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Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation

Ronald L. Sorkness,[1] Eugene R. Bleecker,[2] William W. Busse,[1] William J. Calhoun,[3,4] Mario Castro,[5] Kian Fan Chung,[6] Douglas Curran-Everett,[7] Serpil C. Erzurum,[8] Benjamin M. Gaston,[9] Elliot Israel,[10] Nizar N. Jarjour,[1] Wendy C. Moore,[2] Stephen P. Peters,[2] W. Gerald Teague,[11] and Sally E. Wenzel,[7] for the National Heart, Lung, and Blood Institute Severe Asthma Research Program

[1]*University of Wisconsin, Madison, Wisconsin;* [2]*Wake Forest University, Winston-Salem, North Carolina;* [3]*University of Pittsburgh, Pittsburgh, Pennsylvania;* [4]*University of Texas Medical Branch, Galveston, Texas;* [5]*Washington University, St. Louis, Missouri;* [6]*Imperial College, London, United Kingdom;* [7]*National Jewish Medical and Research Center, Denver, Colorado;* [8]*Cleveland Clinic, Cleveland, Ohio;* [9]*University of Virginia, Charlottesville, Virginia;* [10]*Brigham & Women's Hospital, Boston, Massachusetts;* and [11]*Emory University, Atlanta, Georgia*

Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Curran-Everett D, Erzurum SC, Gaston BM, Israel E, Jarjour NN, Moore WC, Peters SP, Teague WG, Wenzel SE; for the National Heart, Lung, and Blood Institute Severe Asthma Research Program. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* 104: 394–403, 2008. First published November 8, 2007; doi:10.1152/japplphysiol.00329.2007.—Five to ten percent of asthma cases are poorly controlled chronically and refractory to treatment, and these severe cases account for disproportionate asthma-associated morbidity, mortality, and health care utilization. While persons with severe asthma tend to have more airway obstruction, it is not known whether they represent the severe tail of a unimodal asthma population, or a severe asthma phenotype. We hypothesized that severe asthma has a characteristic physiology of airway obstruction, and we evaluated spirometry, lung volumes, and reversibility during a stable interval in 287 severe and 382 nonsevere asthma subjects from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. We partitioned airway obstruction into components of air trapping [indicated by forced vital capacity (FVC)] and airflow limitation [indicated by forced expiratory volume in 1 s (FEV_1)/FVC]. Severe asthma had prominent air trapping, evident as reduced FVC over the entire range of FEV_1/FVC. This pattern was confirmed with measures of residual lung volume/total lung capacity (TLC) in a subgroup. In contrast, nonsevere asthma did not exhibit prominent air trapping, even at FEV_1/FVC <75% predicted. Air trapping also was associated with increases in TLC and functional reserve capacity. After maximal bronchodilation, FEV_1 reversed similarly from baseline in severe and nonsevere asthma, but the severe asthma classification was an independent predictor of residual reduction in FEV_1 after maximal bronchodilation. An increase in FVC accounted for most of the reversal of FEV_1 when baseline FEV_1 was <60% predicted. We conclude that air trapping is a characteristic feature of the severe asthma population, suggesting that there is a pathological process associated with severe asthma that makes airways more vulnerable to this component.

airway closure; difficult asthma; fixed obstruction

SEVERE ASTHMA, broadly defined as asthma that is poorly controlled chronically and refractory to treatment, includes only 5–10% of persons with asthma but accounts for disproportionate asthma-related morbidity, mortality, and utilization of health care resources (31, 34, 39, 48). Although those classified as severe asthma subjects may have more airway obstruction as measured by spirometric variables compared with asthma subjects not classified as severe (10, 33, 41), it is not clear whether the severe asthma group has a distinguishing physiological profile vs. representing a sampling from the more severe tail of the inclusive asthma population. Moore and colleagues (33) compared subjects classified as having severe asthma with subjects having moderate asthma, defined as those with forced expiratory volume in 1 s (FEV_1) <80% predicted and treated with inhaled corticosteroids, but not meeting the criteria for severe asthma. These groups were not statistically different with regard to FEV_1, but the forced vital capacity (FVC) was significantly lower in the severe group compared with the moderate group (33), suggesting that the pattern of airway obstruction might be different in severe asthma.

