Short-term variability in respiratory impedance and effect of deep breath in asthmatic and healthy subjects with airway smooth muscle activation and unloading

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Gobbi A, Pellegrino R, Gulotta C, Antonelli A, Pompilio P, Crimi C, Torchio R, Dutto L, Parola P, Della RL, Brusasco V. Short-term variability in respiratory impedance and effect of deep breath in asthmatic and healthy subjects with airway smooth muscle activation and unloading. J Appl Physiol 115: 708–715, 2013. First published June 13, 2013; doi:10.1152/japplphysiol.00013.2013.—Inspiratory resistance (RINSP) and reactance (XINSP) were measured for 7 min at 5 Hz in 10 subjects with mild asymptomatic asthma and 9 healthy subjects to assess the effects of airway smooth muscle (ASM) activation by methacholine (MCh) and unloading by chest wall strapping (CWS) on the variability of lung function and the effects of deep inspiration (DI). Subjects were studied at control conditions, after MCh, with CWS, and after MCh with CWS. In all experimental conditions XINSP was significantly more negative in subjects with asthma than in healthy subjects, suggesting greater inhomogeneity in the former. However, the variability in both RINSP and XINSP was increased by either ASM activation or CWS, without significant difference between groups. DI significantly reversed MCh-induced changes in RINSP both in subjects with asthma and healthy subjects, but XINSP in the former only. This effect was impaired by CWS more in subjects with asthma than in healthy subjects. The velocity of RINSP and XINSP recovery after DI was faster in subjects with asthma than healthy subjects. In conclusion, these results support the opinion that the short-term variability in respiratory impedance is related to ASM tone or operating length, rather than to the disease. Nevertheless, ASM in individuals with asthma differs from that in healthy individuals in an increased velocity of shortening and a reduced sensitivity to mechanical stress when strain is reduced. 

induced bronchoconstriction; chest wall strapping; deep inspiration; respiratory resistance; respiratory reactance

BRONCHIAL ASTHMA IS FUNCTIONALLY characterized by exaggerated and variable airway narrowing in response to a variety of stimuli. These abnormalities are believed to be the result of airway inflammation and remodeling (9), but the presence of inflammatory cells in the airways is neither necessary (15) nor sufficient (16) to explain airway hyperresponsiveness. These observations and the similarity of bronchoconstrictor responses to widely different stimuli suggest that a key mechanism for exaggerated and variable airway narrowing in asthma is an abnormal response of the target organ, mainly due to an increase in airway smooth muscle (ASM) shortening. Whether this represents an alteration of ASM phenotype in asthma has been the object of recent debate (31, 42).

Studies in vitro comparing the mechanical properties of ASM in subjects with and without asthma have provided conflicting results, with some showing differences (2, 4, 6, 31, 33, 55, 61) and others no differences (12, 13, 14, 60) in contractile properties. In vivo, the picture is more complicated by several mechanisms that may modulate ASM shortening and airway narrowing. Because ASM shortening is the result of the balance between the force ASM generates and the loads it must act against (10, 39), any reduction in load will result not only in a shorter ASM for any given tone (2, 25, 49) but also in an increased velocity of shortening (25, 39, 52). Additional consequences of ASM unloading are that ASM may adapt to operate at reduced length, where it can shorten more (8, 30, 49), and its ability to relax during tidal or deep inspiration (DI) is reduced (1). In addition, an increased velocity in airway narrowing has been found to correlate with an increased within-breath variability in respiratory resistance (47). Both short- and long-term variabilities in respiratory impedance were found to be increased in subjects with asthma (29, 37, 46) and also in healthy subjects after ASM activation by methacholine (MCh) or shifting from upright to supine position (23). Altogether, the above findings would suggest that the variability in lung function may reflect intrinsic properties of ASM or unloading, independent of disease. Yet the relationships between the increased variability in lung function (29, 37, 46), the reduced bronchodilator effect of DI (10), and the increased velocity of airway narrowing observed in bronchial asthma remain elusive.

