Respiratory system reactance is an independent determinant of asthma control

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1Department of Medicine, Pulmonary and Critical Care Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; 2Department of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia; 3Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Prahran, Victoria, Australia; 4Division of Sleep Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; 5Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; 6Woolcock Institute of Medical Research, Glebe, New South Wales, Australia; and 7Co-operative Research Centre for Asthma and Airways, Glebe, New South Wales, Australia

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Kelly VJ, Sands SA, Harris RS, Venegas JG, Brown NJ, Stuart-Andrews CR, King GG, Thompson BR. Respiratory system reactance is an independent determinant of asthma control. J Appl Physiol 115: 1360–1369, 2013. First published August 29, 2013; doi:10.1152/japplphysiol.00093.2013.—The mechanisms underlying not well-controlled (NWC) asthma remain poorly understood, but accumulating evidence points to peripheral airway dysfunction as a key contributor. The present study tests whether our recently described respiratory system reactance (Xrs) assessment of peripheral airway dysfunction reveals insight into poor asthma control. The aim of this study was to investigate the contribution of Xrs to asthma control. In 22 subjects with asthma, we measured Xrs (forced oscillation technique), spirometry, lung volumes, and ventilation heterogeneity (inert-gas washout), before and after bronchodilator administration. The relationship between Xrs and lung volume during a deflation maneuver yielded two parameters: the volume at which Xrs abruptly decreased (closing volume) and Xrs at this volume (Xrscrit). Lowered (more negative) Xrscrit reflects reduced apparent lung compliance at high lung volumes due, for example, to heterogeneous airway narrowing and unresolved airway closure or near closure above the critical lung volume. Asthma control was assessed via the 6-point Asthma Control Questionnaire (ACQ6). NWC asthma was defined as ACQ6 > 1.0. In 10 NWC and 12 well-controlled subjects, ACQ6 was strongly associated with postbronchodilator (post-BD) Xrscrit (R² = 0.43, P < 0.001), independent of all measured variables, and was a strong predictor of NWC asthma (receiver operator characteristic area = 0.94, P < 0.001). By contrast, Xrs measures at lower lung volumes were not associated with ACQ6. Xrscrit itself was significantly associated with measures of gas trapping and ventilation heterogeneity, thus confirming the link between Xrs and airway closure and heterogeneity. Residual airway dysfunction at high lung volumes assessed via Xrscrit is an independent contributor to asthma control.

Researchers have intensively investigated the pathophysiological mechanisms responsible for the severity of asthma symptoms. To date, functional assessment of airflow obstruction, ventilation heterogeneity (inert-gas washout), and airway inflammation with exhaled nitric oxide have been found to be modestly associated with the clinical presentation of asthma (asthma control or severity scores, airway hyperresponsiveness, and exacerbation rates) (1, 14–16, 44). Although less commonly assessed, airway mechanical dysfunction in the form of severe heterogeneous peripheral airway narrowing and closure is gaining increased recognition as a characteristic feature of asthma (6, 11, 24, 32). Such dysfunction may be the result of airway inflammation, airway wall remodeling (25), including elevated airway smooth muscle mass (10) and/or local and regional airway-tissue interactions (49). In asthma, peripheral heterogeneous airway narrowing and closure are considered a major cause of ventilation defects revealed with lung imaging (13, 22, 47) and of the alterations in pulmonary oscillatory mechanics (30, 31), specifically lowered respiratory system reactance (Xrs). Since larger and more numerous ventilation defects occur in more severe asthma (2, 13), our central proposal is that the degree of peripheral airway narrowing and closure is an important contributor to asthma control.

We recently developed a technique that utilizes the changes in Xrs with lung volume to concurrently assess closing volume (Volcrit) and Xrs at this closing volume (Xrscrit) (28). Measuring Xrs from total lung capacity (TLC) to residual volume (RV) shows that Xrs rises very slightly [i.e., as lung tissue compliance increases with reduced lung volume (52)], but, when lung volume decreases below a threshold (Volcrit) Xrs decreases precipitously (becomes more negative). This fall in Xrs is consistent with the onset and development of progressive severe airway narrowing and closure. In principle, severe airway narrowing and closure obstructs a proportion of the lung from the pressure oscillations of the forced oscillation technique and, therefore, decreases the apparent lung compliance (compliance = Δvolume/Δpressure, where Δ is change) seen at the mouth. Volcrit is, therefore, interpreted as a measure of closing volume, much like nitrogen washout; indeed, Volcrit is raised in asthma vs. controls, consistent with the reported increase in closing volume in asthma (35). Xrscrit, which represents the maxima in Xrs with respect to lung volume, is characteristically reduced (more negative) in asthma (28), a finding that demonstrates that reduced apparent compliance occurs even above closing volume in asthma. In asthma, such
lowered apparent compliance can result from the presence of heterogeneous airway narrowing and closure (8, 47).

