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Influence of Lung Parenchymal Destruction on the Different Indexes of the Methacholine Dose-Response Curve in COPD Patients*

Gert T. Verhoeven, MD; Anton F.M. Verbraak, PhD; Sandra Boere-van der Straat; Henk C. Hoogsteden, MD, PhD; and Jan M. Bogaard, PhD

Study objectives: The interpretation of nonspecific bronchial provocation dose-response curves in COPD is still a matter of debate. Bronchial hyperresponsiveness (BHR) in patients with COPD could be influenced by the destruction of the parenchyma and the augmented mechanical behavior of the lung. Therefore, we studied the interrelationships between indexes of BHR, on the one hand, and markers of lung parenchymal destruction, on the other.

Patients and methods: COPD patients were selected by clinical symptoms, evidence of chronic, nonreversible airways obstruction, and BHR, which was defined as a provocative dose of a substance (histamine) causing a 20% fall in FEV1 (PC20) of ≤ 8 mg/mL. BHR was subsequently studied by methacholine dose-response curves to which a sigmoid model was fitted for the estimation of plateau values and reactivity. Model fits of quasi-static lung pressure-volume (PV) curves yielded static lung compliance (Cstat), the exponential factor (KE) and elastic recoil at 90% of total lung capacity (P90TLC). Carbon monoxide (CO) transfer was measured with the standard single-breath method.

Results: Twenty-four patients were included in the study, and reliable PV data could be obtained from 19. The following mean values (± SD) were taken: FEV1, 65 ± 12% of predicted; reversibility, 5.6 ± 3.1% of predicted; the PC20 for methacholine, 4.3 ± 5.2 mg/mL; reactivity, 11.0 ± 5.6% FEV1/doubling dose; plateau, 48.8 ± 17.4% FEV1; transfer factor, 76.7 ± 17.9% of predicted; transfer coefficient for carbon monoxide (KCO), 85.9 ± 22.6% of predicted; Cstat, 4.28 ± 2.8 kPa; shape factor (KE), 1.9 ± 1.5 kPa; and P90TLC, 1.1 ± 0.8 kPa. We confirmed earlier reported relationships between Cstat, on the one hand, and KE (p < 0.0001), P90TLC (p = 0.0012), and KCO percent predicted (p = 0.006), on the other hand. The indexes of the methacholine provocation test were not related to any parameter of lung elasticity and CO transfer.

Conclusion: BHR in COPD patients who smoke most probably is determined by airways pathology rather than by the augmented mechanical behavior caused by lung parenchymal destruction.

Key words: bronchial provocation tests; COPD; dose-response relationship; forced expiratory flow rates; human; lung compliance; lung volume measurements; methacholine bromide/diagnostic use; pulmonary diffusing capacity

Abbreviations: BHR = bronchial hyperresponsiveness; CO = carbon monoxide; Cstat = static lung compliance; FRC = functional residual capacity; IVC = inspiratory vital capacity; KCO = transfer coefficient for carbon monoxide; KE = shape factor; LE = linear-exponential; PC20 = provocative concentration of a substance causing a 20% fall in FEV1; P90TLC = elastic recoil pressure at 90% of total lung capacity; PV = pressure-volume; TLC = total lung capacity; Tlco = transfer factor for carbon monoxide.

Bronchial hyperresponsiveness (BHR) is present in patients with asthma and COPD.1 Approximately half of the subjects with COPD in a general population have BHR.2 In the Lung Health Study,3 BHR was noted in 85.1% of the women and 58.9% of the men with mild-to-moderate airflow limitation. The estimation of BHR is important for the diagnosis of asthma and for determining asthma severity, whereas the meaning of BHR for the clinical management of COPD is still unclear.4 COPD patients with BHR appear to be prone to a more rapid decline of their FEV1.5

Clinical studies suggest that BHR in patients with COPD differs from BHR in patients with asthma.6–9 For example, in patients with COPD, BHR for
physiologic stimuli (eg, cold air) usually is not found in the presence of BHR for pharmacologic agents (eg, histamine). In patients with asthma, both types of stimuli cause bronchoconstriction.6,7 The explanation for these differences might be found in the different pathologic changes in the airways and in the lung parenchyma of asthma and COPD patients.1 The main and clearest difference between asthma and COPD is destruction of the lung parenchyma in COPD, leading to emphysema and loss of lung elasticity. In patients with COPD, compared to those with asthma, there is a relationship between baseline FEV1 and the level of BHR.8,9 The FEV1 is, however, not a good predictor of the amount of parenchymal destruction and loss of elastic recoil.10–13 The most reliable test for lung elasticity is the direct estimation of quasi-static esophageal pressure-volume (PV) curves.10,11,14 The destruction of parenchymal tissue also is shown by the impairment of carbon monoxide (CO) transfer.15–18 We performed these lung function tests in COPD patients who smoked, who fulfilled the established clinical and functional criteria for COPD, and who also had a provocative concentration of a substance (histamine) causing a 20% fall in FEV1 (PC20) of ≤8 mg/mL. In subsequent methacholine dose-response curves, not only PC20 (sensitivity) but also maximal bronchoconstriction (plateau) and the slope of the curve (reactivity) were estimated, because these factors should yield additional information on the causative mechanisms of BHR.19

