Nonreversible conductive airway ventilation heterogeneity in mild asthma

Sylvia Verbanck,1 Daniël Schuermans,1 Manuel Paiva,2 and Walter Vincken1
1Respiratory Division, Academic Hospital, Vrije Universiteit Brussel, 1090 Brussels; and 2Biomedical Physics Laboratory, Université Libre de Bruxelles, 1070 Brussels, Belgium

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Verbanck, Sylvia, Daniël Schuermans, Manuel Paiva, and Walter Vincken. Nonreversible conductive airway ventilation heterogeneity in mild asthma. J Appl Physiol 94: 1380–1386, 2003. First published December 6, 2002; 10.1152/japplphysiol.00588.2002.—A multiple-breath washout technique was used to assess residual ventilation heterogeneity in the conductive and acinar lung zones of asthmatic patients after maximal β2-agonist reversibility. Reversibility was assessed in 13 patients on two separate visits corresponding to a different baseline condition in terms of forced expiratory volume in 1 s (FEV1; average FEV1 over 2 visits: 92 ± 21% of predicted (SE)). On the visit corresponding to each patient’s best baseline, 400 μg salbutamol led to normal acinar ventilation heterogeneity, normal FEV1, and normal peak expiratory flow; i.e., none was significantly different from that obtained in 13 matched controls. By contrast, conductive ventilation heterogeneity and forced expiratory flow after exhalation of 75% forced vital capacity remained significantly different from controls (P ≤ 0.005 on both indexes). In addition, the degree of postdilation conductive ventilation heterogeneity was similar to what was previously obtained in asthmatic individuals with a 19% lower baseline FEV1 and twofold larger acinar ventilation heterogeneity (Verbanck S, Schuermans D, Noppen M, Van Muylem A, Paiva M, and Vincken W. Am J Respir Crit Care Med 159: 1545–1550, 1999). We conclude that, even in the mildest forms of asthma, the most consistent pattern of non-β2-agonist-reversible ventilatory heterogeneity is in the conductive lung zone, most probably in the small conductive airways.

bronchodilation; small airway

IT HAS BEEN SUGGESTED THAT in asthma, inflammatory and chronic structural changes potentially occur down to the level of the lung periphery (23), implicating also the alveolar ducts in the inflammatory process of the early asthma disease state (7). Novel drug delivery devices of anti-inflammatory medication claim enhanced peripheral deposition, assuming that the target is "the small airway" (15). Although the need for measurement of small airway function continues to be regularly emphasized (6, 10, 23, 25, 32), in vivo measurements of small airway alteration in the asthmatic patient remain sparse. Despite radiation exposure, high-resolution computed tomography probably provides the best noninvasive measure of structural alterations in different-sized airways (1, 25). Ventilation distribution tests are an attractive noninvasive alternative, and Woolcock (32) actually suggested the use of the vital capacity single-breath washout (SBW) for monitoring small airway function in the follow-up of asthma patients and their treatment.

Since the introduction of the vital capacity SBW test for epidemiological studies after the pioneering work of Cosio et al. (3), various theoretical and experimental studies have been conducted to investigate the actual role of the small airways in ventilation distribution tests in general. Regarding the phase III slope of a vital capacity SBW maneuver, it is intrinsically impossible to distinguish between ventilation heterogeneity originating from structural change at the first and the last branching generation of the human lung, unless tracer gases with different diffusivities are used. To further complicate the issue, airway closure, which has been suggested as an integral part of asthma (14), is also shown to contribute to the vital capacity SBW phase III slope (5). In this respect, abnormal vital capacity SBW N2 phase III slopes obtained by in ‘t Veen et al. (11) in individuals with severe asthma after inhalation of 400 μg salbutamol do point to a residual structural alteration but cannot be conclusive about the size of the airways involved. Other more sophisticated ventilation distribution studies, such as bolus studies (8) or N2-washout studies (16), also previously used to assess the asthmatic lung, essentially suffer from the same drawback that no distinction whatsoever can be made between structural changes occurring at different lung depths.