Given the marked alterations in $X_{rs}$ and $V_{ol}$ in asthma compared with healthy controls, the central aim of the present study was to investigate whether $X_{rs}$ reflects the physiological dysfunction contributing to poor asthma control. We tested the hypothesis that patients with NWC asthma exhibit reduced $X_{rs}$crit and increased $V_{ol}$crit compared with well-controlled (WC) asthma.

METHODS

Subjects. This study was approved by the Research and Ethics Unit at The Alfred Hospital, Australia. A portion of the data used within the present study has been previously published (28). Twenty-two subjects with asthma (15 men) participated in the study, after providing written, informed consent. All subjects were recruited from the specialist Asthma Clinic at The Alfred Hospital and had doctor-diagnosed asthma according to current guidelines (38). Subjects were current nonsmokers ($\leq$10 pack-yr smoking history) and were asymptomatic for acute respiratory infection. All subjects used short-acting bronchodilators as needed and a combined inhaled corticosteroid and long-acting $\beta_2$-agonist. Subjects had variable lung function over the previous 4 wk (historical lung function measurements reviewed where available); of note, these subjects were previously described (28) as “well-controlled” in this context.

Experimental design. Subjects completed in order: the Asthma Control Questionnaire (ACQ) (27), spirometry, static lung volumes (plethysmography), forced oscillation technique measurements, and multiple-breath nitrogen washout. All tests, excluding ACQ, were completed at baseline and after short-acting $\beta_2$-agonist was administered (300 $\mu$g, salbutamol) via a spacer (Bromchodilator). Before testing, subjects withheld short-acting bronchodilator medications for at least 6 h, and long-acting bronchodilators and inhaled corticosteroid therapies were with-held for at least 12 h.

Equipment and measurements. Spirometry and lung volumes were performed on a Medgraphics Platinum Elite Dx (Medical Graphics, St. Paul, MN) according to American Thoracic Society/European Respiratory Society criteria (37, 51). Spirometric and lung volumes results are reported as percentage predicted, unless otherwise stated. $X_{rs}$ (6 Hz) was assessed using a previously described forced oscillation technique device (43) and analyzed using Matlab (MathWorks, Natick, MA).

Asthma control. Asthma control was assessed using the ACQ (27). The ACQ includes the frequency of night-time awakenings, morning symptoms, limitations to daily activities, shortness of breath, wheeze, short-acting $\beta_2$-agonist use, and forced expiratory volume in 1 s (FEV1). We used the 6-point ACQ (ACQ6) to exclude the contribution of FEV1. Subjects were defined as WC or NWC based on the ACQ6 = 1.0 (WC) or >1.0 (NWC) (26). NWC asthma encapsulates subjects with poorly controlled asthma (ACQ > 1.5) and with partly controlled asthma (1.0 < ACQ < 1.5) (26).

Reactance-lung volume relationship. $X_{rs}$ was assessed across multiple lung volumes, as previously described (28). Subjects performed, at least in duplicate, a specialized breathing protocol containing three deflation maneuvers (Fig. 1). The breathing protocol consisted of 1 min of tidal breathing, followed by a slow vital capacity maneuver and a further 30 s of tidal breathing. Subsequently, three deflation maneuvers were performed in series, separated by periods of tidal breathing. Finally, another slow vital capacity maneuver was performed at the end of the protocol. Each deflation maneuver consisted of an inspiration to TLC followed by tidal breaths with decreasing end expiratory lung volume until RV was reached. End-inspiration and end-expiration measurements of $X_{rs}$ during each deflation maneuver were collated and plotted against the lung volume at which they were obtained from which two primary measures were determined (Fig. 1B). First, the $V_{ol}$crit is taken as a surrogate measure of closing volume. An elevation in $V_{ol}$crit indicates an increased susceptibility for the development of airway closure as lung volume decreases from TLC. Second, $X_{rs}$crit is used as a measure of overall apparent lung compliance that reflects the degree of airway heterogeneity and closure or near closure of airways that persists above closing volume (28).