The aim of our study was to investigate the influence of the impairment of lung parenchymal structure on BHR by the estimation of the interrelationships between indexes related to lung parenchymal destruction (lung elasticity and CO transfer) and indexes from methacholine log-dose response curves.

Materials and Methods

COPD patients were recruited according to generally accepted clinical and functional criteria.20 The inclusion criteria were the following: chronic productive cough: age between 40 and 70 years; current smokers; negative skin tests for standard inhalation allergens; FEV1 or FEV1/inspiratory vital capacity (IVC) ratio ≤70% of the predicted normal value; reversibility of FEV1 of <10% predicted after 750 μg terbutaline administered by metered-dose inhalation; and nonspecific BHR, defined by a PC20 for histamine of ≤8 mg/mL. Exclusion criteria were the following: a history of asthma; complaints of wheezing; radiographic signs of bullous emphysema; recent respiratory tract infection; and recent or concurrent usage of anti-inflammatory drugs. Eligible patients refrained from oral anti-inflammatory medication at least 3 months and from inhaled glucocorticoids for at least 6 weeks before the start of the study.

The study was approved by the Medical Ethics Committee of the University Hospital Dijkzigt, and written informed consent was obtained from all participants.
index was considered to be the elastic recoil index with the lowest variation coefficient. Additionally, we prefer to use the P90TLC values above the recoil pressure at TLC because P90TLC is less dependent on inspiratory muscle force. The shape factor (KE) was determined from the following generally used exponential equation:

\[ V = V_{\text{max}} \left( 1 - \exp\left( KE(P - P_0) \right) \right) \]

where \( V_{\text{max}} \) is the asymptotic value (in liters) and \( P_0 \) is the intercept with the P axis at \( V = 0 \) kPa.

KE can be considered as an elasticity index, independent of lung size. For the fit with the exponential model, we used the same (measured) input data as for the LE model fit. KE was considered as an additional elasticity index.

Linear regression analysis between variables, pairwise multivariate correlation, and statistical significance were calculated with the use of a package of statistical software (Statistical Graphics Corp; Rockville, MD). Test results were considered statistically significant at \( p < 0.05 \).

Results

Twenty-four patients were included in the study. From 19 patients, we obtained reliable PV curves; the remaining patients did not tolerate the esophageal balloon long enough or showed effects of swallowing that hampered an accurate interpretation of the data. The mean age of the patients was 56 years (Table 1). The mean FEV\textsubscript{1} was 65% of predicted. One patient had an FEV\textsubscript{1} > 70% of predicted but was included because his FEV\textsubscript{1}/IVC ratio was 0.51. The mean reversibility of FEV\textsubscript{1} after terbutaline inhalation was 5.6%. Four patients showed no reversibility at all.

The patients had moderate or severe BHR (Table 1). The mean PC\textsubscript{20} for methacholine was higher than that for histamine (4.3 vs 1.7 mg/mL, respectively). This difference also was reported in an earlier study of smokers with mild chronic airflow limitation. After correction for the difference in molecular weight (1 mg of the bromide compound is equivalent to 0.82 mg of the chloride compound), the corrected mean bromide value of the PC\textsubscript{20} became 3.5 mg/mL.

The mean plateau value was 48.8% of the FEV\textsubscript{1}. In Figure 1, we present a curve in which the fitted plateau is almost equal to the measured data (Fig 1, top) and a curve in which the plateau value is derived from extrapolation (Fig 1, bottom). If the experimental plateau estimate was defined by the mean value of the last two provocative concentrations with a variation of < 5%, we observed that the fitted plateau was almost equal to the experimental plateau estimate in 13 of the 24 dose-response curves.

Cstat ranged from 1.06 to 10.52 kPa, which indicates a range from moderately low to clearly increased if a normal range of 1.5 to 2.5 kPa is taken into account. Mean Cstat was 4.6 kPa (Table 1). TLCO was between 34% of predicted and 106% of predicted, and KCO ranged from low (43% of predicted) to higher than normal (139% of predicted).