Imaging studies have shown that ventilation defects develop during acute bronchoconstriction in asthma (5, 36, 48, 56–58), which can be attributed to heterogeneous distribution of airway remodeling (26) and impedance (53). Respiratory impedance is a complex parameter with two dimensions; namely, resistance (Rrs) and reactance (Xrs), the former mainly reflecting the properties of conducting airways and the latter the capacitive properties of peripheral airways and lung parenchyma (19, 21, 50). Because small airways have been shown to be involved in the remodeling process of asthma, it can be hypothesized that ASM activation, unloading, and deep inspiration cause greater changes in Xrs than in people with asthma but not in healthy subjects. Alternatively, Xrs and Rrs should change similarly
in subjects with asthma and those without asthma if they reflect intrinsic properties of ASM. To test these hypotheses, we measured Rrs and Xrs in healthy subjects and those with mild asymptomatic asthma to assess the effects of ASM activation by MCh and unloading by chest wall strapping (CWS) on 1) the temporal and spatial variability of lung function, 2) the bronchodilator effect of DI, and 3) the velocity of airway narrowing after DI.

**METHODS**

**Subjects**

Ten men with mild, intermittent bronchial asthma (27) and 9 age-matched healthy men were studied (Table 1). To be included, subjects with asthma had to be in stable clinical condition in the previous 4 wk without regular asthma treatment. The study protocol was approved by the local Ethical Committee and written informed consent was obtained from each subject before entering the study.

**Lung Function Measurements**

Spirometry, maximal flow-volume curves, and absolute lung volumes were obtained with a body plethysmograph (Autobox; SensorMedics, California) following American Thoracic Society/European Respiratory Society recommendations (41, 59). Briefly, after at least four regular breaths, thoracic gas volume (TGV) was measured while subjects were panting against a closed shutter at a frequency slightly <1 Hz with cheeks supported by hands. After the shutter was opened, the subjects took a full inspiratory capacity (IC) and then forcefully expired from total lung capacity (TLC) to residual volume (RV) for at least 6 s to measure forced vital capacity (FVC) and 1-s forced expiratory volume (FEV1). Functional residual capacity (FRC) was calculated from TGV, corrected for any difference between the volume at which the shutter was closed and the average end-expiratory tidal volume of previous tidal breaths. Predicted values for spirometry and lung volumes were obtained from Quanjer et al. (45).

Respiratory impedance was measured by a forced oscillation system previously described (20, 28, 29). Sinusoidal pressure oscillations (5 Hz frequency, ~2 cmH2O amplitude) were generated by a 16-cm-diameter loudspeaker (CW161N; Ciare, Italy) and applied at the mouth while subjects were breathing normally at a frequency of 5 Hz with cheeks supported by hands. After the shutter was opened, the subjects took a full inspiratory capacity (IC) and then forcefully expired from total lung capacity (TLC) to residual volume (RV) for at least 6 s to measure forced vital capacity (FVC) and 1-s forced expiratory volume (FEV1). Functional residual capacity (FRC) was calculated from TGV, corrected for any difference between the volume at which the shutter was closed and the average end-expiratory tidal volume of previous tidal breaths. Predicted values for spirometry and lung volumes were obtained from Quanjer et al. (45).

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**Study Protocol**

On a prestudy day after spirometry and lung volume measurements, subjects underwent an incremental-dose inhalation challenge to determine the single dose of MCh to be used in the subsequent study days. Doubling MCh doses from 20 to 1,200 µg for subjects with asthma and from 300 to 4,800 µg for healthy subjects, were inhaled until FEV1 was decreased by 20% or more from baseline, or the next dose should have been >5,000 µg. For this purpose, dry-powder MCh chloride (Laboratorio Farmaceutico Lofarma, Italy) dissolved in 3 mL of distilled water was aerosolized by an ampoule-dosimeter system (MB3; MEFAR, Italy) delivering particles with a median mass diameter ranging between 1.53 and 1.61 µm, and inhaled during spontaneous quiet breathing in a sitting position. The dose causing a 20% decrease in FEV1 (PD20FEV1) was calculated by interpolation of the dose-response curve.

Subjects then attended the laboratory on two other occasions at least 1 wk apart to undergo single-dose MCh challenges using the last dose achieved on the prestudy day, and with or without CWS in a random order. On the first study day, after control spirometry and lung volume measurements, respiratory impedance was determined over 7 min of tidal breathing with a DI taken at the end of the fifth minute. All measurements were taken again after a single dose of MCh. On the second study day, a corset constraining the whole chest wall was applied with the help of two elastic and two inelastic corsets extending from axillae to lower abdomen. All measurements were taken before and after MCh as on the first study day. All subjects were instructed to avoid unrestricted larger than regular breaths or sighs during the studies. At the end of each study day, subjects were given aerosol albuterol for symptoms relief.

