Bronchodilating effect of ipratropium bromide in heart failure

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Bronchodilating effect of ipratropium bromide in heart failure. G. Rolla, C. Bucca, L. Brussino, W. Gallo, D. Malara. ©ERS Journals Ltd 1993.
ABSTRACT: The aim of this study was to test the hypothesis that lung oedema causes an obstructive airway impairment, due to an increase in cholinergic bronchial tone in patients with chronic heart failure (CHF).

Ten patients with CHF were tested by inhalation of ipratropium bromide and placebo, given in sequential randomized order, in double-blind fashion, after assessment of baseline lung function, both during acute cardiac decompensation and after 8–10 days of adequate treatment.

The decrease in lung oedema was associated with a significant increase in vital capacity (VC) (from 70 ± 4.4 to $83\pm5.4\%$ pred), forced expiratory volume in one second (FEV_1) (from 59 ± 3.6 to $72\pm4.6\%$ pred), FEV_1/VC (from 61 ± 2.8 to $64\pm2.3\%$) and residual volume (RV) (from 94 ± 7.9 to $99\pm6.8\%$ pred). Ipratropium bromide produced a far better bronchodilatation during acute decompensation when FEV_1 increased from 59 ± 3.6 to $70\pm3.7\%$ pred, than after intensive treatment for heart failure, when FEV_1 increased from 72 ± 4.6 to $76\pm4.8\%$ pred. The maximum absolute increase in FEV_1 induced by ipratropium bromide was 286 ± 32 ml at admission and only 111 ± 15 ml after treatment

In conclusion, in chronic heart failure, airway obstruction is partially reversible after inhalation of an anti-muscarinic drug, when lung oedema is present, supporting the hypothesis that lung oedema increases cholinergic bronchial tone.
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Pulmonary congestion associated with heart failure has been reported to produce both restrictive and obstructive changes of pulmonary function testing [1–3]. Restrictive changes have been attributed to increased lung water and pulmonary blood volume, decreased lung compliance, fibrosis from chronic congestion, and respiratory muscle weakness [4–7]. Obstructive changes, in the absence of chronic obstructive pulmonary disease (COPD), have been attributed to compression and obstruction of the airways by interstitial pulmonary oedema and submucosal oedema, respectively, [2, 5, 8, 9].

Furthermore, there is experimental evidence that, in lung congestion, stimulation of afferent nerve endings in the bronchial wall may trigger sustained, vagally-mediated, bronchoconstriction [10, 11]. An increased cholinergic tone has also been suggested as an explanation for bronchial hyperresponsiveness in patients with mitral stenosis [12]. Pulmonary function generally tends to improve rapidly [3, 13] with treatment for fluid retention.

Few studies have been carried out on the effects of bronchodilating drugs in patients with congestive heart failure, and never during acute exacerbations. Beta-adrenergic stimulants, administered several days after starting diuretic therapy, produced mild or no bronchodilatation [3]. COLLINS et al. [14] obtained only 5.2% increase in forced expiratory volume in one second (FEV_1), administering 200 μg of albuterol to 70 patients with chronic heart disease at the time of elective haemodynamic assessment. This is in contrast to earlier studies by HEYER [15] and PLOTZ [16], who reported a significant increase of forced vital capacity (FVC) in patients with heart failure after the administration of aminophylline and epinephrine, respectively.

To our knowledge, no data are available on the effect of anti-muscarinic agents. We hypothesized that airway narrowing associated with heart failure might have a reversible component due to increased cholinergic bronchial tone, particularly during exacerbation of lung oedema. To explore this hypothesis we evaluated the bronchodilating effect of an anti-muscarinic drug (ipratropium bromide) in patients with heart failure, during acute decompensation and after intensive treatment.

Patients and methods

Patients

Patients referred to out-patient clinic or admitted to hospital for exacerbation of dyspnoea caused by chronic heart failure were considered for the study.