Statistically significant correlations existed among all the parameters of the PV curve (Table 2). The strongest correlation was between Cstat and KE (\( R = 0.81; p < 0.0001 \)). The KCO percent predicted correlated strongly with Cstat (\( R = -0.60; p = 0.006 \); Table 2) but not with KE and P90TLC. The TLCO percent predicted showed no significant correlation with Cstat, KE, or P90TLC.

The indexes of BHR (PC\textsubscript{20}, reactivity, and plateau value) were tested for correlation with the indexes of the PV curve (Cstat, KE, and P90TLC), CO transfer (TLCO and KCO), and FEV\textsubscript{1}. In Table 3, we present the correlations between Cstat and the BHR in-

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### Table 1—Smoking Habits, FEV\textsubscript{1}, Reversibility, BHR, CO Transfer, and Lung Elasticity Data

<table>
<thead>
<tr>
<th>Data</th>
<th>No. of Patients</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>24</td>
<td>55.5 ± 8.5</td>
<td>54</td>
<td>42–69</td>
</tr>
<tr>
<td>Actual smoking, cigarettes/d</td>
<td>24</td>
<td>15.6 ± 6.8</td>
<td>13</td>
<td>6–30</td>
</tr>
<tr>
<td>Pack-years</td>
<td>24</td>
<td>23 ± 10.5</td>
<td>23</td>
<td>5–50</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % predicted</td>
<td>24</td>
<td>64.5 ± 11.9</td>
<td>65</td>
<td>34–93</td>
</tr>
<tr>
<td>Reversibility, % predicted</td>
<td>24</td>
<td>5.6 ± 3.1</td>
<td>3.5</td>
<td>0–9.8</td>
</tr>
<tr>
<td>PC\textsubscript{20} Histamine</td>
<td>24</td>
<td>1.66 ± 2.00</td>
<td>0.87</td>
<td>0.11–8</td>
</tr>
<tr>
<td>Methacholine</td>
<td>24</td>
<td>4.27 ± 5.2</td>
<td>1.46</td>
<td>0.4–17.4</td>
</tr>
<tr>
<td>log2 PC\textsubscript{20} methacholine</td>
<td>24</td>
<td>1.07 ± 1.74</td>
<td>0.53</td>
<td>−1.3–4.1</td>
</tr>
<tr>
<td>Reactivity, % FEV\textsubscript{1}/doubling dose</td>
<td>24</td>
<td>11.0 ± 5.6</td>
<td>8.98</td>
<td>3.9–26.8</td>
</tr>
<tr>
<td>Plateau, %FEV\textsubscript{1}</td>
<td>24</td>
<td>48.8 ± 17.4</td>
<td>48.3</td>
<td>20.8–95.7</td>
</tr>
<tr>
<td>Cstat, kPa</td>
<td>19</td>
<td>4.6 ± 2.8</td>
<td>4.1</td>
<td>1.1–10.5</td>
</tr>
<tr>
<td>KE, kPa</td>
<td>19</td>
<td>2.5 ± 1.5</td>
<td>2.2</td>
<td>0.7–6.3</td>
</tr>
<tr>
<td>P90TLC, kPa</td>
<td>19</td>
<td>1.1 ± 0.8</td>
<td>0.8</td>
<td>0.4–2.7</td>
</tr>
<tr>
<td>TLCO, % predicted</td>
<td>24</td>
<td>76.7 ± 17.9</td>
<td>75</td>
<td>34–106</td>
</tr>
<tr>
<td>KCO, % predicted</td>
<td>24</td>
<td>85.9 ± 22.6</td>
<td>86</td>
<td>43–139</td>
</tr>
</tbody>
</table>
dexes. No significance was found and no significance was found for the additional elasticity indexes and diffusion parameters.

There was a significant correlation between the FEV\textsubscript{1} percent predicted, on the one hand, and log\textsubscript{2} PC\textsubscript{20} for histamine and log\textsubscript{2} PC\textsubscript{20} for methacholine, on the other hand (\(R = 0.44, p = 0.024\); and \(R = 0.46, p = 0.023\), respectively; Table 3). There was also a significant (negative) correlation between the FEV\textsubscript{1} percent predicted and reactivity (\(R = -0.52; p = 0.008\); Table 3). The correlation between the FEV\textsubscript{1} percent predicted and the plateau value was not significant (Table 3).

Because smoking is the most important risk factor for emphysema, we looked at paired correlations among smoking data, CO transfer, and indexes of the PV curve. There was a significant correlation only between KE and the actual number of cigarettes smoked per day (\(R = 0.53; p = 0.019\); Table 2).