A phase III slope analysis of the multiple-breath washout (MBW), originally developed for the study of ventilation distribution in normal subjects by Crawford et al. (4), can distinguish ventilation maldistribution due to structural changes originating in the acinar vs. the conductive lung zone, i.e., with a cutoff around generation 15. The MBW phase III slope analysis is based on a model of convection and diffusion in a realistic human lung geometry (20). The conductive MBW index of ventilation heterogeneity relates to the proximal lung structure where convection dominates gas transport, and the acinar MBW index of ventilation...
heterogeneity relates to the peripheral lung where convection-diffusion interaction occurs. Experimental studies showing a differential response of proximal and peripheral MBW indexes to oleic acid-induced edema in mongrel dogs where indeed only the peripheral MBW index was affected (26), or actual correlations of the peripheral MBW index to histomorphometry in rats with induced emphysema (24), lend support to the potential of the MBW test.

A previous MBW study in 20 patients with moderate asthma indicated structural abnormality at the level of both the acinar and conductive lung zones (28). At both these levels, abnormalities were partly reversible after inhalation of 400 µg salbutamol, yet none of the spirometric nor ventilation heterogeneity indexes under study was fully reversed to normal values. Possibly, the degree of reversibility observed in that study may have been influenced by the baseline spirometry and ventilation heterogeneity of the asthma patients on the study day or by the variability of aerosol delivery characteristics. Neither source of variability had been explicitly explored in that study, and both are in fact rarely considered in any study involving asthmatic patients. In the present work, we investigated the maximum possible reversibility in an experimental setting where variability of aerosol delivery was minimal, intrasubject variability of the asthma patient’s baseline condition was taken into account, and state-of-the-art ventilation distribution tests were used. We also deliberately included individuals with mild asthma so as to maximize the chances of complete reversibility. We hypothesized that if optimal β2-agonist agonist reversibility could be realized in asthma patients under the best of two baseline conditions, a distinctive pattern might be revealed of a residual non-β2-agonist reversible obstruction with a predominantly acinar or conductive component that would then constitute the target for anti-inflammatory medication or any other drug aimed at prevention of remodeling of the asthmatic lung. As this study will show, it is the conductive airways’ contribution to ventilation heterogeneity that shows a distinct failure to normalize after bronchodilation even in individuals with mild asthma, its magnitude being actually similar to the postdilation conductive abnormality previously observed in individuals with moderate asthma (28).

MATERIALS AND METHODS

Spirometry and ventilation distribution testing. Baseline spirometry was obtained by means of standardized equipment (Vmax 20C, SensorMedics Bilthoven, The Netherlands) reporting forced expired volume in 1 s (FEV1), peak expiratory flow (PEF), forced vital capacity (FVC), and forced expiratory flow after exhalation of 75% FVC (FEF75). The MBW test was carried out with a computer-controlled breathing assembly in which data acquisition, pneumatic valve control, and visual feedback to the subjects are handled by Labview software (National Instruments, Austin, TX).

The MBW indexes, Scond and Scanin, were essentially the conductive and acinar components of ventilation heterogeneity, respectively, derived from the normalized phase III slope analysis. During each expiration, the N2 phase III slope is normalized by the mean expired N2 concentration, leading to an increasing normalized slope as a function of breath number or lung turnover; lung turnover is determined as the cumulative expired volume over functional residual capacity (FRC). In such curves, Sacin is computed as the normalized phase III slope of the first MBW expiration minus a correction term to discard any conductive lung zone contribution; this correction term equals the lung turnover corresponding to the first breath multiplied by Scond. Scond is computed as the rate of normalized phase III slope increase as a function of lung turnover, between 1.5 and 6 lung turnovers (without any correction because there is no acinar lung zone contribution in this part of the MBW). The theory of the phase III slope analysis has been previously described (29), and it implies that ventilation heterogeneity can be attributed to different lung levels and that Scond and Scanin are intrinsically independent. Because Scond and Scanin are derived from phase III slopes, their values increase when ventilation heterogeneity increases. In particular, Scanin will increase in value if ventilation heterogeneity is increased in the acinar lung zone, due to an alteration of the intra-acinar asymmetry, before the theory of flow asynchrony. On the other hand, Scond will increase if the conductive airways and their subtended units undergo differences in specific ventilation and deflate in asynchrony, such that the best ventilated unit empties first preferentially early in expiration.