Asthma patients with a history of frequent exacerbations have more airway closure, as measured by elevated closing capacities during stable periods (17) and by relatively greater changes in FVC in response to inhaled histamine challenge (13). Gibbons and colleagues (13) presented the concept that the FEV_1 is sensitive to both airway narrowing and airway closure and that the airway closure component can be evaluated from changes in the FVC, while FEV_1/FVC ratio evaluates the airway narrowing component. They argued that airway closure is a more dangerous type of airway obstruction and that evaluating changes in FVC may reveal information about the underlying asthma pathophysiology that is not apparent from the changes in FEV_1.

We hypothesized that airway closure/near closure is a distinguishing physiological characteristic of severe asthma. Developing further the concept of Gibbons et al. (13), we show that alterations in FEV_1 can be partitioned quantitatively into components of airflow limitation and air trapping, and we evaluate the relative contributions of these components to the airway obstruction of severe vs. nonsevere asthma.

METHODS

Study subjects. The Severe Asthma Research Program (SARP) is a multicenter asthma research group funded by the National Heart, Lung, and Blood Institute (49). Ten SARP sites enrolled subjects for

the purpose of investigating severe asthma and contributed a standardized set of data to a central data coordinating center, with the goal of creating a database of characteristics of a large number of subjects with severe asthma during a period of stable disease. All procedures were approved by site-specific institutional review boards, as well as an independent data safety monitoring board. After providing written informed consent, subjects with physician-diagnosed asthma or with normal airways completed clinical questionnaires and baseline spirometry that were used to determine the severity group classifications. Exclusion criteria were current smoker or >5 pack-year previous smoking; diagnosis of vocal cord dysfunction, chronic obstructive pulmonary disease, cystic fibrosis, or congestive heart failure. General characteristics of the SARP cohort have been summarized previously for the asthma subjects in the age <18 yr subgroup (10) and for the initial 438 asthma subjects >12 yr of age (33). The present study includes 669 subjects with asthma and 85 subjects with normal airways, all age ≥18 yr and included in the SARP database as of December 2006.

Severity group classification. The consensus definition for refractory asthma (Table 1) from the American Thoracic Society (ATS) Workshop on Refractory Asthma (2) was used to determine the severity classifications. Subjects who met at least one of the major criteria and two of the minor criteria were classified as having "Severe asthma." All the subjects with asthma who did not meet the criteria for severe asthma were classified as having "Nonsevere asthma" for this study. Subjects were classified as having "No asthma" if they reported no asthma symptoms or diagnosis, had <20% decrease in FEV_1 with aerosolized methacholine challenge up to 25 mg/ml, and had no other significant health problems.

Physiological measurements. Spirometry, plethysmographic lung volumes, methacholine challenges, and maximum bronchodilation procedures were conducted among the SARP sites according to a SARP Manual of Procedures, which conformed with ATS guidelines for spirometry (32), methacholine challenge (7), and lung volumes measurements (46). For plethysmographic lung volumes, a pant rate of <1 Hz was used during the mouthpiece occlusion, which was activated after the subject had attained a stable end-expiratory volume for at least 4 breaths; after the brief occlusion, subjects exhaled maximally to residual lung volume (RV) and then inhaled maximally to total lung capacity (TLC). Subjects withheld short-acting β-agonist treatments for 4 h, long-acting β-agonist treatments for 12 h, and other medications (theophylline, anticholinergics, leukotriene modifiers, antihistamines, caffeine, alcohol) for an appropriate length of time to avoid interference with the spirometry, methacholine, or lung volumes measurements, unless required to manage asthma symptoms. Subjects were questioned regarding adherence to medication holds, and regarding current asthma symptoms and recent respiratory infections or systemic corticosteroid use, and the studies were delayed or rescheduled if necessary to ensure that the subjects were in a stable state and that the measurements were obtained with safety and validity. Methacholine challenges were administered using the five-breath dosimeter method, and the concentration associated with a 20% decrease in FEV_1 (PC_{20}) was computed by interpolation of the FEV_1 vs. log methacholine concentration plot (7). Methacholine was not administered if the prechallenge FEV_1 was <50% predicted (Prd). Maximal bronchodilation was induced with albuterol via metered dose inhaler equipped with a spacer chamber, measuring FEV_1 before and 15 min after four, six, and a maximum of eight total puffs (720 µg). The final two puffs of albuterol were excluded if the incremental change in FEV_1 after six puffs was ≤5% higher than the FEV_1 after four puffs. Maximal FEV_1, FVC, and FEV_1/FVC were recorded as percent predicted (%Prd) and as the fractional changes relative to the baseline spirometry values obtained after bronchodilator medications had been withheld for an appropriate time. Predicted values for FEV_1, FVC, FEV_1/FVC ratio, forced expiratory flow rate at 25–75% FVC (FEF_{25-75}), and peak expiratory flow rate (PEF) were computed using the equations of Hankinson et al. (15). Predicted values for TLC, functional residual capacity (FRC), FRC/TLC ratio, RV, RV/TLC ratio, and the 95th percentile for RV/TLC were computed using the equations of Stocks and Quanjer (38), with adjustments for African-Americans per ATS recommendations (1).

