Tracheal size is a determinant of the bronchoconstrictive response to inhaled methacholine

J. Bourbeau, R. Delfino, P. Ernst

Tracheal size is a determinant of the bronchoconstrictive response to inhaled methacholine. J. Bourbeau, R. Delfino, P. Ernst. ©ERS Journals Ltd 1993.

ABSTRACT: We hypothesized that the size of the large airways is a determinant of bronchial responsiveness to inhaled methacholine.

This was investigated by measuring the relationship of tracheal size and bronchial responsiveness to methacholine, in 169 male construction insulators, aged 20–50 yrs, as part of a workforce-based, cross-sectional survey of respiratory health. Bronchial responsiveness was expressed as the concentration of methacholine, inhaled for 2 min of tidal breathing, which provoked a 15% fall in forced expiratory volume in one second (FEV₁). Tracheal size was assessed from tracings of standard posteroanterior chest radiographs, at full inspiration.

After accounting for the effect of airway calibre (FEV₁/forced vital capacity (FVC)), age, height, and pack-years of cigarette smoking, on airways responsiveness, there was a significant association (p<0.05) between tracheal length, diameter, or surface area and the degree of bronchoconstriction obtained by inhaling methacholine.

The increase in airway responsiveness with decreasing tracheal size may reflect increased deposition of methacholine, secondary to smaller cross-sectional area and greater linear velocity of air in the trachea and main bronchi.


Bronchial responsiveness is usually defined as the sensitivity of the airways to a variety of nonsensitizing bronchoconstricting stimuli of chemical or physical origin [1, 2]. It is currently measured as a dose-response relationship, by the use of various bronchial challenge tests, that have been standardized to a reasonable extent [3, 4]. Although many mechanisms have been shown to produce hypersensitivity to inhaled bronchoconstricting agents [5], its determinants remain a topic of debate.

In normal subjects, there is a wide variation in the degree of bronchial responsiveness, which is, in part, accounted for by differences in starting airway size [6, 7]. The variation in airway responsiveness in relation to airway calibre is usually attributed to Poiseuille’s law. Since resistance in a single airway is inversely related to the fourth power of the radius, a constrictor stimulus will have a relatively greater effect on resistance in the presence of pre-existing airway narrowing. The degree of aerosol deposition in the tracheobronchial tree has also been shown to influence bronchial responsiveness to constricting agents [8], with a greater effect due to central deposition as compared to diffuse deposition of aerosol [9]. Furthermore, decrease in airway calibre due to airway obstruction, increases proximal deposition of aerosols and bronchial responsiveness [10, 11]. It therefore appears reasonable to suggest that upper airway size should further influence aerosol deposition and bronchial responsiveness to inhaled bronchoconstricting agents. The hypothesis examined in the present study is that the size of large airways, as assessed by tracheal length and diameter, as well as the branching angle at the carina measured from standard chest radiographs, are determinants of bronchial responsiveness, as measured by the provocative concentration of methacholine required to lower forced expiratory volume in one second (FEV₁) by 15% (PC₁₅).

Materials and Methods

Subjects

The study population for the present research consisted of 169 subjects, identified through previous epidemiological surveys of construction insulators, and all members of Local 58 of the International Union of Frost and Heat Insulation and Asbestos Workers in Quebec. The source population consisted of 537 subjects out of 644 union members, who took part in a questionnaire survey in 1982 [12]. The target population consisted of 246 subjects from the source population, without diagnosed asbestosis, who were aged 20–50 yrs, and living within a 25 km radius of Montreal. Of the 215 who participated in a
l lung function study in 1983-1984 [13], chest X-rays and methacholine bronchoprovocation tests were available in 169, the study population reported upon here.

Personal characteristics and smoking

All subjects completed a French version of the standardized American Thoracic Society (ATS)-DLD-78 questionnaire [14], which was administered by an interviewer. Height in stockinged feet was measured.

Measures of lung function

Spirometry was carried out in all subjects, according to the Snowbird workshop criteria of the ATS [15], with an Ohio 827 rolling seal spirometer (Ohio Medical Products, Madison, Wisconsin, USA). The best forced vital capacity (FVC) and FEV\textsubscript{1} were retained for analysis. Functional residual capacity (FRC) was obtained, using a volume displacement body plethysmograph. Residual volume (RV) was obtained by subtracting expiratory reserve volume, and total lung capacity (TLC) by adding maximum inspiratory capacity to RV. Calibration for pressure and volume was performed daily.

Methacholine bronchoprovocation

Testing was carried out using the method described by COCKCROFT [16]. Briefly, during successive 2 min periods of tidal breathing, the subjects first inhaled phosphohate buffered saline, and then, at 3 min intervals, concentrations of methacholine increasing from 2 to 32 mg·ml\textsuperscript{-1}. Aerosol was generated with a hand-held Wright nebulizer, calibrated daily to produce 0.14-0.15 ml·min\textsuperscript{-1}. FEV\textsubscript{1} was measured 30 and 90 s after each dose, and the test was stopped if there was a 20% or more fall in FEV\textsubscript{1}, or if the highest concentration was reached. The concentration required to produce a 15% fall in FEV\textsubscript{1} (PC\textsubscript{15}) was taken from the log dose-response curve, by linear interpolation of the last two points. Subjects who did not reach PC\textsubscript{15} were arbitrarily assigned a value of 64 mg·ml\textsuperscript{-1}. The PC\textsubscript{15} was the \textit{a priori} choice as the measure of airways responsiveness in this study of normal subjects, since it is thought to be more sensitive than, but as reproducible as, PC\textsubscript{20} [17]. We believe PC\textsubscript{15} to be an appropriate choice for studies of workforces exposed to dusts, where asthma is not a concern, and where individuals with asthma may actually be fewer than in the general population [18].