Reversibility testing. A computer-controlled aerosol delivery setup previously used for aerosol bolus experiments (24) was adapted to incorporate a 750-ml spacer (Volumatic, GlaxoSmithKline, Research Triangle Park, NC) and a pressurized metered-dose inhaler (100 µg hydrofluoroalkane-Ventolin, GlaxoSmithKline, Research Triangle Park, NC). The spacer was coated with an anionic detergent, diluted in water 1:2,500 according to recommendations (21), and dried during the night preceding the day of reversibility testing (only 1 reversibility test on any given day). The timing of the salbutamol aerosol release into the spacer and inhalation with respect to the patient’s breathing pattern was strictly controlled: the residence time of the 100-µg aerosol in the spacer was invariably 3 s, and the time between onset of aerosol inspiration and end of the end-inspiratory breath hold was fixed at 20 s. The reversibility protocol started with baseline spirometry and three MBW tests, after which two 100-µg puffs were administered via the spacer-incorporated salbutamol delivery setup (1 inhalation maneuver per 100-µg puff). After exactly 10 min, only spirometry was recorded and a second batch of two 100-µg puffs was delivered in an identical fashion. After another 10-min interval, spirometry was repeated and three MBW tests were carried out.

Patients. The study protocol was approved by the local ethics committee. The 15 patients participating in this study had a clinical history of asthma (>2 yr) and had shown, in the 2-yr period before testing, a positive histamine provocation test or a baseline obstruction with >10% of predicted FEV1 reversibility. Five patients were receiving maintenance treatment (inhaled corticosteroids with or without long-acting bronchodilators), whereas the remaining ten only used salbutamol as rescue medication. All asthma patients were never-smokers. After having obtained informed consent, we requested all patients to withdraw from any medication 12 h before the time of study. Each patient was asked to come to the laboratory for up to 3 separate days at the same time of the day to study the influence of intrasubject baseline variability on reversibility, under experimental conditions that guaranteed minimal variability of the salbutamol aerosol delivery itself. Visit 1 included baseline spirometry and venti-
loration distribution measurement followed by reversibility testing with salbutamol according to the above-described procedure. If, on visit 2, baseline spirometry (FEV₁, PEF, FEF₇₅) or ventilation distribution (S.cond, S.acin) differed from visit 1 by more than preset margins, reversibility was studied again in an identical fashion to what was done during visit 1. If the patient showed a baseline spirometry and ventilation distribution within the preset margins from visit 1 for all five parameters, reversibility testing was not included in visit 2 and the patient was asked to come back for a third visit, again at the same time of day, to undergo the same reversibility protocol as on visit 1.

Margins on FEV₁, PEF, FEF₇₅, S.cond, and S.acin were established from variability of baseline spirometry and ventilation distribution data previously obtained from 35 nonhyperresponsive never-smoker subjects assessed on 2 separate days in a study comparing different bronchial challenge agents (30). The average intrasubject standard deviation from the two repeat measures for each parameter from these 35 subjects was doubled to provide the margins on FEV₁ (6% of predicted), PEF (8% of predicted), FEF₇₅ (12% of predicted), and with use of these margins, nine asthma patients showed sufficient intervisit intrasubject variability over two visits. Of the six remaining patients who were due to come back for a third visit, two did not return. In this way, 13 asthma patients completed the entire reversibility study, including intrasubject variability.