Partitioning FEV_1 into volume and airflow components. The FEV_1 is a highly reproducible measurement that is sensitive to changes in vital capacity or maximal expired airflow. While of considerable value as an independent variable for diagnosis and monitoring of lung disease, FEV_1 is a nonspecific measure. We suggest that FEV_1 may be treated as a dependent variable, partitioned quantitatively into its components of vital capacity and airflow. By evaluating these components individually, additional information regarding the underlying mechanisms of airway obstruction may be gained (13).

Algebraically:

$$FEV_1 = FVC \times FEV_1/FVC \qquad (1)$$

Dividing both sides of the equation by predicted FEV_1 (FEV_1Prd) and predicted FVC (FVCPrd) and multiplying both sides by 100 yields

$$100(FEV_1/FEV_1Prd)/FVCPrd$$
$$= 100(FVC/FVCPrd) \times (FEV_1/FVC)/(FEV_1Prd) \qquad (2)$$

Expressing FEV_1 and FVC as percentages of their predicted values, and rearranging:

$$FEV_1\%Prd = FVC\%Prd \times (FEV_1/FVC)/(FEV_1Prd/FVCPrd) \quad (3)$$

We assume that the predicted value for FEV_1/FVC ratio [(FEV_1/FVC)Prd] is approximately equal to the ratio of the individual predicted values for FEV_1 and FVC, in that the predictive equations were all derived from the same data set (15). The validity of this assumption is supported by the high concordance between (FEV_1/FVC)Prd and FEV_1Prd/FVCPrd computed for subjects in the present study using the Hankinson predictive equations (R^2 > 0.9999). Substituting (FEV_1/FVC)Prd for FEV_1Prd/FVCPrd, multiplying both sides by 100, and expressing FEV_1/FVC as a percentage of its predicted value:

$$FEV_1\%Prd = FVC\%Prd \times [(FEV_1/FVC)\%Prd]/100 \qquad (4)$$

Equation 4 shows that $FEV_1\%Prd$ is described by the product of FVC%Prd and (FEV_1/FVC)%Prd, and is therefore a dependent variable based on these two components. Figure 1 is a representation of *Eq. 4*, illustrating that a given value of $FEV_1\%Prd$ may result from a

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Table 1. *American Thoracic Society workshop consensus for definition of severe/refractory asthma*

Definition of Severe/Refractory Asthma*
Major criteria (need ≥1)
1) Treatment with continuous or near continuous (≥50% of year) oral corticosteroids
2) Requirement for treatment with high-dose inhaled corticosteroids
Minor criteria (need ≥2)
1) Requirement for additional daily treatment with a controller medication (e.g., long-acting β-agonist, theophylline or leukotriene antagonist)
2) Asthma symptoms requiring short-acting β-agonist use on a daily or near-daily basis
3) Persistent airway obstruction (FEV_1 <80% predicted, diurnal PEF variability >20%)
4) One or more urgent care visits for asthma per year
5) Three or more oral steroid "bursts" per year
6) Prompt deterioration with a ≤25% reduction in oral or inhaled corticosteroid dose
7) Near-fatal asthma event in the past