**Discussion**

The aim of our investigation was to study the interrelationships among indexes describing BHR, lung elasticity, and CO transfer in patients with COPD. For the estimation of BHR and the degree of impairment of lung mechanics, detailed information was obtained by fitting models of methacholine dose-response curves and quasi-static PV curves.

Several mechanisms have been proposed for explaining enhanced bronchoconstriction as a reaction to inhaled stimuli.\textsuperscript{1,19,31} Detailed analysis of methacholine log-dose response curves is supposed to offer additional information on the causative mechanisms.

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**Table 2—Correlations of the Indexes of BHR With Quasi-Static Compliance and FEV\textsubscript{1} by Pairwise Multivariate Analysis**

<table>
<thead>
<tr>
<th>Variable 1</th>
<th>Variable 2</th>
<th>No. of Patients</th>
<th>(R) Value</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC\textsubscript{20} histam</td>
<td>Cstat</td>
<td>19</td>
<td>0.282</td>
<td>0.24</td>
</tr>
<tr>
<td>PC\textsubscript{20} meth</td>
<td>Cstat</td>
<td>19</td>
<td>0.061</td>
<td>0.82</td>
</tr>
<tr>
<td>Reactivity</td>
<td>Cstat</td>
<td>19</td>
<td>0.291</td>
<td>0.24</td>
</tr>
<tr>
<td>Plateau</td>
<td>Cstat</td>
<td>19</td>
<td>0.321</td>
<td>0.19</td>
</tr>
<tr>
<td>PC\textsubscript{20} hist</td>
<td>FEV\textsubscript{1}</td>
<td>24</td>
<td>0.483</td>
<td>0.01</td>
</tr>
<tr>
<td>PC\textsubscript{20} meth</td>
<td>FEV\textsubscript{1}</td>
<td>24</td>
<td>0.470</td>
<td>0.02</td>
</tr>
<tr>
<td>Reactivity</td>
<td>FEV\textsubscript{1}</td>
<td>24</td>
<td>-0.522</td>
<td>0.0075</td>
</tr>
<tr>
<td>Plateau</td>
<td>FEV\textsubscript{1}</td>
<td>24</td>
<td>-0.194</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*hist = histamine; meth = methacholine.

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**Table 3—Correlations of the Indexes of BHR With Quasi-Static Compliance and FEV\textsubscript{1} by Pairwise Multivariate Analysis**

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<tr>
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<td>Cstat</td>
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<td>0.24</td>
</tr>
<tr>
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<td>Cstat</td>
<td>19</td>
<td>0.321</td>
<td>0.19</td>
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<tr>
<td>PC\textsubscript{20} hist</td>
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<td>PC\textsubscript{20} meth</td>
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<td>0.02</td>
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<tr>
<td>Plateau</td>
<td>FEV\textsubscript{1}</td>
<td>24</td>
<td>-0.194</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*hist = histamine; meth = methacholine.

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**Figure 1.** Two examples of sigmoid fitting of the methacholine provocation tests. Top: the measured data (●) are almost equal to the fitted plateau. Bottom: the measured data (■) show that the plateau was not reached during the test.
of BHR, PC_{20}, and reactivity are considered to be determined by prejunctional mechanisms, and the plateau value is more dependent on postjunctional mechanisms. In patients with COPD, both prejunctional mechanisms (ie, epithelial damage, neural control, and inflammation) and postjunctional mechanisms (ie, loss of lung elasticity, swelling of airway wall, and intraluminal secretions) can be responsible for the occurrence of BHR. Because lung elasticity in stable patients with asthma is not appreciably disturbed, this would be an attractive explanation for the occurrence of BHR in patients with COPD and to relate it to the loss of elastic recoil. Theoretically, a decrease in lung elasticity can facilitate an amplified bronchomuscular response.

First, we have studied the functional indexes of lung parenchymal destruction. Some degree of emphysema, which is present in patients with mild COPD, already influences the PV relationships. A PV curve can be obtained with relatively simple techniques but has the disadvantage of being an invasive test. The reproducibility of estimates, especially of KE, was reported to be good, at least for healthy adults. KE was found to be a good indicator for the presence of mild emphysema. We found that Cstat and P90TLC from the LE model fit and KE from the exponential model fit correlated well with each other, indicating that these indexes were linked to elastic properties of the lung (Table 2).

An additional index of lung parenchymal destruction is CO diffusion. Berend et al were the first to report a correlation between CO transfer and severity of emphysema. Others have confirmed the relationship between emphysema and KCO. We found also a significant correlation of Cstat with KCO (Table 2). KCO can be considered as an index, related to structural aspects of the lung parenchyma, whereas TLCO is a measure of overall gas transport.