By imposing baseline intervisit intrasubject variability in this manner, we wanted to avoid that any outcome related to variability (e.g., whether intervisit intrasubject baseline FEV₁ variability persists after bronchodilation) would be biased by including also patients with similar baseline on the two visits under study. Throughout the study, the two visits will be termed “best” and “worst” visit by considering the visit corresponding to respectively the highest and lowest baseline FEV₁ value (where the baseline FEV₁ value during any given visit is selected on basis of European Respiratory Society criteria, i.e., obtained from the best of 3 spirometric curves). All patients accepted in this study had an FEV₁ ≥ 70% of predicted on their best visit.

Control subjects. To establish the degree of spirometric and ventilation distribution abnormality after bronchodilation of the 13 asthma patients who completed the study (7 women and 6 men, age range 25–48 yr), a group of 13 gender- and age-matched never-smoker subjects was recruited to provide reference values. After the baseline MBW measurements, all subjects were checked for absence of bronchial hyperresponsiveness to histamine before being included in the control group (<20% decrease in FEV₁ after 2-mg cumulative dose histamine). We also verified a posteriori that FRC was not significantly different between asthmatic and control subjects.

Statistical analysis. With use of Statistica 5.1 (StatSoft, Tulsa, OK), nonparametric tests were performed to detect differences between asthmatic individuals and matched controls (Mann-Whitney), to test for the significance of postdilation changes on any given visit or for difference in baseline (or dilation) between best and worst visit on the same patients (Wilcoxon), and to assess potential correlations between dilation change and baseline (Spearman rank). The significance level was set at P = 0.05.

RESULTS

Spirometry was measured at baseline, after a cumulative dose of 200 µg salbutamol, and after a cumulative dose of 400 µg salbutamol. After 200 µg salbutamol, FEV₁ and FEF₇₅ amounted to 98 ± 3 (SD) and 95 ± 10% of their respective value obtained after 400 µg salbutamol. With ventilation distribution only assessed after 400 µg salbutamol, all of the following dilation results relate to spirometric and ventilation distribution results obtained after the 400-µg dose.

The 13 asthma patients participating in this study were characterized by mean baseline values of FEV₁ = 92 ± 21% of predicted (SD) and FEV₁/FVC = 70 ± 13%, averaged over two visits. We then considered each visit separately and classified either visit as best or worst visit according to the patient’s baseline state assessed in terms of FEV₁. On their best visit, the 13 asthma patients had an average FEV₁ of 96.6% of predicted (range 70–130% of predicted). When considering the same 13 patients on their worst visit, average FEV₁ was 87.1% of predicted (range 39–118% of predicted). Thus, depending on the day of study, these patients would be roughly classified as mild or mild-to-moderate asthma patients (18). Table 1 shows average baseline and postdilation FEV₁, FVC, PEF, FEF₇₅, S.cond, and S.acin values obtained on the best and worst visit. For example, on average, the baseline FEV₁ differed by 9.5% of predicted between best and worst visit, a highly significant difference (P = 0.002) due to this way of

Table 1. Spirometry and ventilation distribution data obtained on all asthma patients on two visits each, with visits classified as “best” or “worst” according to baseline FEV₁ and corresponding dilation