**Data Analysis**

The variability in RINSPIR and XINSPIR was estimated from the interquartile range (IQR) of their respective probability density estimations (RINSPIR_IQR and XINSPIR_IQR) using all regular breaths before DI. A linear regression analysis was applied to all values of RINSPIR and XINSPIR measured from the end of DI to the point at which a clear plateau was observed (Fig. 1). The intercepts of regression lines at the time DI was terminated (RINSPIRInter and XINSPIRInter) were compared with the average pre-DI values to estimate the bronchodilator effects of DI, and slopes (RINSPIR_Slope and XINSPIR_Slope) were taken as estimates of re-narrowing rates (44).

An unpaired t-test was used to evaluate the statistical significance of differences in anthropometric and baseline functional characteristics between groups. A within-between groups repeated measures ANOVA with the Holm-Sidak multiple comparison test was used to assess differences between conditions and groups. Relationships between variables were tested by simple regression analysis. P < 0.05

Table 1. Subjects’ anthropometric and functional characteristics

<table>
<thead>
<tr>
<th></th>
<th>With Asthma</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>37 ± 13</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 ± 6</td>
<td>177 ± 7</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>26 ± 3</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>FEV1, % of predicted</td>
<td>94 ± 14</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>104 ± 18</td>
<td>105 ± 8</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>97 ± 16</td>
<td>94 ± 8</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>90 ± 26</td>
<td>91 ± 11</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>93 ± 22</td>
<td>77 ± 20</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>26 ± 6</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>PD20FEV1, ln-µg</td>
<td>5.05 ± 1.56*</td>
<td>&gt;8.48</td>
</tr>
</tbody>
</table>

BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume. PD20FEV1, dose of methacholine causing a 20% fall of FEV1. There were no significant differences between groups (unpaired t-test) except for PD20FEV1 (*P < 0.001). Data are means ± SD.
was considered statistically significant. Data are presented as means ± SD or confidence interval.

RESULTS

There were no significant differences in anthropometric characteristics, spirometry, or lung volumes between subjects with asthma and healthy subjects (Table 1). Presumably, this was because subjects had a very mild form of bronchial asthma and were free from functional defects at the time of the study. PD_{20}FEV_{1} was expectedly less (P < 0.001) and XINSP was more negative (P = 0.021) in subjects with asthma under all experimental conditions (Table 2).

Effects of MCh

Inhalation of MCh caused variable decrements in FEV_{1} (P < 0.001) and FVC (P = 0.007), and increments in FRC (P < 0.001) and RV (P < 0.001) that were not significantly different between subjects with asthma and healthy subjects (Table 2). R_{INS} increased significantly from control conditions (P < 0.001) and X_{INS} became more negative (P = 0.001), but without significant difference between groups. Also, R_{INS,IQR} and X_{INS,IQR} increased significantly (P = 0.006 and P = 0.002, respectively) without significant difference between groups (Fig. 2). DI reduced R_{INS} significantly (P < 0.001) in both healthy subjects and those with asthma and made X_{INS} less negative in those with asthma (P = 0.001) and healthy subjects (P = 0.107), reaching values that were not significantly different from control (P = 0.133 and P = 0.914, respectively), and without significant difference between groups (Fig. 3). R_{INS,Slope} and X_{INS,Slope} increased significantly in subjects with asthma (P = 0.001 for both) but not in healthy subjects (P = 0.133 and P = 0.708, respectively; Fig. 4).

Effects of CWS

Expectedly, CWS caused significant reductions in TLC (P < 0.001), FRC (P < 0.001), FVC (P < 0.001), and FEV_{1} (P < 0.001), but not RV (P = 0.617), without significant difference between healthy subjects and those with asthma (Table 2). R_{INS} increased significantly from control (P = 0.009) but less than with MCh (P = 0.001) without difference between groups. X_{INS} was more negative than at control (P < 0.001), but not significantly different from MCh (P = 0.105). R_{INS,IQR} and X_{INS,IQR} were significantly increased (P = 0.003 and P < 0.001, respectively) to values that were similar to those with MCh (P = 0.842 and P = 0.707, respectively), without significant difference between groups (Fig. 2). DI had no significant effects on R_{INS} and X_{INS} (Fig. 3); R_{INS,Slope} and X_{INS,Slope} were not significantly different from control (Fig. 4).
Effects of MCh in the Presence of CWS

Inhalation of MCh caused greater decrements in FEV1 (\(P < 0.001\)) and FVC (\(P < 0.001\)), and increments in FRC (\(P < 0.001\)) and RV (\(P = 0.026\)) than in the absence of CWS, without significant differences between groups (Table 2).

