Bronchial Hyperreactivity in Patients With Moderate Pulmonary Circulation Overload*

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The clinical course of congestive heart failure (CHF) and mitral valve stenosis (MVS) is accompanied by episodes of dyspnea, wheezing, and cough, symptoms also observed in patients with bronchial hyperreactivity. However, it is still controversial whether bronchial hyperreactivity is demonstrable in patients with chronic overload of the pulmonary circulation. In order to examine the effects of CHF on the respiratory function, we performed pulmonary function tests, titrated bronchial acetylcholine provocations, and left and right heart catheterization in 21 patients with impaired left ventricular function (mean ejection fraction, 37 percent, NYHA class 3), 5 patients with MVS, and 17 control patients with coronary artery disease (mean ejection fraction, 63 percent). Bronchial hyperresponsiveness was defined as an obstructive response to increased doses of inhaled acetylcholine. A 20 percent fall in forced expiratory volume in the first second (FEV₁), a 100 percent increase in total airway resistance (Rtot), and a 60 percent reduction of pulmonary conductance (SGtot) were considered positive. Patients with impaired left ventricular function showed significantly higher airway resistance, and lower airway conductance at the maximal tolerated acetylcholine dose compared with control patients. Patients with MVS had a significant lower airway conductance. The induced bronchial obstruction was completely reversible upon inhalation of a β₂-mimetic. We conclude that chronic overload of the pulmonary circulation is accompanied by bronchial hyperreactivity that may augment the symptoms of dyspnea in patients with CHF and MVS. (Chest 1993; 103:1477-81)

ACE = angiotensin-converting enzyme; LVF = left ventricular ejection fraction; MVS = mitral valve stenosis; NYHA = New York Heart Association; Rtot = total airway resistance; SGtot = total airway conductance

Episodes of nocturnal dyspnea, wheezing, and cough are associated with congestive heart failure (CHF) and mitral valve stenosis (MVS), descriptively known as "cardiac asthma." Similar symptoms can be found in patients with bronchial asthma, induced by bronchial hyperreactivity to nonspecific stimuli.

It is still controversial whether bronchial hyperreactivity is demonstrable in patients with chronic left heart failure, and if so, how it is mediated. Studies have described interstitial edema, airway edema, dilatation of bronchial vessels, and decreased airway caliber as possible causes for bronchial hyperreactivity.

To assess whether bronchial hyperresponsiveness is present in patients with moderately impaired left ventricular function and patients with moderate MVS, we performed pulmonary function tests and titrated bronchial acetylcholine challenges in these patients.

METHODS

Study Population

A total of 30 patients underwent complete cardiac catheterization, including biplanar ventriculography, selective coronary angiography, and hemodynamic measurement using standard procedures. Twenty-one patients (3 female, 18 male; age range, 47 to 89 years; mean, 56.2 years) with impaired left ventricular function either to secondary coronary artery disease (17 patients) or to dilated cardiomyopathy (4 patients) were included in this study. All patients were in New York Heart Association (NYHA) functional class 2 to 2 for CHF at the time of the study. All patients had a left ventricular ejection fraction (LVEF) of <45 percent (37.3 percent ± 6.9 percent). All patients were receiving medical treatment with diuretics (furosemide, amiloride), calcium antagonists (diltiazem, verapamil), isosorbide dinitrate, or angiotensin-converting enzyme (ACE) inhibitors (enalapril).

Five patients (four female, one male; age range, 25 to 66 years; mean, 46.9 years) with MVS functional class 2, confirmed by Doppler echocardiography and heart catheterization (mitral valve area index <1.5 cm²/m²), were also included in this study.

Thirteen patients (2 female, 11 male; age range, 30 to 75 years; mean, 55.7 years) with coronary artery disease and normal ventricular function (LVEF >55 percent; 63.2 percent ± 6.7 percent) were studied as a control.

Patients with known pulmonary diseases (eg, bronchial asthma, chronic obstructive lung disease, chronic and acute bronchitis), allergic diseases, history of rash symptoms, and smokers (in the last six months) were excluded. All patients were tested by standard skin tests prior to bronchial challenges to exclude asymptomatic atopic patients. Asymptomatic patients, who showed signs of ventilatory obstruction in body plethysmography/spiroometry or reacted to bronchial baseline saline solution challenge were also excluded from this study (n = 4). Informed consent was obtained from each patient for our protocol.