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<th>Baseline Value</th>
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<td>Worst visit</td>
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<td>FEV₁, %pred</td>
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<td>87.1 ± 6.2</td>
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<td>FVC, %pred</td>
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<td>107.2 ± 4.1</td>
<td>112.9 ± 3.4</td>
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<td>PEF, %pred</td>
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<td>87.1 ± 5.5</td>
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<td>FEF₇₅, %pred</td>
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<td>44.9 ± 8.7</td>
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<td>S.cond, liter⁻¹</td>
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<td>0.072 ± 0.009</td>
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<td>S.acin, liter⁻¹</td>
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<td>0.113 ± 0.019</td>
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Values are means ± SE for 13 asthma patients. Best and worst visit, visit corresponding to, respectively, best and worst baseline FEV₁ for each patient (see text for details). FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF₇₅, forced expiratory flow after exhalation of 75% of FVC; S.acin, S.cond, multiple-breath washout indexes of acinar and conductive lung zone ventilation heterogeneity, respectively (see text for details); P values indicate the significance of differences between each patient’s worst and best baseline, or between corresponding dilation values. *Significant difference between baseline and dilation on worst visit, P < 0.05. †Significant difference between baseline and dilation on best visit, P < 0.05.

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classifying the visits. The parameters in Table 1 other than FEV\textsubscript{1} showed a consistent picture of generally higher PEF, FVC, and FEF\textsubscript{75} values and lower \( S_{\text{cond}} \) and \( S_{\text{acin}} \) values on the best visit, with a difference between best and worst visits still reaching significance on all five parameters at baseline (baseline values of Table 1). After bronchodilation (postdilation values in Table 1), the visit corresponding to the best baseline FEV\textsubscript{1} also led to the best postdilation FEV\textsubscript{1}, with a significant intrasubject intervisit average difference still amounting to 6.6% of predicted (\( P = 0.01 \)). The same tendency was seen for postdilation FVC (\( P = 0.02 \)), FEF\textsubscript{75} (\( P = 0.02 \)), and \( S_{\text{cond}} \) (\( P = 0.03 \)), maintaining significant intrasubject intervisit differences. By contrast, the intrasubject intervisit baseline PEF and \( S_{\text{acin}} \) differences completely disappeared after bronchodilation.

Despite the inability of the \( \beta_2 \)-agonist to completely abolish residual intrasubject intervisit variability in FEV\textsubscript{1} and \( S_{\text{cond}} \) (postdilation values in Table 1), it did elicit FEV\textsubscript{1} and \( S_{\text{cond}} \) responses that depended on baseline smooth muscle tone, with the greatest dilation obtained for the worst baseline FEV\textsubscript{1} or \( S_{\text{cond}} \) value. Indeed, by using two data points per patient on all 13 patients, significant correlations were found between \( S_{\text{cond}} \) changes (i.e., \( S_{\text{cond}} \) after 400 \( \mu \)g minus \( S_{\text{cond}} \) at baseline) and baseline \( S_{\text{cond}} \) (\( r = -0.81; P < 0.001 \)); the corresponding correlation for FEV\textsubscript{1} was \( r = -0.65 \) with \( P < 0.001 \). By contrast, bronchodilator \( S_{\text{cond}} \) or FEV\textsubscript{1} response did not correlate significantly with postdilation \( S_{\text{cond}} \) or FEV\textsubscript{1}. Finally, the \( \beta_2 \)-agonist also elicited greater \( S_{\text{acin}} \) reversibility when baseline \( S_{\text{acin}} \) was greater (\( r = -0.81; P < 0.001 \)).