R_{INSPIR} tended to increase (\(P = 0.070\)) and \(X_{INSPIR}\) became significantly more negative (\(P < 0.001\)) than in the absence of CWS, without significant difference between groups. Both \(R_{INSPIR}\) and \(X_{INSPIR}\) further increased compared with MCh alone (\(P = 0.004\) and \(P < 0.001\), respectively), without significant difference between groups (Fig. 2). The attenuating effects of DI on \(R_{INSPIR}\) were maintained only in healthy subjects (\(P = 0.048\), though at a significantly lower level than with MCh alone (\(P < 0.001\) for both). Neither \(R_{INSPIR}\) nor \(X_{INSPIR}\) were significantly different from control (Fig. 4).

Relationships Between Variables

\(R_{INSPIR}\) was significantly correlated with \(R_{INSPIR}\) in all conditions and in both groups, except in the healthy subjects at control conditions, with similar regression coefficients that tended to increase with MCh plus CWS (Table 3), whereas \(X_{INSPIR}\) correlated with \(X_{INSPIR}\) in subjects with asthma only. With MCh alone, \(R_{INSPIR}\) was significantly correlated with \(R_{INSPIR}\) in both subjects with asthma (\(r^2 = 0.50\)) and healthy subjects (\(r^2 = 0.69\)), whereas \(X_{INSPIR}\) correlated with \(X_{INSPIR}\) only in the former (\(r^2 = 0.88\)). In addition, in subjects with asthma but not in healthy subjects, \(R_{INSPIR}\) was negatively correlated with \(X_{INSPIR}\) (\(r^2 = 0.85, P < 0.001\)).

DISCUSSION

The main results of the present study are as follows: 1) in subjects with mild asthma and standard lung function tests within normal range, \(X_{INSPIR}\) was significantly more negative than in healthy subjects; 2) the variability in both \(R_{INSPIR}\) and \(X_{INSPIR}\) was increased by either ASM activation or CWS without significant differences between healthy subjects and those with asthma; 3) DI significantly reversed MCh-induced changes in \(R_{INSPIR}\) in both healthy subjects and those with asthma, and it also reduced \(X_{INSPIR}\) in subjects with asthma; 4) the effect of DI was impaired by CWS more in subjects with asthma than healthy subjects; and 5) recondition after DI, as estimated from \(R_{INSPIR}\) and \(X_{INSPIR}\), was faster in subjects with asthma than healthy subjects.
Comments on Methodology

This study has strengths and limitations. Methodological strengths include the following: 1) at variance with previous studies, Rrs and Xrs were computed over the inspiratory portion of tidal breathing only (R_{INS} and X_{INS}, respectively), which avoids the artifacts of expiratory flow limitation (17–19); 2) impedance measurements were taken at a fixed breathing frequency of \( \frac{1}{2} \text{ breaths/min} \), which preliminarily has been shown to provide a probability density estimation of R_{INS} that is substantially narrower than at variable breathing frequency; and 3) the variability in R_{INS} and X_{INS} was estimated from IQR rather than coefficient of variation to minimize the effects of skewed probability density estimation, especially under conditions of severe airflow obstruction. Limitations include the following: 1) CWS was used to unload ASM by decreasing the operative lung volume and to limit the amplitude of strain during DI, although it is known to increase lung elastic recoil (51, 54), thus increasing the stress on ASM particularly at full lung inflation; 2) only individuals with mild asthma were studied to minimize the confounding effects of airway inflammation, which makes our results not generalizable to the entire population of people with asthma; and 3) a single frequency of 5 Hz was used to assess lung mechanics in asthma, as in previous studies (17, 18, 20, 23, 28, 29, 38, 46), but it is possible that multiple higher frequencies may provide more information on ventilation heterogeneities (38, 50).

Interpretation of Results

Although PD_{20}FEV_{1} was expectedly lower in subjects with asthma than healthy subjects, no differences in standard lung
function data were observed between the groups in response to the single dose of MCh corresponding to the last cumulative dose given on the prestudy day. Therefore, it seems reasonable to interpret the results of the present study in the frame of ASM dynamics with minimal confounding effects.

Variability in respiratory impedance. In all experimental conditions, XINSPl was significantly more negative in subjects with asthma than healthy subjects. Because the two groups had very close FRC under any condition, this finding suggests an increased mechanical inhomogeneity (50). However, the similarity in XINSPl between groups suggests that the temporal variability of spatial inhomogeneity was not increased in these subjects with mild asthma.