*Requires that other conditions have been excluded, exacerbating factors have been treated, and that patient be generally adherent. FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow rate.
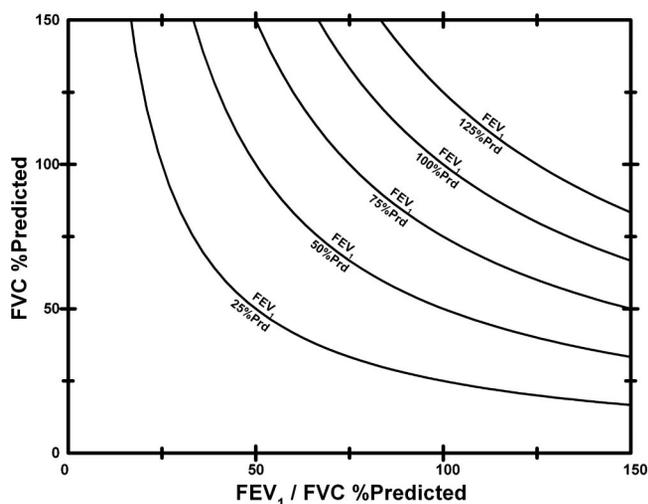
Fig. 1. Graphical representation of *Eq. 4*, showing the relationship of percent predicted forced expiratory volume in 1 s (FEV$_1$%Prd) to percent predicted forced vital capacity (FVC%Prd) and percent predicted FEV$_1$/FVC [(FEV$_1$/FVC)%Prd].

range of combinations of (FEV$_1$/FVC)%Prd and FVC%Prd, as a hyperbolic function of the two components. It follows that a fractional deviation of FEV$_1$%Prd from a reference value of FEV$_1$%Prd also may be described by the relative fractional deviations of FVC%Prd and (FEV$_1$/FVC)%Prd from their respective reference (ref) values.

Placing reference values in *Eq. 4*:

$$FEV_1\%Prd_{ref} = FVC\%Prd_{ref} \times [(FEV_1/FVC)\%Prd_{ref}]/100 \quad (5)$$

Dividing *Eq. 4* by *Eq. 5*:

$$FEV_1\%Prd/FEV_1\%Prd_{ref} = FVC\%Prd/FVC\%Prd_{ref}$$
$$\times [(FEV_1/FVC)\%Prd]/[(FEV_1/FVC)\%Prd_{ref}] \quad (6)$$

or, equivalently:

$$FEV_1/FEV_{1ref} = FVC/FVC_{ref} \times [(FEV_1/FVC)/(FEV_1/FVC)_{ref}] \quad (7)$$

Equations 6 and *7* show that a fractional change in FEV$_1$ is the product of the fractional changes in FVC and FEV$_1$/FVC. Therefore, a reduction in FEV$_1$%Prd relative to normal (i.e., 100%Prd) may be partitioned into reductions in FVC%Prd and (FEV$_1$/FVC)%Prd from their respective normals of 100%Prd. If TLC is not reduced, a decrease in FVC%Prd implies the presence of air trapping during the forced expiratory maneuver. The FEV$_1$/FVC ratio is the proportion of available FVC that is exhaled in the first second, and thus is a measure of relative maximal airflow, and it follows that a decrease in the (FEV$_1$/FVC)%Prd indicates airflow limitation. Thus a reduction in FEV$_1$%Prd may be partitioned into components that reflect relative contributions of air trapping and airflow limitation. Similarly, fractional changes in FEV$_1$ associated with bronchoconstriction or bronchodilation may be partitioned into the respective fractional changes in FVC and FEV$_1$/FVC, with the attendant implications regarding air trapping and airflow limitation (13).