RESULTS

Of the 22 subjects, 10 were defined as NWC and 12 as WC. The WC and NWC groups had similar age, weight, and body mass index; however, the NWC group had a lower height compared with the WC group (Table 1). All subjects were Caucasian. Pulmonary function testing was performed at a similar time of day in the NWC and WC groups. As designed, the NWC group had significantly higher ACQ6 scores compared with the WC group (Table 1). The Global Initiative for Asthma Treatment Step (4), determined based on medication doses, was also significantly higher in the NWC group compared with the WC group. Pulmonary function results, reported as the percentage of predicted (12, 20), are included in Table 1.
The NWC group had a significantly greater degree of airflow obstruction (reduced FEV₁ and FEV₁/forced vital capacity), and a greater degree of gas trapping [indicated by a higher RV and RV/TLC (23)] compared with the WC asthma group.

Reactance and multiple-breath nitrogen washout: NWC vs. WC. The differences between the groups (WC vs. NWC) and conditions (baseline vs. post-BD) for Xₚcrit, Volₚcrit, Sₐcin, and Sₕcond, as determined from two-way repeated-measures ANOVA, are included in Fig. 2; detailed statistics are provided in Table 2. There was a significant effect of group and condition for Xₚcrit. Post hoc analysis demonstrated that baseline Xₚcrit was significantly lower (more negative) in NWC compared with WC subjects, a difference that became more distinct following bronchodilator. Despite the significant increase in Xₚcrit with bronchodilator (main effect, two-way repeated-measures ANOVA), the increase in Xₚcrit within WC and NWC groups was not significant (post hoc analysis).

Comparison of post-BD Xₚcrit between NWC and WC asthma groups and previously reported healthy controls (n/H₁₁005₁₁₁₁002) (28) found no difference between WC asthma and healthy controls (₀.₆₂ ± ₀.₁₁ cm²·L⁻¹·s⁻¹) and NWC asthma (₋₂.₀₂ ± ₀.₂₀ cm²·L⁻¹·s⁻¹), which was significantly lower (more negative) than both WC asthma and controls (one-way ANOVA with Student-Newman-Keuls post hoc analysis, both P < 0.001).

Baseline Volₚcrit was significantly higher in NWC compared with the WC group. In both WC and NWC groups, Volₚcrit decreased following bronchodilator (main effect, P < 0.001). Following bronchodilator, Volₚcrit remained significantly greater in the NWC group compared with the WC group. Post-BD Volₚcrit increased progressively with disease severity from healthy controls (₅₁.₁ ± ₂.₃ vs. ₆₃.₁ ± ₃.₈%predicted TLC, P < ₀.₀₁) to NWC asthma (₇₈.₇ ± ₃.₆%predicted TLC, P < ₀.₀₁ vs. WC and P < ₀.₀₀₁ vs. controls; one-way ANOVA with Student-Newman-Keuls post hoc analysis).

Sₐcin was higher in NWC vs. WC, both at baseline and after bronchodilator. Overall, Sₕcond was greater in NWC vs. WC, but only reached significance post-BD. Bronchodilator administration had no effect on Sₐcin or Sₕcond. Overall, there were no differences between WC and NWC groups in terms of the effect size of bronchodilator on Xₚcrit, Volₚcrit, Sₐcin, or Sₕcond (group × condition).

Factors associated with asthma control. The ACQ6 score was linearly associated with multiple variables, including Xₚcrit, Volₚcrit, Sₐcin, Sₕcond, FEV₁, RV, and RV/TLC (univariate regression; Table 3). Bronchodilator strengthened the associations between ACQ6 and Xₚcrit, Volₚcrit, Sₐcin, and Sₕcond. The strongest association was observed between ACQ6 and Xₚcrit post-BD (Fig. 3); Xₚcrit explained 43% of the variance in the ACQ6 (R² = ₀.₄₃, P < ₀.₀₀₁). Forward stepwise regression

Fig. 1. A: breathing protocol performed to obtain respiratory system reactance (Xrs) vs. lung volume, as recorded from a well-controlled (WC) asthma subject. Shaded regions identify the deflation maneuvers performed that enable Xrs to be calculated between total lung capacity (TLC) and residual volume (RV) at points of zero flow (solid circles at end inspiration and end expiration). Each protocol shown was performed at least in duplicate. B: volume and reactance vs. time during one deflation maneuver, with the zero-flow measurements outlined by the solid circles. C: example Xrs vs. lung volume relationship with bilinear regression. Volₚcrit is defined as the lung volume where the onset of airway closure occurs. Xₚcrit is reactance at this volume, to the right of the precipitous decline with airway closure. Lowered Xₚcrit (more negative) reflects a reduced apparent lung compliance (i.e., due to heterogeneous airway narrowing and closure) at high lung volumes (above Volₚcrit).
performed using those variables with significant univariate correlations demonstrated that post-BD Xrscrit was the only independent determinant of ACQ6. No additional variance in ACQ6 was explained by height, or post-BD Volcrit, Sacin, Scond, FEV1, RV, or RV/TLC.