In accord with a recent study (44), ASM activation by MCh caused an increase in Rrs that was associated with a more negative Xrs, which is consistent with several studies showing that induced bronchoconstriction is associated with increased ventilation inhomogeneities (5, 11, 26, 36, 50–58). Imaging studies in animals and humans have documented that induced bronchoconstriction is associated with large and patchy ventilation defects, occurring presumably as a result of heterogeneous closure or near-closure of small airways (5, 11, 26, 36, 50–58). Model simulations showed that small, random perturbations in airway wall thickness upon ASM activation can be interpreted as suggesting that ventilation inhomogeneity is the observation that when the airway strain was reduced by CWS, then the bronchodilator effect of DI was almost abolished in both groups, but it was significantly less in healthy subjects than in those with asthma. Because CWS is associated with the exception of control, were similar with MCh or CWS.

### Table 3. Regression analysis between variability and mean values of respiratory impedance

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCh</th>
<th>CWS</th>
<th>CWS + MCh</th>
</tr>
</thead>
<tbody>
<tr>
<td>RINSPl vs. RINSPl</td>
<td>0.58</td>
<td>0.50</td>
<td>0.45</td>
<td>0.44</td>
</tr>
<tr>
<td>R²</td>
<td></td>
<td>0.13 (0.04, 0.21)</td>
<td>0.12 (0.03, 0.21)</td>
<td>0.14 (0.01, 0.26)</td>
</tr>
<tr>
<td>Slope</td>
<td></td>
<td>0.55</td>
<td>0.88</td>
<td>0.58</td>
</tr>
<tr>
<td>XINSPl vs. XINSPl</td>
<td>0.05</td>
<td>0.17 (0.02, 0.03)</td>
<td>0.14 (0.03, 0.01)</td>
<td>0.14 (0.02, 0.04)</td>
</tr>
<tr>
<td>R²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td></td>
<td>0.11 (0.04, 0.17)</td>
<td>0.19 (0.11, 0.26)</td>
<td>0.18 (0.01, 0.34)</td>
</tr>
</tbody>
</table>

RINSPl, interquartile range of RINSPl; XINSPl, interquartile range of XINSPl. See Table 2 for other abbreviations. Slope values are presented as means (95% confidence interval).
with an increase in transpulmonary pressure, and thereby bronchial transmural pressure, the present results suggest that strain is the major determinant of the bronchodilator effect of DI, whereas stress has a marginal effect in healthy subjects. This is in line with a recent study in ovine trachea showing that stress may in part compensate for the reduction of strain in preserving the effect of simulated DIs in isolated ASM (43). The present study, however, adds that this effect of stress is reduced more in people with asthma than in healthy individuals. It must be noted, however, that in more severe asthma, strain and stress may be reduced at the same time because of a loss of interdependence, thus more severely impairing the bronchodilator effect of DI.

The significant correlations between $R_{\text{INSPIRATORY IQR}}$ and $R_{\text{INSPIRATORY Slope}}$ in both groups and between $X_{\text{INSPIRATORY IQR}}$ and $X_{\text{INSPIRATORY Slope}}$ in subjects with asthma suggest that short-term fluctuations in airway caliber are related to ASM velocity of shortening. These findings extend the results of Salome et al. (47) who reported that airway renarrowing after DI as estimated from the changes in $R_{\text{rs}}$ over time was faster in subjects with asthma than in healthy subjects, and that this was significantly correlated with the fluctuation in airway tone within tidal breaths. That the ASM velocity of shortening may be a major determinant of bronchial tone control in asthma is also suggested by the significant correlation we observed between $R_{\text{INSPIRATORY Slope}}$ and $X_{\text{INSPIRATORY Slope}}$ after MCh, as a confirmation that when ASM shortening velocity is increased, it contributes not just to a faster reconstriction but also to a faster reappearance of airway closure. The lack of significance between $X_{\text{INSPIRATORY IQR}}$ and $X_{\text{INSPIRATORY Slope}}$ in healthy subjects is likely due to the small change in $X_{\text{INSPIRATORY with MCh}}$, consistent with the hypothesis of a more central airway narrowing than in asthma.

Conclusions

Altogether, the results of the present study confirm that the short-term variability in respiratory impedance is mostly related to the intrinsic properties of ASM and is increased by operating at short length, due to either unloading or contractile shortening. Nevertheless, there are differences in behavior between ASM in subjects with asthma and healthy subjects, consisting of an increased velocity of shortening and a reduced sensitivity to mechanical stress when strain is limited.

REFERENCES


