, No. (%)	296 (28.4)	1,060 (16.9)	1.54 (1.3–1.83)	1.30 (1.08–1.55)
New dialysis, No. (%)	20 (2)	90 (1.5)	1.03 (0.85–1.25)	1.36 (0.83–2.21)
ED endotracheal intubation/mechanical ventilation, No. (%)	35 (3.4)	65 (1.0)	1.60 (1.36–1.87)	1.39 (0.83–2.32)
ED BiPAP	76 (7.3)	182 (2.9)	1.40 (1.18–1.67)	1.37 (0.81–2.32)
Inpatient mechanical ventilation, No. (%)	63 (6)	148 (2.4)	2.63 (1.99–3.46)	3.31 (2.18–5.02)
Median length of stay (days), median (Q1, Q3)	4.1 (2.7, 6.3)	3.9 (2.4, 6.1)	2.23 (1.45–3.45)	1.57 (0.97–2.54)
Asymptomatic at discharge, No. (%) [†]	449 (55.5)	2,911 (60.1)	2.66 (1.96–3.59)	2.13 (1.55–2.92)
			1.69 (1.21–2.37)	1.69 (1.21–2.37)
			NA	NA
			0.83 (0.71–0.96)	0.83 (0.71–0.96)
			0.79 (0.68–0.92)	0.79 (0.68–0.92)
			0.84 (0.71–0.99)	0.84 (0.71–0.99)

*Adjusted ORs included covariates for baseline BUN level, serum creatinine level, systolic BP, diastolic BP, pulse, age, sex, and the presence of dyspnea at rest.

[†]Denominator for bronchodilator-treated patients n=809; denominator for nonbronchodilator-treated patients n=4,846.

Table 3B. Clinical outcomes in patients with a history of COPD.

Outcome	Patients With COPD		
	Bronchodilator, N=1,275	No Bronchodilator, N=2,404	Adjusted OR (95% CI)*
Mortality, No. (%)	35 (2.7)	83 (3.5)	0.85 (0.55–1.32)
Discharged alive from ED, No. (%)	58 (4.5)	130 (5.4)	1.02 (0.72–1.46)
ICU admission, No. (%)	211 (16.5)	342 (14.2)	1.08 (0.89–1.32)
ED intravenous vasodilators, No. (%)	247 (19.4)	448 (18.6)	0.87 (0.73–1.05)
New dialysis, No. (%)	20 (1.6)	41 (1.8)	1.06 (0.60–1.87)
ED endotracheal intubation/mechanical ventilation, No. (%)	25 (2)	36 (1.5)	0.96 (0.56–1.65)
ED BiPAP, No. (%)	27 (2.1)	33 (1.4)	1.72 (1.28–2.32)
Inpatient mechanical ventilation, No. (%)	58 (4.5)	99 (4.1)	0.98 (0.69–1.38)
Median length of stay (days), median (Q1, Q3)	4.3 (2.9, 6.9)	4.3 (2.8, 7.0)	NA
Asymptomatic at discharge, No. (%)	529 (51)	989 (53.5)	0.88 [†] (0.76–1.04)

*Adjusted ORs included covariates for baseline BUN level, serum creatinine level, systolic BP, diastolic BP, pulse, age, sex, and the presence of dyspnea at rest.

[†]Denominator for bronchodilator-treated patients n=1,038; denominator for nonbronchodilator-treated patients n=1,847.

nonspecific treatment approach may be associated with poor outcomes in patients whose cause of dyspnea is acute decompensated heart failure in the absence of chronic obstructive pulmonary disease. Physicians should use caution when treating patients with dyspnea of unknown origin. Bronchodilators should be used cautiously among patients in whom acute decompensated heart failure is suspected, unless a

diagnosis of chronic obstructive pulmonary disease or other reactive airway disease (ie, asthma) can be confirmed.