Receiver operator characteristic analysis (Table 4) identified multiple significant discriminants of NWC and WC asthma, including post-BD values of Xrscrit, Volcrit, Sacin, Scond, and RV, and baseline values of FEV1 and RV/TLC. Most notably, post-BD Xrscrit had a high sensitivity (90%) and specificity.
was also an association between Volcrit and \(0.78, R\) gas trapping: RV %predicted (S\(0.01\), RV %predicted (S\(R\)).

Results: RV %predicted (FEV\(_1\), %predicted S\(0.01\)).

Table 3. Univariate correlations (r value) between ACQ6 and variables at baseline and post-BD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Post-BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_r)crit cm(\text{H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1})</td>
<td>-0.53*</td>
<td>-0.66‡</td>
</tr>
<tr>
<td>Volcrit %predicted TLC</td>
<td>0.50*</td>
<td>0.59†</td>
</tr>
<tr>
<td>(S_{\text{acin}}) liter(^{-1})</td>
<td>0.45*</td>
<td>0.55†</td>
</tr>
<tr>
<td>(S_{\text{cond}}) liter(^{-1})</td>
<td>0.48*</td>
<td>0.51†</td>
</tr>
<tr>
<td>FEV(_1), %predicted</td>
<td>-0.50*</td>
<td>-0.38*</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>-0.26*</td>
<td>-0.18</td>
</tr>
<tr>
<td>RV, %predicted</td>
<td>0.58†</td>
<td>0.59†</td>
</tr>
<tr>
<td>TLC, %predicted</td>
<td>0.33</td>
<td>0.37</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>0.49*</td>
<td>0.47*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

\(*P < 0.05, \dagger P < 0.01, \ddagger P < 0.001\).

Table 2. Comparison of \(X_{r}\)crit, Volcrit, \(S_{\text{acin}}\), and \(S_{\text{cond}}\) between WC and NWC groups (two-way repeated-measures ANOVA)

<table>
<thead>
<tr>
<th></th>
<th>WC</th>
<th>Post-BD</th>
<th>WC</th>
<th>Post-BD</th>
<th>Two-Way Repeated-Measures ANOVA, P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_{r})crit</td>
<td>-1.13 ± 0.16</td>
<td>-0.83 ± 0.14</td>
<td>-2.19 ± 0.32(^a)</td>
<td>-2.02 ± 0.20(^b)</td>
<td>WC vs. NWC group, BD effect, Interaction</td>
</tr>
<tr>
<td>Volcrit</td>
<td>69.4 ± 4.1</td>
<td>63.1 ± 3.8(^R)</td>
<td>84.5 ± 2.8(^b)</td>
<td>78.7 ± 3.6(^b)</td>
<td>0.001</td>
</tr>
<tr>
<td>(S_{\text{acin}})</td>
<td>0.20 ± 0.02</td>
<td>0.17 ± 0.02</td>
<td>0.38 ± 0.08(^*)</td>
<td>0.39 ± 0.06(^b)</td>
<td>0.001</td>
</tr>
<tr>
<td>(S_{\text{cond}})</td>
<td>0.034 ± 0.005</td>
<td>0.027 ± 0.005</td>
<td>0.047 ± 0.006</td>
<td>0.045 ± 0.007(^†)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(X_{r}\)crit, respiratory system reactance measured at the critical lung volume (Volcrit); \(S_{\text{acin}}\) and \(S_{\text{cond}}\), ventilation heterogeneity within the acinar and conductive lung regions, respectively. \(^*P < 0.05, \dagger P < 0.01, \ddagger P < 0.001\): WC vs. NWC post hoc analysis. \(^aP < 0.05, \dagger P < 0.01\): baseline vs. post-BD post hoc analysis.