After cardiological assessment, those patients who did not need immediate therapy were evaluated for eligibility to the study, on the basis of the following preliminary investigations: 1) a clear and documented history of chronic heart failure, with an aetiological diagnosis; 2) a questionnaire for

respiratory disease [17], to exclude patients with a previous diagnosis of COPD. Patients who had smoked more than 10 pack-years and patients with an occupational history at risk for respiratory diseases were also excluded; and 3) prick-test panel, including six common allergens, plus animal danders when indicated. All tested allergens were required to be negative.

Patients clinically suspected to have myocardial infarction were not considered. Moreover, in all the patients acute myocardial infarction was ruled out by analysis of serum enzymes and electrocardiography (ECG). No patient was taking beta-blocking drugs; two were taking a calcium-channel blocking agent. All patients were taking diuretics, eight digitalis and five angiotensin converting enzyme (ACE) inhibiting drugs.

Study design

After the preliminary investigations, patients were asked to participate in the following investigations: 1) clinical assessment of weight, blood pressure, cardiac rhythm, signs of left cardiac failure (pulmonary rales) and right cardiac failure (distension of jugular veins, hepatomegaly, ankle and/or leg oedema); 2) chest X-ray film; and 3) lung function tests with bronchodilator test and arterial blood gas analysis.

The patients then underwent intensive treatment with increased diuretics, ACE inhibitors, anti-arrhythmic drugs, when appropriate, for a period from 7–10 days (mean 8±2 days). At the end of this period, when clinical assessment had clearly improved, chest X-rays, lung function tests with bronchodilator test and arterial blood gas analysis were repeated.

A signed consent form was obtained from each subject.

Chest roentgenograms were performed in the upright position (standard posteroanterior (PA) and lateral) and were blindly evaluated by a radiologist, who calculated a radiological score for lung oedema for each single roentgenogram [18]. Radiographs were presented at random, and the radiologist was not informed whether they had been taken before or after treatment.

Spirometric evaluation, including FEV_1 and FVC, was performed according to the American Thoracic Society (ATS) criteria [19] on a computerized water-sealed spirometer (Biomedin, Padova, Italy). Functional residual capacity was determined by helium dilution technique. Reference values of the European Community for Coal and Steel (ECCS) were used [20] for static and dynamic lung volumes.

Patients were treated with inhaled ipratropium, 60 µg (3 puffs) (Atem), or placebo, at random, after baseline spirometry, followed by repeat spirometry at 30, 60 and 90 min later. Patients crossed-over and inhaled the second medication after 90 min; once again, spirometry was measured at 30, 60 and 90 min later (120, 150 and 180 min from the start of the study). The drug and placebo were delivered *via* metered dose inhalers (MDIs) attached to a spacer. Neither the physician nor the patient knew the order in which the drugs were administered.

Statistics

Analysis of variance for repeated measures was used to compare the drug regimen for the post-treatment improvement in FEV_1, expressed as absolute improvement above baseline. Student's t-test for paired samples was used to compare the difference between means of clinical and respiratory function data observed before and after therapy for heart failure.

Results

Ten patients, five with valvular heart disease, two with chronic ischaemic heart disease, three with dilatative cardiomyopathy, completed the study. They were re-evaluated after 8±2 days of intensive therapy for heart failure. Clinical data, along with drug therapy, for each patient are reported in table 1.

Mean data±SEM of respiratory function tests, before and after intensive therapy for heart failure, are reported in table 2. Chest X-ray score for lung oedema and body

Table 1. – Clinical data and medication of patients

No.	Sex	Age yrs	Smoking habit p/y	Diagnosis	Therapy	Illness duration yrs
1	M	73	ES 10	CAD	E+ND+F+CA	15
2	M	64	NS	DC	E+F+D+W	7
3	M	52	ES 7	DC	E+F+D+W	4
4	F	70	NS	MVD+TR	D+F+W	40
5	M	70	ES 10	CAD	E+ND+F+CA	12
6	F	64	NS	MVD+TR	D+F+W	35
7	M	64	ES 5	MVD+TR	D=F=W	35
8	M	76	NS	MVD+AVD+TR	D+F+W	40
9	F	66	NS	MVD+AVD	D+F+W	30
10	F	73	NS	DC	E+F+D	10

NS: nonsmoker; ES: ex-smoker; p/y: packyears; CAD: coronary artery disease; DC: dilatative cardiomyopathy; MVD: mitral valve disease; TR: tricuspidal regurgitation; AVD: aortic valve disease; E: enalapril (ACE inhibitor); ND: nitroderivates; F: furosemide; CA: calcium antagonists; W: warfarin; D: digitalis; ACE: angiotensin converting enzyme.