Chest radiographs and measurements

For each subject, chest radiographs were obtained on maximal inspiration in posteroanterior projection, with the conventional 1.83 m focus film distance, and the grid technique. The technique results in a mid-plane magnification factor of 1.10. Exposures were made at 45 kVp and 500 mA. Subjects were included in the study only when their chest films, at maximal inspiration, were technically adequate for accurate measurement of the intrathoracic trachea.

Four airway measurements were taken from each of the 169 chest films.

Airway measurements (fig. 1)

1. Subcarinal angle (SCA): the angle between the medial walls of the right and left main bronchi.
2. Tracheal diameter (TD): taken as the widest internal diameter of the trachea below the superior aspects of the clavicular heads and 2–2.5 cm above the carina (in order to avoid inflated measurements due to mainstem take-off effects).
3. Clavicle-carinal tracheal length (CCL): the distance between the superior aspects of the clavicular heads to a horizontal line parallel to the bottom of the X-ray and drawn through the carina (carinal line).
4. T1-carinal tracheal length (TCL): from the top of the spinous process of T1 to the carinal line.

The airway measurements were taken by one reader, measuring from pencil tracings made directly on the film. A standard 1 mm ruler and a protractor were used.

![Fig. 1. - Airway measurements as traced on posteroanterior (PA) chest radiographs. TD: intrathoracic tracheal diameter; TCL: T1 spinous process to carina tracheal length; CCL: clavicular head to carina tracheal length; SCA: subcarinal angle.](image)

Statistical analysis

All statistics were computed using SAS programs (SAS Institute Inc., 1982). Descriptive statistics were first computed for different variables, such as personal
characteristics, working habits, lung function, airway responsiveness, and airway size. Relationships between pairs of variables were examined using simple correlations. Finally, to explore the relationship between airway size and airway responsiveness, multiple linear regression was used. For each measure of airways size and disposition (tracheal diameter, surface area and subcarinal angle), its ability to predict airway responsiveness (log \( PC_{15} \)) was examined by entering it singly into a model. Analysis of covariance was used to adjust for the effect of FEV/FVC as an estimate of baseline airway calibre, age, height, and smoking as a categorical variable (current, ex-lifelong and nonsmoker) in order to estimate the independent effect of the measures of tracheal size and geometry.

**Results**

Table 1 presents subject characteristics, lung function, and airways responsiveness to methacholine. The population was composed of men, aged 20-50 yrs. Smoking is presented both as average amount smoked among current and former smokers, and as percentage prevalence in each smoking category. The great majority were either current or former smokers, with nonsmokers accounting for only 12.4% of subjects. Despite this, spirometric volumes were on average better than predicted from general population studies, suggesting a healthy worker effect.

The average level of airways responsiveness was in the non-asthmatic range. This is expected, since the study is workforce- not clinic- based, and also because of the reduction in availability for employment in relation to increasing airways responsiveness previously described in this population [13]. Table 2 presents mean values for the measures of airway size taken from the chest radiographs.

**Table 1. Personal characteristics, lung function and airway responsiveness in the study population (n=169)**

<table>
<thead>
<tr>
<th><strong>Personal characteristics</strong></th>
<th><strong>Mean ± SE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>38 (5.4)</td>
</tr>
<tr>
<td>Height cm</td>
<td>170.0 (5.8)</td>
</tr>
<tr>
<td>Cumulative smoking* pack-yrs</td>
<td>19.0 (12.6)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>never %</td>
<td>12</td>
</tr>
<tr>
<td>former %</td>
<td>29</td>
</tr>
<tr>
<td>current %</td>
<td>59</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>106 (13.1)</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>108 (11.9)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.81 (0.06)</td>
</tr>
<tr>
<td>TLC % pred</td>
<td>105 (15.2)</td>
</tr>
<tr>
<td><strong>PC_{15} methacholine</strong></td>
<td></td>
</tr>
<tr>
<td>Geometric mean mg·ml⁻¹</td>
<td>44.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.05-64</td>
</tr>
</tbody>
</table>

*: Data presented as mean and so in parenthesis. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; PC_{15}: provocative concentration of methacholine producing a 15% fall in FEV1.

**Table 2. Airway size in the study population (n=169)**

<table>
<thead>
<tr>
<th><strong>Subcardinal angle (SCA)</strong></th>
<th>55.5±12.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tracheal diameter (TD)</strong></td>
<td>1.9±0.2</td>
</tr>
<tr>
<td><strong>Tracheal surface area (TSA)</strong></td>
<td>72.0±10.9</td>
</tr>
<tr>
<td><strong>Tracheal volume (TV)</strong></td>
<td>34.8±8.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean±so.