Factors associated with \(X_{r}\)crit. To assess whether \(X_{r}\)crit truly reflects peripheral heterogeneity and airway closure, we examined the factors associated with \(X_{r}\)crit. Univariate analysis showed that post-BD \(X_{r}\)crit was significantly associated with measures of ventilation heterogeneity, \(S_{\text{acin}}\) (\(R = -0.57, P < 0.01\)) and \(S_{\text{cond}}\) (\(R = -0.52, P < 0.05\)), and indexes of gas trapping and airway closure, RV %predicted (\(R = -0.58, P < 0.01\)) and RV/TLC (\(R = -0.75, P < 0.0001\)). No associations between \(X_{r}\)crit and FRC or TLC were observed. All regressions were performed using post-BD data.

To confirm the generalizability of associations between \(X_{r}\)crit and measures of heterogeneity, we repeated the above univariate analysis, including the 19 control subjects from our previous study (28, and found similar results. \(X_{r}\)crit was significantly associated with \(S_{\text{acin}}\) (\(R = -0.62, P < 0.0001\)), \(S_{\text{cond}}\) (\(R = -0.43, P < 0.01\)), RV %predicted (\(R = -0.54, P < 0.001\)), and RV/TLC (\(R = -0.61, P < 0.0001\)). The associations between \(X_{r}\)crit, \(S_{\text{acin}}\), \(S_{\text{cond}}\) and RV/TLC are included in Fig. 4. Post-BD \(S_{\text{acin}}\) and \(S_{\text{cond}}\) in the healthy controls was 0.12 ± 0.02 and 0.018 ± 0.006 liter\(^{-1}\), respectively.

Factors associated with Volcrit. Using univariate regression, Volcrit was strongly associated with lung volumes, indicating a close connection with available indexes of hyperinflation and gas trapping: RV %predicted (\(R = 0.83, P < 0.00001\)), FRC %predicted (\(R = 0.67, P < 0.001\)), TLC %predicted (\(R = 0.78, P < 0.00001\)), and RV/TLC (\(R = 0.62, P < 0.01\)). There was also an association between Volcrit and \(S_{\text{acin}}\) (\(R = 0.48, P < 0.05\)) but not \(S_{\text{cond}}\). Including controls yielded similar results: RV %predicted (\(R = 0.85, P < 0.00001\)), FRC %predicted (\(R = 0.61, P < 0.0001\)), TLC %predicted (\(R = 0.68, P < 0.00001\)), RV/TLC (\(R = 0.77, P < 0.01\)), \(S_{\text{acin}}\) (\(R = 0.61, P < 0.0001\)), and \(S_{\text{cond}}\) (\(R = 0.45, P < 0.01\)). All regressions were performed using post-BD data.

Lung volume dependence of \(X_{r}\)crit and asthma control. To examine whether the strong link between ACQ6 and \(X_{r}\)crit relies on the measurement of \(X_{r}\) at specific lung volumes, post-BD \(X_{r}\)s (determined from the \(X_{r}\)-lung volume relationship) was measured at RV, FRC, TLC, and a volume midway between FRC and TLC (MID). In general, RV and FRC lie on or near the steep portion of the \(X_{r}\) vs. lung volume curve. By contrast, MID and TLC lie exclusively on the upper, flatter portion of the \(X_{r}\)-volume curve. \(X_{r}\) assessed at each lung volume was compared between WC and NWC (unpaired t-test). \(X_{r}\) measured at RV and at FRC were not significantly different between WC and NWC (Fig. 5). However, \(X_{r}\) measured at MID and TLC maintained the statistical difference between the WC and NWC group as seen with \(X_{r}\)crit.

DISCUSSION

Our study shows for the first time that \(X_{r}\) measured above closing volume (\(X_{r}\)crit), is strongly associated with asthma control. Post-BD \(X_{r}\)crit explains 43% of the variability in asthma symptom scores, independent of all other variables measured in this study. A more negative \(X_{r}\) reflects a reduced apparent lung compliance; we propose that this reduced apparent compliance in NWC asthma is a consequence of greater peripheral airway closure and heterogeneity (30, 31) vs. WC asthma. This proposal is supported by our finding that the reduced \(X_{r}\)crit is linked with increased gas trapping (greater RV/TLC) and greater ventilation heterogeneity (\(S_{\text{cond}}\), \(S_{\text{acin}}\)).

Fig. 3. Association between 6-point Asthma Control Questionnaire score (ACQ6) and post-BD \(X_{r}\)crit using all subjects, \(P < 0.001\). The vertical dashed line indicates the \(X_{r}\)crit value that best distinguishes between NWC and WC asthma.
Taken together, our findings strongly suggest that the presence of peripheral airway heterogeneity and closure is a key identifiable feature of NWC asthma. Moreover, our study demonstrates that this distinguishing dysfunction persists, despite the dilatational forces on the airways provided by the parenchyma at “high” lung volumes (above closing volume), and the dilatational action of inhaled bronchodilator. It follows that the continued presence of elevated peripheral airway heterogeneity and closure at high lung volumes may represent a novel and powerful contributor to asthma control.