In this study, we also tested the indexes of the impairment of lung parenchymal structure for correlation with cigarette smoke exposure, pack-years and actual smoking. There was a significant correlation of KE only with actual smoking (Table 2). There are few data about the correlation of smoking with emphysema. In one study, there was no detectable effect of smoking on lung elastic recoil in healthy men. Other investigators have reported a quantitative relationship between the total exposure to cigarette smoke and both alveolar and airway pathologic features in a necropsy study. So, although the assumption is plausible that there is a relationship between cigarette smoke exposure and loss of elastic recoil, it is not yet clear how this influences the derivatives of the PV curve. We have assumed that differences in vulnerability of the lung parenchyma to cigarette smoke influence the measured loss of elastic recoil more than the amount of cigarette smoke exposure.

In patients with \( \alpha_1 \)-antitrypsin deficiency, Cheung et al found a relationship between the loss of elastic recoil and maximal airflow narrowing (plateau). It should be noted that their patient group was selective; five of eight patients had an FEV\(_1\) > 80% of predicted, patients were clinically stable, and patients were ex-smokers or nonsmokers. These patients seemingly had only parenchymal disease. The effect of the involvement of airways disease was shown in a study by Eidelman et al. They described different patterns of mechanical abnormalities between smoking and nonsmoking patients with \( \alpha_1 \)-antitrypsin deficiency. In COPD patients, especially in those who smoke, it is likely that there are both parenchymal and airway changes. In our study and in the study by Koyama et al, no significant correlations were found among indexes of the PV curve, on the one hand, and BHR, on the other hand. This means either that PV curves do not represent elastic recoil changes or that BHR is also influenced by airway pathology. There are several arguments that support the last mechanism. First, as discussed above, indexes of PV curves have been found to correlate with pathologic assessment of lung parenchyma. Second, the significant correlations among the different indexes of the PV curve, and between elasticity and KCO, indicate that our results are a good reflection of the loss of elastic recoil of the lung. Third, there were significant relationships between the determinant of airways obstruction (FEV\(_1\)) and PC\(_{20}\) (Table 3).

In the present study, not only were the PC\(_{20}\) for histamine and the PC\(_{20}\) for methacholine correlated with the FEV\(_1\) percent predicted, but also with reactivity. The first correlation was reported elsewhere and was found also by Cheung et al and Koyama et al. This indicates that the definition of PC\(_{20}\) as a 20% fall of the starting FEV\(_1\) makes the outcome highly dependent on measurement of FEV\(_1\) in patients with a low FEV\(_1\). Our finding that reactivity (the slope of the dose-response curve) is steeper at a lower FEV\(_1\) percent predicted, indicates that reactivity also was hampered by the way in which the response is expressed. This appeared to be distinct for the plateau value, which was not correlated with the starting FEV\(_1\) (Table 3). The clinical significance of the level of a plateau value is that it is a measure of the maximal acute bronchoconstriction that can be provoked in an individual. The application of the plateau value in combination with the PC\(_{20}\) for methacholine has been suggested for the distinction between asthma and COPD. While BHR can be found both in patients with asthma and
patients with COPD when considering PC_{20}, the plateau value usually is not reached in patients with moderately severe or severe asthma. In our study of patients with COPD who have moderately severe BHR, the plateau was reached in the majority of the patients, but not in all. It appears, therefore, that the estimation of the plateau does not always provide a clear distinction between asthma and COPD.

Because none of the indexes of BHR is related to any of the functional data of lung elasticity or CO transfer in COPD patients who smoke, airway pathology determines the response to methacholine at least to such an extent that it overrules a possible correlation with parenchymal destruction. The nature and extent of airways disease seem to be more important for the occurrence of BHR in patients with COPD than does parenchymal pathology. Taylor et al.\(^3\) have compared PC_{20} for methacholine in vivo with the function of bronchial smooth muscle strips from surgical specimens. No correlation was found, which led to their conclusion that smooth muscle pathophysiologic changes were not responsible for BHR in COPD. One other study provided evidence that BHR in patients with emphysema is related to differences among types of emphysema and to the cell infiltrate in the airway walls.\(^3\)

In conclusion, we found no relationship between the impairment of lung parenchymal structure, either from PV curves or CO diffusion, and indexes of BHR. Nonspecific BHR in COPD patients who smoke is determined by small airway pathology to such an extent that it overrules a possible correlation with parenchymal impairment. The combination of our findings with those from clinicopathologic studies suggests that the plateau value (maximal airway constriction) is a better indicator of small airways pathologic changes than are PC_{20} and reactivity.

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