Figure 1 represents all individual data points obtained for the five parameters of Table 1 (except for FVC). Data were again classified in terms of worst (○) and best (●) visit. The most relevant comparison in Fig. 1 was between the asthmatic individuals on their best visit after optimal \( \beta_2 \)-agonist reversibility (individual data: ●; corresponding average: ● ± SD) and the reference values from the matched controls (horizontal bar ± SD). This comparison revealed that after maximal \( \beta_2 \)-agonist reversibility, the asthmatic individuals showed significantly lower FEF\textsubscript{75} [78.0 ± 11.2 (SE) vs. 102.7 ± 6.2% of predicted; \( P = 0.005 \)] and significantly higher \( S_{\text{cond}} \) [0.043 ± 0.003 (SE) vs. 0.030 ± 0.001 liter\textsuperscript{-1}; \( P < 0.001 \)] than matched controls. By contrast, postdilation FEV\textsubscript{1}, PEF, and \( S_{\text{acin}} \) values in the asthmatic individuals were indistinguishable from the matched controls (\( P > 0.1 \) for all). Figs. 1A and 1B are representative of all 13 asthmatic individuals before and after postdilation salbutamol on "worst" (○) and "best" (●) visit, where the best visit and worst visit are determined on the basis of baseline FEV\textsubscript{1} (see text for details). Also represented is the average value (● ± SD) corresponding to the postdilation data from the 13 asthmatic individuals on their best visit, for comparison with the reference values obtained from 13 matched control subjects (horizontal bar ± SD). %pred, Percentage of predicted value.
nally, we repeated the same comparison after removing the three patients from the asthma group who were receiving maintenance steroid treatment. The comparison of the remaining 10 asthmatic subjects with the corresponding 10 matched controls led to the same conclusions: normal postdilation values with respect to controls for FEV\textsubscript{1} [110.1 ± 4.0 (SE) vs. 113.3 ± 3.3% of predicted; \(P > 0.1\)], PEF [102.3 ± 3.8 (SE) vs. 105.0 ± 5.2% of predicted; \(P > 0.1\)], and \(S_{\text{acín}}\) [0.065 ± 0.009 (SE) vs. 0.070 ± 0.009 liter\(^{-1}\); \(P > 0.1\)], and abnormal with respect to control values for FEF\textsubscript{75} [86.0 ± 13.0 (SE) vs. 104.1 ± 7.8% predicted; \(P = 0.04\)] and \(S_{\text{cond}}\) [0.040 ± 0.002 (SE) vs. 0.029 ± 0.002 liter\(^{-1}\); \(P = 0.003\)].

**DISCUSSION**

The foremost important finding of the present study is the considerable abnormality of ventilatory heterogeneity in the conductive airways of asthmatic patients, persisting after bronchodilation with a \(\beta\text{-agonist}\) (Fig. 1). This was the case, despite a relatively mild baseline obstruction in these patients and despite a mode of salbutamol aerosol administration designed to maximize any possible \(\beta\text{-agonist}\) reversibility. The fact that \(S_{\text{cond}}\) had been previously shown to return to normal values with 200 \(\mu\)g salbutamol after a twofold increase after a histamine challenge in otherwise normal nonhyperresponsive subjects (29) indicates that \(S_{\text{cond}}\) is able to respond to such stimuli. The incomplete reversal of \(S_{\text{cond}}\), even in this group of relatively mildly asthmatic subjects in whom \(S_{\text{acín}}\) could be completely recovered, is therefore thought to be a true effect. Although the FEF\textsubscript{75} deficit after salbutamol suggests that there is a non-\(\beta\text{-agonist}\)-reversible component of abnormality in the small airways, the abnormal \(S_{\text{cond}}\) locates this abnormality within the conductive zone of the small airways. Such an observation implies that drugs aimed at the relief of the non-\(\beta\text{-agonist}\)-reversible component in mild asthma should be preferentially targeted to the small conductive airways. This corresponds to a volumetric lung depth for drug delivery of no more than ~200 ml, with all the more peripherally located air spaces being particularly prone to unwanted side effects.

The decreased intrasubject variability after dilation (Table 1) makes it more meaningful to compare our data with those previously obtained after dilation. In doing so, it is interesting to note that the average \(S_{\text{cond}}\) value after 400 \(\mu\)g salbutamol obtained here [0.050 ± 0.004 (SE) liter\(^{-1}\)] is almost identical to that previously obtained after 400 \(\mu\)g salbutamol [0.049 ± 0.004 (SE) liter\(^{-1}\)] in a group of moderate-asthma patients characterized by an 19% of predicted lower baseline FEV\textsubscript{1} (28). This suggests a pathophysiological picture of the mild-to-moderate asthmatic lung with a persistent structural alteration in the conductive zone of the small airways that could be present from very early on in the disease process. A large cohort study of children in US cities followed up between the ages of 6 and 18 yr is consistent with early involvement of the small airways in asthma because a clear-cut forced expiratory flow after exhalation of 25–75% FVC deficit (15–20% lower at age 18 yr) in asthmatic vs. nonasthmatic children (FEV\textsubscript{1} deficit was 5–7% at age 18 yr) is shown (9).