Table 2. – Respiratory function tests, body weight and radiological score for lung oedema before and after intensive therapy for heart failure

	At admission	After therapy	Statistical significance
TLC *l*	4.5±0.5	5.0±0.5	
% pred	77±4.8	85±4.5	p<0.01
VC *l*	2.43±0.29	2.59±0.21	
% pred	70±4.4	83±5.4	p<0.01
RV *l*	2.0±0.17	2.2±0.21	
% pred	94±7.9	99±6.8	p<0.01
FEV₁ *l*	1.47±0.18	1.69±0.19	
% pred	59±3.6	72±4.6	p<0.01
FEV₁/VC %	61±2.8	64±2.3	p<0.02
Pao₂ kPa	10.2±0.25	10.5±0.21	NS
Paco₂ kPa	4.8±0.16	5.0±0.08	NS
Weight kg	62.2±3	57.8±2.8	p<0.01
Rx score	59.8±2.9	31.6±2.6	p<0.01

Data are presented as mean±SEM. TLC: total lung capacity; VC: vital capacity; RV: residual volume; FEV_1: forced expiratory volume in one second; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; Rx score: radiological score; NS: nonsignificant.

weight both decreased significantly after heart failure therapy, from 59.8±2.9 to 31.6±2.6 (p<0.01) and from 62.2±3 to 57.8±2.8 kg (p<0.01), respectively (table 2).

The results of bronchodilating tests, obtained at admission and after 8±2 days of heart failure therapy, are reported in the figure 1. Data obtained after placebo have been omitted, as there was no significant change in FEV_1 in patients who received placebo first (from 59.1±5.8 to 59.2±5.8% predicted (% pred) at admission and from 74.4±7.4 to 74.2±7.2 % pred after therapy for heart failure), and there was no significant change in FEV_1 from 90±150 min after the beginning of test in patients who received ipratropium first
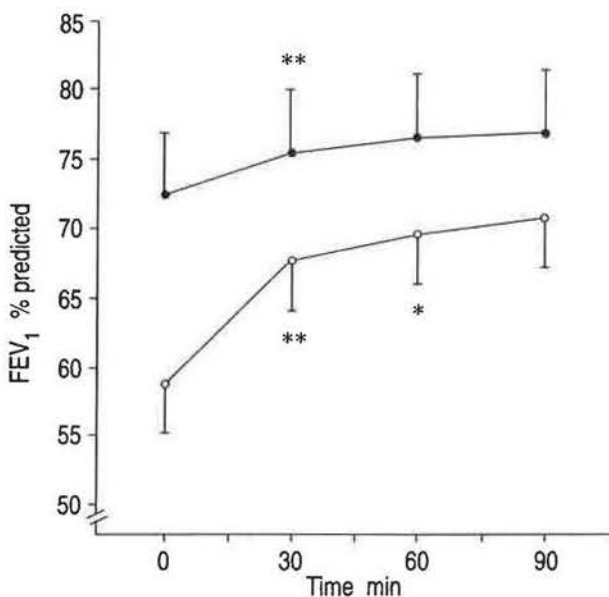

Fig. 1. – Changes in mean FEV_1 (±SEM) after inhaling ipratropium bromide at admission (open circles) and after intensive therapy for heart failure (closed circles). **: p<0.01 comparison with baseline; *: comparison between 30 and 60 min. FEV_1: forced expiratory volume in one second.

(from 70.8±5.4 to 69.6±5.1 % pred at admission and from 74.4±6.3 to 73.8±6.4 % pred after therapy for heart failure).

After ipratropium, FEV_1 increased from 58±3.6 to 70±3.7 % pred (p<0.01) at admission and from 72±4.6 to 76±4% pred (p<0.01) after intensive heart failure therapy. The absolute maximum increase in FEV_1 after ipratropium was 286±32 ml at admission and 111±15 ml after intensive therapy for heart failure (p<0.01). The percentage FEV_1 increase above baseline after ipratropium bromide was significantly greater at admission than after heart failure therapy (20±2.8 *vs* 6±0.7, respectively, p<0.01).