The safety of bronchodilators in patients with cardiovascular disease has long been debated. Inhaled bronchodilators did not appear to be arrhythmogenic in a small group of patients with chronic obstructive pulmonary disease and ischemic heart disease.¹⁶ However, inhaled β -agonists have been associated

with an increased risk of myocardial infarction.^{3,8} Au et al³ conducted an analysis of 1,444 myocardial infarction cases and 4,094 hospitalization controls and explored the association between inhaled bronchodilators and myocardial infarction. After adjusting for other risk factors, the OR for myocardial infarction was 1.67 (95% CI 1.07 to 2.6) for patients who received a bronchodilator within the preceding 3-month period. On further analysis, the risk was present only among those with an existing history of cardiovascular disease. All subjects had symptoms consistent with a diagnosis of asthma or chronic obstructive pulmonary disease. Acute myocardial infarction associated with albuterol in the absence of coronary artery disease has also been reported.⁸

Coughlin et al⁷ identified an association between β -agonist inhalers and the development of idiopathic dilated cardiomyopathy. The authors reported significant associations between the development of idiopathic dilated cardiomyopathy and a history of emphysema, chronic bronchitis, oral β -agonists, and inhaled β -agonists. The adjusted OR for developing cardiomyopathy associated with inhaled β -agonist use was 3.2 (95% CI 1.1 to 11).⁷ A separate analysis conducted by Sengstock et al¹⁷ did not find an association between β -agonist use and the development of idiopathic dilated cardiomyopathy. The prevalence of pulmonary disease was similar among the 69 idiopathic dilated cardiomyopathy cases and 130 controls in this analysis. The rate of β -agonist use was also similar, but the number of patients was small (10 cases and 19 controls). In this small cohort, no significant association was detected between the development of heart failure and pulmonary disease or β -agonist use.¹⁷

β -Agonists have been associated with a greater risk of heart failure hospitalization among patients with systolic dysfunction or a history of heart failure. Au et al⁴ identified an increased risk of heart failure hospitalization among patients with left ventricular systolic dysfunction who received a β -agonist within 3 months of the hospitalization. The risk increased as the number of canisters used per month increased, and the effect persisted after adjustment for other pulmonary therapies, including ipratropium and steroids. The mortality risk was also higher for patients treated with a β -agonist, but the effect was only significant in patients who received greater than or equal to 3 bronchodilator canisters per month. In a separate analysis, these authors failed to demonstrate an association between the use of β -agonists and the incidence of new heart failure, but they did detect an increased risk of heart failure hospitalization among patients with a previous heart failure diagnosis.⁵ Similar to their previous findings, a dose-response relationship was apparent between the number of bronchodilator canisters used per month and the risk of heart failure hospitalization.

Salpeter et al⁹ conducted a meta-analysis of randomized, placebo-controlled trials of β -agonists in patients with obstructive airway disease. Studies were included if they reported data on pulse rate, potassium concentration, or adverse

cardiovascular events. The analysis included 33 studies and 6,855 patients. β -Agonist use was associated with significant increases in pulse rate and decreases in serum potassium concentrations compared to placebo. A tendency was observed toward a higher relative risk for major cardiovascular events (ventricular tachycardia, atrial fibrillation, syncope, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death), but it was not statistically significant (RR 1.61; 95% CI 0.76 to 3.42). A higher risk of sinus tachycardia was observed for patients receiving a β -agonist.⁹

The findings of this ADHERE-EM registry analysis suggest that inhaled bronchodilators are not associated with adverse outcome when used appropriately in patients with concomitant chronic obstructive pulmonary disease and acute decompensated heart failure. However, bronchodilator use in acute decompensated heart failure patients without chronic obstructive pulmonary disease may be associated with the need for more aggressive intravenous therapy or mechanical ventilation. We cannot determine from these data whether this effect is directly related to bronchodilator administration. Prospective evaluation of bronchodilators in acute decompensated heart failure patients without chronic obstructive pulmonary disease is warranted, given the number of potentially affected patients and our findings that bronchodilators may be associated with worse outcomes.

In conclusion, although use of inhaled bronchodilators in patients with acute decompensated heart failure and without a history of chronic obstructive pulmonary disease did not influence short-term mortality, this analysis provides data to suggest that bronchodilator use in this group of patients may be associated with adverse outcomes. Prospective evaluations are needed to definitively determine whether bronchodilators are harmful in acute decompensated heart failure patients who present with dyspnea and without a history of chronic obstructive pulmonary disease. Although causality cannot be established from these data, it is reasonable for physicians to use bronchodilators cautiously in these patients and to consider reserving bronchodilators for use in patients with pulmonary disease and a clear indication for the therapy.

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