Reactance, airway heterogeneity, and closure. On the surface, the lowered (more negative) $X_r$ in NWC vs. WC asthma might appear to reflect a reduction in the intrinsic tissue compliance of the lung, for example, due to interstitial pulmonary fibrosis (48). However, in general, pulmonary fibrosis is not a phenomenon linked with asthma. Furthermore, lung pressure-volume relationships typically indicate normal lung compliance in asthma (5, 7, 18). Hence, a reduction in the intrinsic tissue compliance is an unlikely explanation for the reduced $X_r$ in NWC vs. WC asthma.

On the other hand, reactance is known to reflect the proportion of closed airways and the degree of peripheral airway heterogeneity by decreasing the apparent lung compliance (29–31) and effectively “hiding” regions of alveolar tissue. Indeed, the associations we report between $X_{r\text{crit}}$, $V_{ol\text{crit}}$, and measures of gas trapping (RV, RV/TLC) are consistent with the proposal that $X_r$ is sensitive to the proportion of closed or severely narrowed airways. RV reflects the portion of lung volume that cannot be passively expired and is influenced by lung elastic recoil and airway closure and narrowing (42). It follows that, in asthma, RV may be elevated due to either an increased susceptibility for airway closure (increased closing volume) or an increased presence of airways that remain functionally closed at all lung volumes (persistent airway closure). Importantly, the presence of functionally closed airways is unlikely to result in regional absorption atelectasis due to the presence of very slow ventilation or collateral ventilation, as has been demonstrated in chronic obstructive pulmonary disease (34).

The relative dominance of $X_r$ by airway mechanical dysfunction in the peripheral lung is supported by the demonstration that ventilation defects and altered $X_r$ measured in asthma subjects can be optimally recreated using mathematical modeling by invoking heterogeneous narrowing and closure of peripheral airways, as defined by airway generations 12–16 and below, $-0.2$–$2.0$ mm diameter (9, 47). This proposal is supported by the associations we observed between $X_{r\text{crit}}$ and ventilation heterogeneity measured via $S_{\text{acin}}$ and $S_{\text{cond}}$. While further validation is required, $S_{\text{cond}}$ theoretically reflects the heterogeneity in specific ventilation due to regional differences in pressure-volume characteristics (compliance), and $S_{\text{acin}}$ the asymmetry in lung structure at the acinar level (50). Both of these parameters may be influenced directly by heterogeneities in airway narrowing that results in either different time constants of ventilation ($S_{\text{cond}}$) or an elevation in acinar asymmetry ($S_{\text{acin}}$). In addition, the presence of large contiguous areas of airway closure and near closures (“ventilation defects”) may lead to an exacerbation of the pressure-volume heterogeneities within the lung and therefore act to indirectly elevate $S_{\text{cond}}$. The recently demonstrated relationship between airway closure visualized with SPECT and $S_{\text{cond}}$ supports this putative mechanism (17).

In summary, we interpret the reduced (more negative) $X_{r\text{crit}}$ in NWC vs. WC asthma as a reflection of a greater severity of peripheral airway closure and heterogeneous narrowing at high lung volumes in these patients.

Reactance and asthma control. The observation that $X_r$ is linked to asthma control when measured above closing volume suggests that the pulmonary deficit that contributes to symptoms is only made visible to the forced oscillation measurement when any additional “volume-dependent” dysfunction below closing volume is minimized. The insensitivity of $X_r$ at FRC to asthma control suggests that the factor driving poor control is not a reduced $X_r$ within the tidal breathing range per se; that is, patients may not explicitly sense low apparent compliance at FRC. In fact, we find a poor relationship between $X_{r\text{crit}}$ and $X_r$ at FRC ($R^2 = 0.07$, $P = 0.2$), presumably due to the highly variable position of FRC relative to $V_{ol\text{crit}}$ (post-BD $V_{ol\text{crit}} - $ FRC: WC = $0.23$ ± $0.22$, NWC = $0.66$ ± $0.18$ liters) and the profound effect of lung volume on $X_r$ below $V_{ol\text{crit}}$. We, therefore, infer that the highly variable peripheral airway dysfunction present at FRC, as evidence by the high slope of the $X_r$ vs. lung volume relationship near this lung volume reduces the specificity of $X_r$ at FRC to the important peripheral dysfunction exposed at higher lung volumes that is captured in the $X_{r\text{crit}}$ measurement.