No significant changes in heart rate or blood pressure were observed after ipratropium bromide inhalation.

Discussion

The results of this study show that, during exacerbation of chronic heart failure, inhaled ipratropium bromide produced a significant bronchodilatation, with a mean FEV_1 increase of 20% from baseline. In this phase, most of the patients had severe heart failure, as testified by increasing dyspnoea and, retrospectively, by the consistent weight loss, over 4 kg, and by the decrease in chest X-ray score of lung oedema obtained after intensive treatment (table 2). In agreement with prior observations [1–3], lung function tests revealed a restrictive ventilatory dysfunction, total lung capacity (TLC) being 77% pred (table 2), associated with an obstructive defect, the decrease in FEV_1 being greater than that in FVC. After intensive treatment for heart failure, clinical and radiological signs of lung oedema greatly improved, and lung function tests were also significantly improved. However, despite the persistence of restrictive and obstructive defect, inhalation of ipratropium bromide produced only a mild increase in FEV_1 in this phase. These findings suggest that the bronchodilator effect of ipratropium bromide in patients with chronic heart failure is related to the severity of lung congestion.

Unfortunately, only a few trials exist in the literature concerning the effects of bronchodilators on the lung function of patients with chronic heart failure, and none during acute exacerbation. Available data indicate a slight bronchodilator effect of beta-agonists in patients with well-compensated heart failure [3–14].

These results are similar to our observations with ipratropium bromide after intensive heart failure treatment. The greater bronchodilator effect that we found during acute exacerbation of heart failure might simply be due to the different clinical setting of our patients, rather than being related to the mechanism of action of the drug. In other words, we cannot exclude that beta₂-agonists, if given during acute exacerbation of heart failure, would achieve a similar bronchodilator effect.

Several hypotheses may be advanced to explain the greater bronchodilatory effect produced by ipratropium bromide during acute decompensation than that after intensive heart failure treatment. Firstly, we may suppose that during pulmonary oedema, bronchoconstriction is partially sustained by increased cholinergic tone [10–11], suggesting a specific effect for ipratropium bromide. On the other hand, after recovery of acute decompensation, the residual

bronchoconstriction may be mainly sustained by irreversible anatomical alterations of the bronchial wall. In fact, increased thickness of the airway wall, with engorged bronchial veins, submucosal oedema [21, 22], and fibrosis [23], has been reported in patients with chronic heart failure. Irreversible pathological alterations may also account for the poor bronchodilatory effect of beta-agonists found by others in patients with heart failure [3–14].

Other possible explanations may be given by considering the altered physical properties of the bronchial wall in heart failure. Both the degree of airway dilatation produced by a given amount of bronchial smooth muscle lengthening and the degree of airway narrowing by a given amount of muscle shortening are increased by the thickening of the bronchial wall [24]. It is likely that during acute decompensation the airway walls of our patients was more oedematous, i.e. thicker, than after treatment. This could explain why, during exacerbation of heart failure, even an equal smooth muscle relaxation induced by ipratropium would result in a greater bronchodilating effect.

Could some of our patients have chronic obstructive pulmonary disease (COPD)? The selection criteria excluded patients with a prior diagnosis of COPD, those who were receiving any sort of bronchodilating drugs or who had documented atopy, and heavy smokers (most of the patients being actually nonsmokers). On the other hand, in patients with COPD, ipratropium bromide has been found to have the same bronchodilatory effect whether they were studied during acute exacerbation of airway obstruction or in the stable clinical setting [25].

We do not know whether the acute bronchodilatation observed in our patients with increasing dyspnoea from exacerbation of chronic heart failure is clinically useful. Unfortunately we did not perform any objective measurement of dyspnoea during the ipratropium test. Based on the consistent increase in FEV_1 produced by this drug, it seems worthwhile to test the clinical utility of adding ipratropium bromide to the more traditional therapy of cardiac dyspnoea.

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