Data analysis. The general linear model was used in least-squares regression, analysis of variance (ANOVA), and analysis of covariance (ANCOVA) contexts for data that conformed to parametric assumptions. Residuals from each analysis were confirmed to be normally distributed, and randomly associated with regard to the model estimates and to the independent variables, using visual inspection of normal probability plots and scatterplots. When nonlinearities or inhomogeneous slopes precluded using a continuous independent variable as a covariate, the continuous independent variable was

converted to intervals, each having a width of 20%Prd units, and only those intervals containing ≥10 subjects from both severity groups were included in the analyses. The intervals were used as a categorical independent variable in an ANOVA model, along with the appropriate interactive terms. The maximum bronchodilated:baseline ratios and the methacholine responsiveness data were log-transformed for analyses. Linear correlations were tested using the Pearson correlation coefficient (r) and the coefficient of determination (R^2), and nonlinear correlations with the Spearman rank order correlation coefficient (r_s). Pairwise group comparisons were done with the least significant difference test or with the Mann-Whitney test. The Wilcoxon signed-rank test was used to evaluate relative contributions of FVC%Prd and (FEV$_1$/FVC)%Prd to reversibility and to persistent airway obstruction after maximal bronchodilation. All analyses were performed with SYSTAT v.12 software (SYSTAT Software, Richmond, CA).

RESULTS

Group summaries. Table 2 compares subjects with Severe asthma, Nonsevere asthma, and No asthma classifications with regard to demographic characteristics, spirometry variables, and lung volumes. The subjects classified as Severe asthma differed significantly from the Nonsevere asthma group with regard to higher age, longer duration of asthma, and lower %Prd values for all the spirometric variables. In the subgroup with plethysmographic lung volume measurements, the Severe asthma subjects had significantly higher residual lung volumes compared with the other two groups. Demographic data and some of the spirometric data from SARP subjects were reported previously (33). Although the data in Table 2 include additional adult SARP subjects enrolled after the previous report and exclude subjects of age <18 yr, the group summa-

Table 2. *Group characteristics*

	Group		
	No asthma	Nonsevere asthma	Severe asthma
Demographics			
n	85	382	287
%Female sex	65	71	67
Age	32±10.1	34±11.6	43±12.9*
Age of asthma onset	NA	15±13.0	17±15.6
Years asthma duration	NA	20±12.7	26±14.1*
Baseline spirometry‡			
n	85	382	287
FEV$_1$, %Predicted	102±10.6	84±16.8†	61±22.0*†
FVC, %Predicted	103±11.6	94±15.3†	75±19.2*†
(FEV$_1$/FVC), %Predicted	99±7.1	89±11.3†	79±15.4*†
FEF$_{25–75}$, %Predicted	101±23.2	67±26.9†	42±28.8*†
PEF, %Predicted	103±18.3	88±19.7†	67±23.7*†
Lung volumes‡			
n	20	75	84
TLC, %Predicted	107±11.3	108±12.7	112±18.9
RV, %Predicted	107±25.4	114±36.8	153±51.3*†
(RV/TLC), %Predicted	97±19.7	102±25.1	131±31.0*†
Post max bronchodilation			
n	58	348	244
FEV$_1$ Max, %Predicted	106±12.1	94±14.5†	75±20.0*†
FVC Max, %Predicted	105±13.5	99±13.8†	88±17.3*†
(FEV$_1$/FVC) Max, %Predicted	101±7.2	95±10.0†	84±14.4*†

Values are group means ± SD. FVC, forced vital capacity; FEF$_{25–75}$, forced expiratory flow rate at 25–75% FVC; RV, residual lung volume; TLC, total lung capacity; Max, maximal. *$P < 0.0001$ vs. Nonsevere group; †$P < 0.004$ vs. No-asthma group. ‡Measured after withdrawal of bronchodilator medications. NA, not applicable.

ries for demographics, FEV_1, and FVC are consistent with those reported earlier (33). Subjects in the No asthma group were excluded from the subsequent analyses, to focus on comparisons of Severe vs. Nonsevere asthma groups.