Table 3 provides the coefficients for the determinants of log \( PC_{15} \). FEV/FVC is the strongest determinant of methacholine responsiveness; it accounts for more than half of the variability explained by the model as a whole (\( R²=0.25 \)). After accounting for airway size in this way, age, height and pack-years of cigarette consumption do not contribute significantly to the prediction of \( PC_{15} \).

**Table 3. Estimates and standard errors for the variables used to predict bronchial responsiveness to methacholine (log \( PC_{15} \))**

<table>
<thead>
<tr>
<th><strong>Estimate</strong></th>
<th><strong>SEE</strong></th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.025</td>
<td>3.367</td>
</tr>
<tr>
<td>Tracheal diameter cm</td>
<td>1.256</td>
<td>0.547</td>
</tr>
<tr>
<td>Age yrs</td>
<td>-0.011</td>
<td>0.014</td>
</tr>
<tr>
<td>Height cm</td>
<td>-0.031</td>
<td>0.017</td>
</tr>
<tr>
<td>Pack-years</td>
<td>-0.006</td>
<td>0.009</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>9.080</td>
<td>1.559</td>
</tr>
</tbody>
</table>

Model \( R²=0.25 \). For abbreviations see legend to table 1. SEE: standard error of the estimate.

![Fig. 2. Slope and standard error (dashed lines) of the relationship between tracheal diameter and bronchial responsiveness, the latter measured as the log of \( PC_{15} \), methacholine, adjusted for starting airway calibre (FEV1/FVC). FEV1/FVC: forced expiratory volume/forced vital capacity. \( PC_{15} \): provocative concentration of methacholine producing a 15% fall in FEV1](image-url)
Tracheal diameter does, however, contribute independently to the prediction of the level of airways responsiveness in individual subjects. Figure 2 illustrates this relationship. Similar slopes were obtained when substituting either tracheal surface area or volume, for tracheal diameter. FEV₁/FVC was found to be the major determinant of PC₂₀. Airway responsiveness increased as tracheal length (p<0.05), tracheal diameter (p<0.05), or surface area (p<0.01) decreased, both before and after adjustment for FEV₁/FVC. No relationship was found between PC₁₅ and subcarinal angle.

**Discussion**

It is well known that a constrictor stimulus will have a relatively greater effect in the presence of pre-existing airway narrowing, as predicted by Poiseuille's law. In this study, starting airway calibre, as reflected by FEV₁/FVC, was found, as in previous studies, to be the major determinant of response to a bronchoconstricting stimulus. After accounting for FEV₁/FVC, and other potential determinants, such as smoking, some of the residual variability in bronchial responsiveness could be accounted for by tracheal size, though not by the branching angle of the main-stem bronchi.

Tracheal size, although imperfectly assessed by tracing on standard posteroanterior chest radiographs, can be considered to reflect the overall size of the proximal tracheobronchial tree. This is supported by KoBILNER and HOPMAN [19], who analysed morphometric data on replica casts of human tracheobronchial airway, and demonstrated that parent airways with larger diameters have daughter airways with larger diameters. Maximum diameters decrease monotonically and at a quasi uniform rate for generations 6–19 [19], although there is considerable variability in the lengths, diameters, and branching angles within the same generation [20].

Our findings could be explained by differences in the distribution of aerosol deposition, which is influenced by many factors, such as particle size, minute ventilation, flow rate, breathing pattern or airway size. As the same nebulizer was used in all subjects, particle size should have been similar for all subjects. Whilst interindividual differences in minute ventilation, flow rates and breathing pattern may have determined aerosol deposition and the degree of airway bronchoconstriction, there is no reason here to anticipate these factors to be correlated with tracheal size, and, therefore, such differences would not account for our results.

The airflow velocity is inversely related to the cross-sectional area of an airway generation, whilst the probability of particle impaction is directly related to linear airflow velocity. Model calculations have shown that particle impaction efficiencies and higher surface concentrations of particles occur in the segmental bronchi, where the cross-sectional area is the least, and the mean linear airflow velocity the highest [21]. This would explain the observations by PAVIA et al. [10] of an increased proximal deposition of technetium-99 particles with a decreased FEV₁, and by DOLOVICH et al. [11] of an increased peripheral lung deposition with an increased FEV₁. This may also explain the findings in our study of an increase in airway responsiveness with decreasing tracheal size, after accounting for FEV₁/FVC. The consequences of particle deposition on bronchoconstriction were shown for histamine by RUFFIN et al. [9], who found that an increased central deposition of technetium-labelled histamine causes more airway constriction than diffusely deposited aerosol.

In conclusion, our results indicate that tracheal size contributes to the variation in airway responsiveness between individuals. The findings of an increase in airway responsiveness with decreasing tracheal size may reflect increased deposition of methacholine, secondary to smaller cross-sectional area, and greater linear velocity of air in the trachea and parent main bronchi.

**References**

15. American Thoracic Society. – Snowbird workshop on