We found that $X_{r\text{crit}}$ explains a greater proportion of the variability in asthma control when measured post-BD than when measured at baseline (43 vs. 28%, respectively; Table 2). Likewise, associations between ACQ and $V_{ol\text{crit}}$, $S_{\text{acin}}$, and $S_{\text{cond}}$ all strengthened following bronchodilator. This improvement occurred despite a minimal overall effect of bronchodilator on these variables in each group. The cause of the improved associations after bronchodilator may be due to the almost universal reduction in the within-group standard deviation in these measurements after bronchodilator (Table 2). Reduced variability following bronchodilator may be the result.

### Table 4. Receiver operator characteristic analysis

<table>
<thead>
<tr>
<th>Variable (Optimal Cutoff)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Area Under Curve</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_{r\text{crit}}$ (-1.23 cmH2O·l-1·s)</td>
<td>Post-BD 90</td>
<td>83</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V_{ol\text{crit}}$ (65.8% predicted TLC)</td>
<td>Post-BD 90</td>
<td>67</td>
<td>0.79</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$S_{\text{acin}}$ (0.20 liter-1)</td>
<td>Post-BD 90</td>
<td>67</td>
<td>0.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$S_{\text{cond}}$ (0.030 liter-1)</td>
<td>Post-BD 80</td>
<td>67</td>
<td>0.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1 (64.6% predicted)</td>
<td>Baseline 80</td>
<td>67</td>
<td>0.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV (126% predicted)</td>
<td>Post-BD 90</td>
<td>75</td>
<td>0.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV/TLC (42.6%)</td>
<td>Baseline 70</td>
<td>67</td>
<td>0.81</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Note: The optimal cutoff point for sensitivity and specificity was determined as the value that maximized both sensitivity and specificity (value closest to the optimal classification).
of improved test performance with familiarity of the test procedures; however, the lack of associations between the number of test protocols performed and the resulting Xrs and Volcrit at either baseline or after bronchodilator makes this proposal unlikely. Alternatively, it is also possible that some components of the ACQ score may more closely reflect the symptoms (and physiological deficits) that remain after bronchodilator is used to provide initial symptom relief, such as airway edema, remodeling, or inflammation. Similarly, bronchodilator and lung inflation may serve to remove mild constriction and thereby highlight more fixed pulmonary deficits, which may be responsible for ongoing symptoms.

Our finding that ACQ is associated with peripheral airway dysfunction in the forms of closure and heterogeneity is supported by previous work showing that increased closing volume is a risk factor for asthma exacerbations (24). Further support is provided by the previously demonstrated associations between asthma control and exacerbation rates with ventilation heterogeneity and RV/TLC (6). In addition, a more recent study has demonstrated a modest association between the change in ACQ following inhaled corticosteroid dose titration (up-titration or down-titration) and ventilation heterogeneity, specifically, Sacin ($R^2 = 0.13$) and Scond ($R^2 = 0.07$) (15). It follows that there is mounting evidence to support the relevance of peripheral airway heterogeneity and closure in asthma. Our study illuminates the importance of the airway heterogeneity and closure that remains, despite the bronchodilating actions of elevated lung volumes and airway smooth muscle relaxation.

Methodological considerations. A limitation of the present study is the use of a single excitation frequency (6 Hz) for the...
assessment of $X_r$ and the inherent inclusion of chest wall compliance in the $X_r$ measurement. It is well established that $X_r$ is frequency dependent (21), and, therefore, it is possible that the $X_r$-lung volume relationship may have improved sensitivity, if determined across multiple frequencies, as is possible with pseudorandom noise signals (36) or multifrequency sinusoidal signals (33). However, for simplicity, we chose to limit our present investigation to a single frequency. Furthermore, no alterations in chest wall compliance have been reported in asthma, such that our results are unlikely to be explained by a systematically lower chest wall compliance within the NWC asthma group. However, we cannot exclude the possibility that the elevated lung volumes in these subjects have caused some deformation of the chest wall that has lowered its compliance. Furthermore, pleural pressure, at or near TLC, has been reported to be less negative in moderate to severe asthma subjects compared with healthy controls and subjects with mild asthma (7, 18, 19, 53). However, this finding is not universal (5) and remains unexplained. If true, a less negative pleural pressure would result in a reduced airway distending pressure, which may contribute to the preponderance for airway closure at high lung volumes in NWC asthma.