Air trapping relative to airflow limitation. Although the Severe asthma group had significantly greater airway obstruction by measures of spirometry (Table 2), there was considerable overlap between Severe and Nonsevere asthma groups for each of the variables. We reasoned that, by evaluating FVC and FEV_1/FVC as components of FEV_1 relating to relative changes in air trapping vs. airflow limitation (Fig. 1), it might be possible to discern whether air trapping and airflow limitation were related similarly in Severe vs. Nonsevere groups. Comparing FVC%Prd relative to (FEV_1/FVC)%Prd, it was found that FVC%Prd was significantly lower in the Severe asthma group compared with the Nonsevere asthma group ($P <$ 0.0001, ANOVA, $R^2 = 0.26$), over the range of FEV_1/FVC of 55–115%Prd (Fig. 2A). Subjects with FEV_1/FVC of <55%Prd were not included in the group comparison because of the lack of Nonsevere asthma subjects in this range; however, the Severe asthma group subjects in this range showed a further

Fig. 2. Air trapping, as indicated by FVC (*A*) and residual lung volume (RV)/total lung capacity (TLC) (*B*), relative to FEV_1/FVC in subjects with "severe" and "nonsevere" asthma classifications. Each symbol is the mean $\pm$ SE for the subjects of each severity group in each interval of (FEV_1/FVC)%Prd, and the nos. of subjects (*n*) in each interval are indicated. *$P <$ 0.01, **$P <$ 0.0001 for severe vs. nonsevere groups in the same interval of FEV_1/FVC.

decrease in FVC%Prd (Fig. 2A). Comparisons within each of the intervals for (FEV_1/FVC)%Prd confirmed that FVC%Prd was significantly lower in the Severe asthma group within each interval of the overlapping range (Fig. 2A). These results indicate that subjects in the Severe asthma group have a greater component of air trapping, relative to the airflow limitation component, contributing to their airway obstruction. Further, the lower FVC%Prd over the entire range of (FEV_1/FVC)%Prd in the Severe group suggests that air trapping is a characteristic broadly associated with severe asthma, even when severe airflow limitation is not present. To confirm this finding, we repeated the analysis using (RV/TLC)%Prd as an alternative indicator of air trapping for the subgroup of subjects with lung volume data, with similar conclusions (Fig. 2B): (RV/TLC)%Prd was significantly higher in the Severe group ($P =$ 0.0001, ANOVA; $R^2 = 0.33$) over the 55–115%Prd range of FEV_1/FVC and significantly higher in each of the individual intervals between 55 and 95%Prd (Fig. 2B). Because changes in FVC may affect FEV_1/FVC under some conditions, we also confirmed that substituting intervals of PEF%Prd for the (FEV_1/FVC)%Prd intervals as the indicator of airflow in the analyses resulted in the same conclusions: both FVC%Prd ($P <$ 0.0001, ANOVA; $R^2 = 0.40$) and (RV/TLC)%Prd ($P =$ 0.009, ANOVA; $R^2 = 0.27$) were altered more prominently in the Severe asthma group, indicating more air trapping relative to the decrease in PEF%Prd compared with the Nonsevere asthma group.

Corticosteroid treatment. Corticosteroid treatment intensity was the major criterion for the severity classification (Table 1), but within the Severe asthma classification, there were 92 subjects on systemic steroids and 195 on high-dose inhaled steroid therapy, and within the Nonsevere asthma group, there were 213 subjects on inhaled steroids (8 of these high dose), 1 subject on systemic steroids, and 160 subjects receiving no steroid therapy. To test whether the type of corticosteroid therapy affected the patterns of air trapping vs. airflow limitation, the ANOVA analyses were repeated, including inhaled and systemic steroid subgroupings of the Severe asthma group and inhaled vs. no steroid subgroupings within the Nonsevere asthma group as nested variables. The FVC%Prd relative to the level of (FEV_1/FVC)%Prd was significantly associated with the intensity of corticosteroid therapy within the severity groups ($P <$ 0.0001 for the nested treatment categories), such that in the Nonsevere asthma group the FVC%Prd was lower in the subgroup receiving inhaled steroids compared with those receiving no steroid therapy (least square means 91 vs. 95%Prd), and in the Severe asthma group the FVC%Prd was lower in the subgroup receiving systemic steroids (71 vs. 80%Prd). Including the treatment subgroups in the analysis did not alter the difference in FVC%Prd attributed to the severity group classification ($P <$ 0.0001). These results suggest that within the severity classifications determined with the ATS Workshop criteria, the intensity of corticosteroid therapy may serve as a further indicator of asthma severity.