Bronchial Challenge

All patients underwent the following protocol: first, baseline body plethysmography with spirometry (constant volume method, Jäger Masterlab, Würzburg, Germany) to determine the forced expiratory volume in the first second (FEV₁), total specific conductance of the lung (SGtot), and total airway resistance (Rtot) was performed. The Rtot was calculated through the average of five normal breaths, then the best of three forced expirations was used to determine FEV₁. After determination of the end-expiratory volume (shutter method), SGtot was calculated (L[Rtot × residual volume]). All evaluations

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were performed computer assisted. Patients with signs of bronchial obstruction (FEV₁<90 percent of predicted or Rtot>100 percent of normal or SGtot<40 percent of normal) were excluded (n=2). Next, the patients inhaled 20 normal tidal breaths of 0.9 percent NaCl, delivered by an inhalation triggered nebulizer (Igepar), calibrated to deliver 1 μl (± 4 percent) of solution within 0.2 s, followed by a body plethysmography to record FEV₁, SGtot, and Rtot. Patients with signs of bronchial obstruction after the saline solution challenge were excluded (n=2). All remaining patients then inhaled increasing doses of acetylcholine (50 mg/ml in 0.9 percent NaCl, Dispersa, Germany) with the same nebulizer, delivering 50 μg of acetylcholine per breath. Immediately after 1, 2, 4, 8, 16, and 32 inhalations (50, 100, 200, 400, 800, and 1,600 μg of acetylcholine), body plethysmography was performed. The bronchial challenge was terminated when either the patients reacted with bronchial obstruction (20 percent fall in FEV₁ and/or 100 percent increase in Rtot and/or 60 percent increase in SGtot) or the final dose of 1,600 μg of acetylcholine was reached. Immediately after the body plethysmography following the last bronchial challenge, 400 μg of salbutamol was administered as a powder inhalation, followed after 10 min by final body plethysmography to determine the reversibility of the induced bronchoconstriction. The dose of acetylcholine that induced a 100 percent rise in Rtot (PD100 Rtot), 60 percent fall in SGtot (PD60 SGtot), and a 20 percent fall in FEV₁ (PD20 FEV₁) were determined as follows: the percentage of difference of the different parameters compared with NaCl challenge was plotted against the dose of acetylcholine (logarithmic scale) and the linear regression was calculated from the definite downpointing part of the curve. This allowed interpolation of the dose of acetylcholine for a given percentage deviation of normal. In cases where calculated doses would be beyond twice the actual applied maximal dose of 1,600 μg of acetylcholine, we annotated a value of 6,400 μg. Statistics were performed with ranking tests so that the actual annotated value did not influence the results obtained. Figure 1 gives an example of this procedure.

**Statistics**

Statistical analysis was performed on a computer (Macintosh IIci, Apple Inc, Cupertino, Calif) using software (StatView II, BrainPower Inc, Calabasas, Calif, and the Excel add-in StatS, Spreadware, Palm Desert, Calif). The following were applied: for independent variables (eg, control subjects vs patients with impaired left ventricular function), the two-tailed, distribution-independent U test (Mann and Whitney); for dependent variables (eg, prechallenge/postchallenge), the two-tailed, distribution-independent matched pairs signed rank test (Wilcoxon); and for correlations between parameters in the same collective, the distribution-independent Spearman rank correlation coefficient. All results are expressed as mean±1 SD; results with a p value <0.05 were considered significant.

**RESULTS**

The CHF and the control group showed no significant differences in age, body surface, baseline pulmonary function, and former smoking habits. The MVS group had a significant lower body surface, a different sex distribution, and fewer former smokers (Table 1).

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<thead>
<tr>
<th>Table 1—Cardiac Parameters*</th>
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<td><strong>Control Subjects</strong></td>
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<td><strong>Age, yr</strong></td>
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<td><strong>Body surface, m²</strong></td>
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<td><strong>Left ventricular ejection fraction, %</strong></td>
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<td><strong>Right ventricle</strong></td>
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<td><strong>Pulmonary wedge</strong></td>
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*Values are mean±1 SD; range is given in parentheses. CHF = congestive heart failure; MVS = mitral valve stenosis.

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group. The pulmonary wedge pressure was significantly augmented in the CHF group compared with control subjects (Table 1).

The pulmonary function test results are listed in Table 2. Twenty-one patients with impaired left ventricular function and 13 control patients with coronary artery disease underwent serial bronchial challenges with acetylcholine. Nineteen of 21 (90 percent) patients with reduced ejection fraction were hyperreversible as defined by a bronchoconstrictive reaction (at least two of the three parameters: ΔFEV1, >20 percent, ΔRtot>100 percent, ΔSGtot>60 percent) to inhaled acetylcholine (maximal dose, 1,600 μg) (p<0.001 vs control subjects). Four of five patients with MVS showed increasing reactivity toward inhaled acetylcholine (p<0.05). In contrast, only 2 of the 13 control patients (15 percent) were hyperreactive according to the above definition. Figure 2 represents the dose responses of Rtot, SGtot, and FEV1 to the inhaled acetylcholine in all groups. The increase of airway resistance (top, A) was significantly higher at acetylcholine doses ≥100 μg in the CHF group. The dose response curve of the specific airway conductance (SGtot) (center, B) showed an even more pronounced shift to the left in the CHF (significant differences at doses ≥50 μg) and the MVS group (significant differences at doses ≥200 μg). In contrast, the dose-dependent changes in FEV1 (bottom, C) compared with control group did not reach significance.