It had been suggested that, even in the early stages of asthma, structural abnormality may be present as peripherally as the alveolated air spaces (6). The \(S_{\text{acín}}\) data in Fig. 1 indicate that acinar ventilation heterogeneity can be fully reversible by a \(\beta\text{-agonist}\) in mild asthma. This indicates that smooth muscle constrictions in the first acinar airway generations (terminal, respiratory bronchioles) was the major determinant of \(S_{\text{acín}}\). In our patients, further supported by a consistent pattern of larger \(S_{\text{acín}}\) reversibility for a greater baseline \(S_{\text{acín}}\). By contrast, a previous study with subjects with moderate asthma (with a 19% lower baseline FEV\textsubscript{1}) showed a greater acinar abnormality (on average \(S_{\text{acín}}\) was double that obtained in the present group) that was only partly reversible (28). Hence, the appearance of non-\(\beta\text{-agonist}\)-reversible structural impairment at the acinar level of the lung periphery may just depend on the definition of “early disease.” An interesting point of comparison with respect to \(S_{\text{acín}}\) obtained in asthmatic individuals can be found in a ventilation distribution study in asthmatic children by Cooper et al. (2). Because these authors used a \(N_2\) SBW maneuver that did not include volumes below FRC at inhalation, their phase III slopes can be roughly considered as a surrogate for \(S_{\text{acín}}\). Cooper et al. showed that, of all the asthmatic children under study, the patients with abnormally steep \(N_2\) phase III slopes were also those patients having shown the most severe clinical course over the year preceding the study. This finding at least points to \(S_{\text{acín}}\) as one major determinant of disease severity (the contribution from \(S_{\text{cond}}\) to those single-breath phase III slopes being negligible). Taken together with our observation that a previous group of asthma patients with a 19% lower FEV\textsubscript{1} were characterized by a twofold greater \(S_{\text{acín}}\) but similar \(S_{\text{cond}}\) (28) with respect to the present group of mildly asthmatic individuals, this leads to the intriguing hypothesis that \(S_{\text{acín}}\) may be related to disease severity, whereas \(S_{\text{cond}}\) appears to result from a more consistent abnormality, present even in mild degrees of asthma.

Studies of lung mechanics with different degrees of invasiveness and sophistication have reached conclusions that concur, at least in part, with our ventilation distribution findings in mildly asthmatic individuals during near-tidal breathing. Yanai et al. (33) used a catheter-tipped micromanometer wedged into the right upper lobe of patients breathing normally at FRC in the sitting position. Although they found no changes in central resistance, significant increases in peripheral resistance were present, but only in individuals with moderate-to-severe asthma (average FEV\textsubscript{1}: 54% of predicted). The authors conceded that their technique may have been less sensitive to subtle peripheral changes than the wedged-bronchoscope technique used by Wagner et al. (31). With subjects supine and breath holding...
at FRC, these authors found a sevenfold increase in peripheral lung resistance in individuals with mild asthma (mean FEV₁: 95% of predicted), part of which could have been exaggerated by the supine posture, but that was essentially attributed to peripheral airway narrowing and/or closure (derecruitment). With a slightly modified technique, Kaminsky et al. (13) found a higher peripheral resistance and lower peripheral compliance in asthmatic vs. normal individuals. These observations were interpreted to reflect narrowing and/or closure of peripheral collateral airways, thought to be located in the bronchioles and alveolar ducts, and a stiffening or derecruitment of distal parenchymal units. Finally, lung impedance measurements by Kaczkka et al. (12) showed that in mildly asthmatic subjects (mean FEV₁ = 97% of predicted) both airway and tissue properties can respond to salbutamol.