Lung volumes. Plethysmographic lung volumes were measured at some of the SARP sites, providing data for 75 Nonsevere and 84 Severe asthma group subjects. Demographic and spirometric variables in the subjects with lung volume data were comparable in ranges and means to those of their respective inclusive groups shown in Table 2.
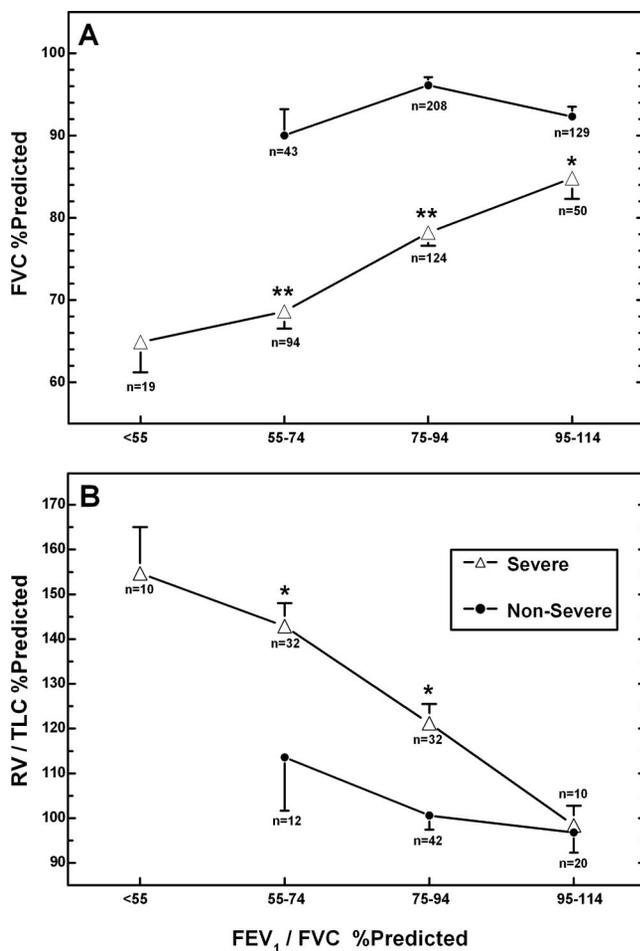
TLC%Prd varied directly with (RV/TLC)%Prd ($r = 0.31$, $P = 0.004$; Fig. 3); this association was not different in Severe vs. Nonsevere asthma groups ($P > 0.9$ for differences in regression slopes between the groups). This indicates that air trapping in stable asthma is associated with increased TLC. The (FRC/TLC)%Prd varied in parallel with (RV/TLC)%Prd and had a similar association with TLC%Prd ($r = 0.29$, $P = 0.0006$ for the pooled regression; $P = 0.7$ for differences in regression slopes between the groups).

If TLC increases with air trapping, there may be an incremental increase in FVC, which would make FVC%Prd a less sensitive indicator of air trapping (3). FVC%Prd correlated well with (RV/TLC)%Prd ($r = -0.64$, $R^2 = 0.41$, $P < 0.0001$; Fig. 4), and the slopes were not different for Nonsevere vs. Severe asthma ($P = 0.1$), indicating that FVC%Prd was adequate to assess air trapping for group comparisons. We also compared the absolute volume differences between measured and predicted values for FVC vs. RV (which would be expected to be equal if the TLC were unaltered) in 45 subjects (39 Severe asthma, 6 Nonsevere asthma) who had RV/TLC higher than the 95th percentile. The FVC was lower than its predicted value in parallel with the RV being higher than its predicted value ($R^2 = 0.63$, $P < 0.0001$), but not in a 1:1 ratio. The slope of the linear regression was 0.67, suggesting that elevation in TLC associated with air trapping served to limit the deviation of FVC from its predicted value to about two-thirds of the concomitant deviation of RV from its predicted value.