After inhalation of 400 μg of salbutamol, all obstructive lung function parameters in the CHF group returned to baseline values (shown for Rtot in Fig 3). In the control group with coronary artery disease but normal LVEF, we found a small, but significant improvement in Rtot (p<0.05) and SGtot (p<0.005) when compared with saline solution challenge.

The ACE inhibitor treatment in patients with CHF (n = 15) showed a significant difference in FEV1 (p<0.05); the means of all other analyzed pulmonary function parameters pointed in the direction of higher bronchial reactivity, but failed to reach significance when compared with CHF patients without ACE inhibitor therapy (n = 6).

Eighteen of the 21 patients in the CHF group (72 percent), 11 of the 13 control subjects (85 percent), and 1 of the 5 patients in the MVS group (20 percent) were former smokers. Two of the three never-smokers in the CHF group but none of the two never-smokers in the control group were hyperreactive.

**DISCUSSION**

Various studies have evaluated airway function in different stages of CHF with controversial results. This study demonstrates that patients with moderately impaired left ventricular function display a bronchial hyperresponsiveness. This hyperreactivity toward inhaled acetylcholine was detected in patients with decreased LVEF due to ischemic heart disease (n = 16) or due to dilated cardiomyopathy (n = 5). Furthermore, we found elevated bronchial reactivity in a small group of patients with MVS. Our control group consisted of patients with coronary artery disease with normal LVEF in order to avoid different baselines in cardiac risk factors, drug administration, etc. These results were found in strictly selected groups of nonatopic patients without history of pulmonary diseases, and normal pulmonary functions at baseline conditions.

We measured the response to titrated acetylcholine challenges with body plethysmography to record Rtot and SGtot which are more sensitive parameters for...
In comparison to the investigation of Cabanes et al., we found similar results, although our patients showed a lesser degree of left ventricular dysfunction and symptoms, and we observed a total reversibility of the induced bronchial obstruction by a $\beta_2$-mimetic.

Acetylcholine is not only a constrictor of bronchial smooth muscle, but also a dilator of bronchial vessels, thereby reducing pulmonary artery resistance and increasing the thickness of the bronchial wall. Since the acetylcholine-induced obstructive changes in pulmonary function are completely reversible on inhalation of salbutamol (a $\beta_2$ mimetic), a potent relaxing agent for the bronchial smooth muscle, that also has a dilating effect on bronchial vessels, we conclude that the obstructive effect of acetylcholine in this study is mainly due to an increase in bronchial smooth muscle tone rather than to vasodilatation of the pulmonary vessels.

We observed bronchial hyperreactivity in patients with CHF due to coronary artery disease and cardiomyopathy and patients with MVS. The common consequence of these conditions is elevated pressures in the pulmonary vasculature due to either a reduced LVEF or obstruction at the pulmonary outflow, leading to chronic edema of the bronchial wall. It was demonstrated that rapid saline solution infusion in healthy men led to an increasing bronchial reactivity toward methacholine, suggesting that acute minimal interstitial pulmonary edema led to bronchial hyperresponsiveness. Hogg et al. describe a relationship between airway edema and increased bronchial reactivity in asthmatic patients. The pathomechanism for this hyperreactivity remains to be solved. One possible mechanism is an increased vagal reactivity that is

bronchial obstruction than flow-dependent parameters as FEV$_1$. Additionally, the measurement of these parameters is less dependent on patient cooperation. This allowed us to terminate the challenge procedure without the need for reaching a 20 percent reduction of FEV$_1$, which explains the failing significance of the FEV$_1$ data. This might also explain the contradictory results of Eichacker et al. who were unable to demonstrate bronchial hyperreactivity in patients with severe left heart failure by measuring the FEV$_1$ response alone. Since the repeated measurement of FEV$_1$ is an exhausting maneuver, fatigue might have influenced these results.
related to excitation of the J receptor and/or pulmonary C fibers in the pulmonary interstitium by interstitial edema. Organic remodeling with geometric narrowing of small airways is described after chronic lung edema; however, we found a complete reversibility of the induced bronchial obstruction with an inhalative β2 mimetic, and in the control group a small, but significant improvement of pulmonary function after inhaled salbutamol. Another contributing factor might be the activation of the prekallikrein-factor XII contact system through plasma leakages into the interstitium and consecutive generation of proinflammatory kinins. We found a tendency toward higher bronchial responsiveness in patients with ACE inhibitor treatment. Since inhibition of ACE decreases kinin metabolism, this finding supports a role for the kallikrein/kinin system in the pathogenesis of this bronchial hyperreactivity. Studies to determine whether the bradykinin level is elevated in bronchoalveolar lavage fluid of patients with CHF are underway. We conclude that the increased bronchial reactivity to inhaled acetylcholine seen in patients with CHF and MVS is a sign of unspecific bronchial hyperreactivity that might play a role in the pathogenesis of "cardiac asthma," possibly in part mediated via local kinin generation.

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