Overall, these findings of abnormal peripheral lung mechanics and β₂-agonist reversibility elicited down to the lung parenchyma in asthmatic individuals with close to normal FEV₁ can be brought into agreement with our findings if we consider that, whatever the exact nature of the structural changes, they will probably occur in a heterogeneous way across the lung. At the level of the acinar lung zone, this will effectively change the asymmetry of subtended intra-acinar units, which would affect Sacin. At the level of the conductive lung zone, possibly small airways just proximal to the acinar entrance, heterogeneity would result in unequal narrowing of parallel units and affect Scond. Although the non-β₂-agonist-reversible Scond could potentially be increased by heterogeneity originating in large and small conductive airways, the combination of an abnormal Scond with abnormal FEF 75% but normal PEF (Fig. 1) does suggest the predominant involvement of the smaller conductive airways. However, conclusions about the exact airway size within the conductive airway tree based on comparison of indexes of heterogeneity, such as Scond, and spirometric indexes reflecting overall change, such as FEF 75%, may not be unequivocal. Possibly, the additional measurement of frequency dependence of dynamic lung function, which is thought to be particularly sensitive to structural heterogeneity at different lung depths (17), could confirm the involvement of the small conductive airways in the mildly asthmatic lung.

Considering that asthma is tagged as variable airways obstruction, we also wanted to consider the variability of intrasubject reversibility in this experimental setting with minimal instrumental variability in terms of aerosol delivery. If, for instance, intrasubject visit differences were solely due to variability in reversible smooth muscle constriction, these differences should be entirely abolished by optimal β₂-agonist delivery. This was true for Sacin, showing an association between baseline and dilation change and disappearance of intervisit Sacin differences after dilation. In fact, not only were intervisit Sacin differences abolished but also Sacin was normalized after dilation, suggesting that reversible smooth muscle constriction was the main determinant of structural alterations in the first acinar generations of these asthmatic patients. The association between baseline Scond and dilation change indicates that Scond behavior was also partly determined by variable smooth muscle tone in the conductive airways. However, the abnormal postdilation Scond (Fig. 1) with residual intervisit intrasubject variability (postdilation values in Table 1) points to another source of variable conductive airways malfunction.

Richmond et al. (22) observed considerable intrasubject intervisit variability of inflammatory cells retrieved from endobronchial biopsies on two visits in 12 mildly asthmatic patients (mean post-salbutamol FEV₁: 92% of predicted). Although the actual correlation between FEV₁ and inflammatory cells was not addressed in that study, others have demonstrated the potential for an association between wall thickness of large airways (the apical bronchus) and FEV₁, even in mildly asthmatic individuals (19). In fact, the 7% of predicted difference between best and worst post-salbutamol FEV₁ computed from the data provided in Richmond et al. compares well with the 6.6% of predicted difference obtained here (Table 1). The residual intervisit intrasubject variability in Scond (and PEF 75%), paralleling FEV₁ variability in the present study, suggests that inflammation as a source of non-β₂-agonist-reversible variability could also be present in the smaller airways of the conductive airway tree.

In summary, the present study used the noninvasive MBW test to demonstrate that the most consistent structural impairment encountered in asthma, however mild, is located in the conductive airways. In this respect, the main target for other bronchodilator drugs (e.g., anticholinergics or methylxanteines), anti-inflammatory medication (e.g., inhaled corticosteroids or antileukotrienics), or any other drug aimed at prevention of remodeling of the asthmatic lung from its earliest stages on should not include the acinar lung zone. In more advanced, moderate asthma, an additional benefit could be gained from a MBW assessment of possible abnormality in the acinar lung zone before adding it to the target zone for drug delivery.

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