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Bronchodilator responsiveness in patients with chronic heart failure

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of inhaled bronchodilators on pulmonary function and dyspnea in patients with chronic heart failure (HF).
Background: Conflicting data exist on whether bronchodilators may improve pulmonary function and dyspnea in patients with chronic HF.
Methods: In this retrospective observational study we analyzed data of 116 chronic HF outpatients with systolic dysfunction who underwent spirometry and Borg dyspnea measurements before and after inhalation of 400 μg salbutamol and 80 μg ipratropium. Patients with chronic obstructive pulmonary disease (COPD) or asthma were excluded.
Results: Bronchodilators fully reversed airway obstruction (AO) in 25 of 64 (39.1%) patients with pre-bronchodilator AO. All spirometric measurements, except for forced vital and inspiratory capacities, improved significantly post-bronchodilation. Absolute and percent improvements in forced expiratory volume in 1 s (FEV_1) were more pronounced in patients with persistent AO post-bronchodilation compared to those without AO (0.19 ± 0.18 L and 8.4 ± 7.3% versus 0.11 ± 0.12 L and 4.3 ± 4.0%, $p < 0.05$). Significant bronchodilator responsiveness of FEV_1 (>200 mL and >12%) was noted in 12.1% and was more frequent in patients with persistent AO and fully reversible AO than in those without AO (23.1% and 16.0% versus 1.9%, $p < 0.05$). We measured a small, albeit significant improvement in dyspnea (0.7 ± 1.2 versus 0.9 ± 1.3, $p = 0.002$).
Conclusions: Inhaled bronchodilators may have an additional role in the management of patients with chronic HF because of their potential to improve pulmonary function, especially in those with AO. The clinical usefulness and possible adverse events of bronchodilators need to be further established.

Introduction

Pulmonary function abnormalities, such as diffusion impairment, restriction, and airway obstruction (AO), are common in patients with heart failure (HF)[1,2] and may contribute to the perception of dyspnea and exercise intolerance.[3] Treatment directed at reversing AO with bronchodilators may have an additional role in the management of these patients. There are, however, only few studies concerning the beneficial effects of bronchodilators in patients with HF. Improvements in pulmonary function,[4–10] dyspnea,[10] and exercise performance[7] have been reported. Some investigators have even observed an increase of mean forced expiratory volume in 1 s (FEV_1) greater than 200 mL and 12% in patients with HF,[6,8,9] especially in those with AO,[8] left ventricular systolic dysfunction (LVSD),[9] and during acute decompensation of HF.[6] However, not all could confirm these findings.[7,10–14] Contrasting results across the studies might be attributed to the small number of patients studied and to the differences in study population, bronchodilators used, and definition of bronchodilator responsiveness (BDR).

The purpose of this study was to evaluate the effect of maximal bronchodilation with combined inhaled salbutamol and ipratropium bromide on pulmonary function and dyspnea in patients

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Abbreviations

ACE-I	angiotensin-converting enzyme inhibitor
AO	airway obstruction
ARB	angiotensin receptor blocker
Asthma	asthma is a chronic inflammatory disorder of the airways which is associated with often reversible airflow obstruction and airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
BDR	bronchodilator responsiveness
BMI	body mass index
CABG	coronary artery bypass grafting
COPD	chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease is a preventable and treatable disease with some significant extrapulmonary effects. Its pulmonary component is characterized by airflow limitation (i.e. post-bronchodilator FEV_1/FVC ratio < 0.7) that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases
CRT	cardiac resynchronization therapy
FEF50	forced expiratory flow at 50% of forced vital capacity. FEF50 is the flow at the 50% point of forced expiration; abnormalities usually indicate small airways disease
FEV_1	forced expiratory volume in 1 s. FEV_1 is the volume of gas exhaled in a specific time (1 s) from the start of the forced vital capacity maneuver
FVC	forced vital capacity. FVC is the volume of gas delivered during an expiration made as forcefully and completely as possible starting from full inspiration
HF	heart failure
IC	inspiratory capacity. IC is the maximal volume of gas that can be inspired, starting from the average resting end-expiratory level, i.e. functional residual capacity; it is equal to the sum of tidal volume (the volume of gas which is inspired or expired during a respiratory cycle) and the inspiratory reserve volume (the maximal volume that can be inspired from the mean end-inspiratory level)
ICD	implantable cardioverter defibrillator
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
NT-pro-BNP	N-terminal pro-B natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PEF	peak expiratory flow. PEF is the maximal flow during a forced expiratory vital capacity maneuver starting from a position of full inspiration
Pre/post-BD	pre/post-bronchodilator
PY	pack-years

with chronic HF. In addition, we determined the proportion of patients with significant BDR (i.e. responder), defined as post-bronchodilator (BD) increase in FEV_1 greater than 200 mL and 12% from the baseline value.[15]

Methods

Study design and participants

In this retrospective observational study we analyzed data of chronic HF[16] outpatients with left ventricular ejection fraction (LVEF) below 40%, New York Heart Association (NYHA) class I–IV, and age $\geq$ 18 years. These patients were recruited prospectively in an other study from two outpatient cardiology departments of a large general hospital in The Netherlands between October 2009 and December 2010 for the purpose of evaluating the prevalence of chronic obstructive pulmonary disease (COPD) and pulmonary function impairment in chronic HF (ClinicalTrials.gov Identifier NCT01429376). Only patients with both pre- and post-BD spirometry results were included in the current study. Patients who were not able to cooperate or undergo spirometry or had a history of asthma[17] were excluded. Other exclusion criteria were malignancy with a bad prognosis (survival $<$ 6 months) and participation in another study. In addition, patients with a history of COPD[15] or not further specified obstructive lung disease (OLD) were excluded from the current study. Echocardiography was performed in patients without a recent ($\leq$6 months) echocardiography to confirm persisting LVSD.

Patients were classified as having stable HF in the absence of hospitalization due to HF $\leq$3 months, change in diuretics $\leq$1 month, $\geq$3% weight gain $\leq$3 days, and $>$50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) $\leq$1 month (baseline NT-pro-BNP $\geq$ 100 pmol/L) or $>$100 pmol/L increase of NT-pro-BNP $\leq$1 month (baseline NT-pro-BNP $<$ 100 pmol/L).[18]

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including length and height measurement, spirometry and a 10-point Borg dyspnea score[19] before and after bronchodilators, a chest radiograph, and a second blood sample (NT-pro-BNP). Additional data were collected from medical records and personal interviews. Smoking status was defined as never ($<$100 cigarettes in a lifetime), former ($\geq$3 months ago), or current smoker ($<$3 months). Smoking pack-years (PY) were based only on the tobacco cigarette history and one PY was defined as smoking 20 cigarettes a day for 1 year.

Pulmonary function tests

Participants performed spirometry (MasterLab Pro, Jaeger, Würzburg, Germany) before and 30 min after inhalation of four doses of 100 μg aerosolized salbutamol and four doses of 20 μg aerosolized ipratropium bromide via Volumatic spacer. Beta-blockers were not discontinued prior to testing. Spirometry was performed by trained and certified operators using standard techniques and according to European Respiratory Society standards for acceptability and reproducibility.[20] Reference values of the European Community for Coal and Steel were used.[20] AO was defined as the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) < 0.7.[15]

Chest radiographs

Standard posteroanterior and lateral chest radiographs were performed and evaluated on the presence or absence of congestion: alveolar edema, pleural effusion, Kerley-B lines, and/or redistribution of pulmonary blood flow.