Our study is also inherently limited by the lack of a true gold standard for defining asthma control. An ACQ6 score of $<1.0$ has been shown to discriminate between NWC and WC asthma when defined by a composite Global Initiative for Asthma/National Institutes of Health gold standard based on asthma symptom diaries and daily peak flow (26); this study reported that this ACQ6 cutoff score has a positive predictive value of 0.83 and a negative predictive value of 0.72 for detecting NWC asthma (26). We feel that major misclassification in the present study is unlikely, given that only 3/22 subjects in the present study had ACQ6 scores in the intermediate range of $0.7 \leq ACQ6 < 1.6$. Furthermore, an ACQ5 score $< 1$ (ACQ6 minus rescue inhaler use) was recently shown to be equivalent to a Global Initiative for Asthma definition of WC/partly controlled asthma and a GOAL (Gaining Optimal Asthma Control) definition of totally controlled/WC asthma (39).

We considered the possibility that the lower (more negative) $X_r$ at TLC in NWC vs. WC asthma may be driven by the greater hyperinflation (elevated resting lung volumes) present in NWC vs. WC asthma and thus the higher lung volumes at which the $X_r$ measurement is made (note: $X_r$ falls with increasing volume). However, the change in $X_r$ across the entire volume range from Vol$_{crit}$ to TLC is minimal ($\Delta X_r$ between Vol$_{crit}$ and TLC: WC = $-0.26 \pm 0.07$; NWC = $-0.57 \pm 0.56$ cmH$_2$O l$^{-1}$ s$^{-1}$) compared with the differences between groups. To illustrate this point, we note that $X_r$ in the NWC subjects is still considerably lower than $X_r$ at TLC in the WC subjects (NWC $X_r$ = $-2.02 \pm 0.20$ vs. WC $X_r$ = $-1.10 \pm 0.11$ cmH$_2$O l$^{-1}$ s$^{-1}$, $P < 0.001$), demonstrating that differences in lung inflation cannot account for the differences in $X_r$ between NWC and WC groups.

A final potential limitation of the present study was the difference in height between the WC and NWC groups. We accounted for this difference by including it as a covariate within the regression analysis; we found that height was not significantly associated with ACQ6 (univariate regression) and also did not explain any additional variance in ACQ6 that was not explained by $X_r$ (stepwise regression). In addition, we reexamined data from healthy controls (28) to assess whether height and/or gender might generally explain the intersubject variance in $X_r$ and Vol$_{crit}$. We found that $X_r$ was not significantly associated with height. However, height did explain 36% of the variance in Vol$_{crit}$ in controls ($R^2 = 0.355$, $P < 0.01$; Vol$_{crit} = -3.575 + 0.0384 \times$ height), a finding that may be expected, given the correlation between lung volumes and height (12). There was also no effect of gender on $X_r$ or Vol$_{crit}$. Thus it may be important to account for height when assessing the influence of Vol$_{crit}$ on clinical variables, but there is no evidence to suggest that height contributes significantly to $X_r$.

Clinical implications. Reduced apparent lung compliance that is likely due to airway dysfunction that remains at high lung volumes and following bronchodilator represents a novel contributor to asthma control and a major challenge for the treatment of NWC asthma. Inhaled rescue treatments and/or inhaled controller medications may be particularly ineffective in this group at improving symptoms on the basis that closed/narrowed airways may continue to remain undertreated with inhaled preventative treatments, unless they can be reopened or dilated. Our findings, therefore, highlight the need for novel alternative therapies or techniques that act to dilate persistently narrowed or closed airways to ultimately facilitate appropriate delivery of treatment and, potentially, to aid in the maintenance/achievement of asthma control.

Conclusion. The present study revealed a powerful association between asthma control and the mechanical properties of the lung periphery ($X_r$) that is independent of measurements of closing volume, inert-gas washout measures of airway heterogeneity ($S_{h}$ and $S_{c}$), lung volumes, and airflow obstruction (spirometry). Our data provide evidence that strongly suggests that NWC asthma is characterized by the presence of persistent airway closure and heterogeneous narrowing that persists, despite bronchodilation and the dilatational forces applied by the lung parenchyma at high lung volumes. By contrast, $X_r$ measured at FRC is not related to asthma control. Longitudinal clinical studies are warranted to assess the utility of $X_r$ to guide medical therapy and predict treatment outcomes in patients with asthma.

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