Reversibility of obstruction with bronchodilator treatment. As shown by *Eq. 7* (see METHODS), the fractional change in FEV_1 is the product of the fractional changes in FVC and FEV_1/FVC, and so the reversibility of obstruction after maximal bronchodilation may be assessed as relative changes in the air trapping and airflow limitation components of obstruction. A post-maximal bronchodilation-to-baseline (Max:Baseline) ratio was computed for FEV_1, FVC, and FEV_1/FVC as the values measured after maximal bronchodilation divided by the baseline values measured after an appropriate period of withheld asthma medications. Figure 5 illustrates the relationship of each of the Max:Baseline ratios with the baseline FEV_1%Prd for 244 Severe asthma and 348 Nonsevere asthma group
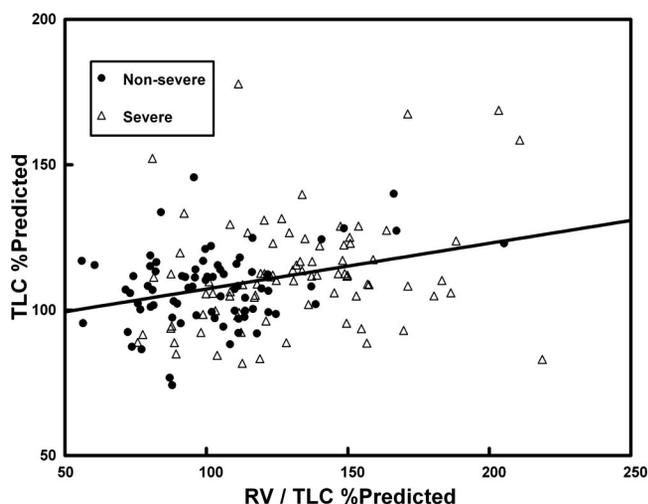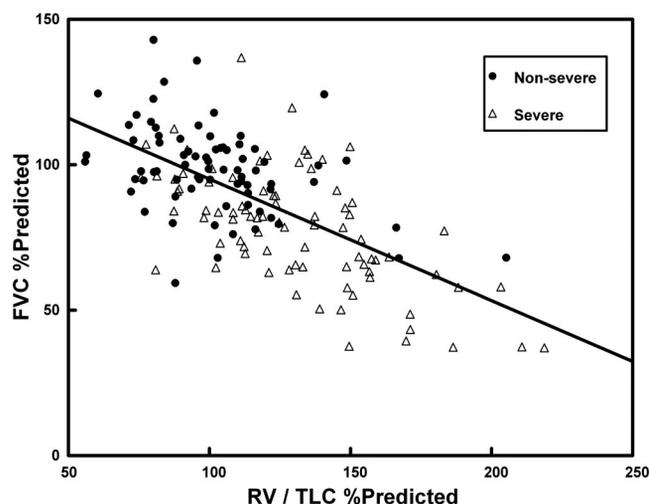

Fig. 4. Correlation between FVC and RV/TLC. Linear regression line is for the pooled severe and nonsevere asthma subjects.

subjects in whom maximal bronchodilation procedures were completed. Per *Eq. 7*, the ratio for FEV_1 reversal (Fig. 5A) is the product of the reversal ratios for FVC (Fig. 5B) and for FEV_1/FVC (Fig. 5C). Both severity groups were adequately represented in the intervals of baseline FEV_1%Prd within the 40–120%Prd range for comparative analysis, and the Severe asthma group with baseline $FEV_1 < 40$%Prd is included on Fig. 5 to illustrate the continuation of the data patterns. The reversal of FEV_1 with bronchodilation was related nonlinearly to the baseline FEV_1%Prd (Fig. 5A). While the magnitude of reversal for FEV_1/FVC increased by small increments for each decrease in baseline FEV_1%Prd (Fig. 5C), the reversal of FVC contributed largely to the marked increases in bronchodilator reversibility that occurred at baseline FEV_1 below 60%Prd. There was no significant difference between Severe and Nonsevere asthma groups with regard to the reversal of FEV_1 when compared at the same levels of baseline FEV_1%Prd. However, the severity groups exhibited small differences in the relative reversals of the FVC and FEV_1/FVC: when compared at equal levels of baseline FVC%Prd, the Severe asthma group averaged ~2% more reversal of FVC than the Nonsevere asthma group ($P = 0.049$), and when compared at equal levels of baseline (FEV_1/FVC)%Prd, the Nonsevere asthma group averaged ~2% more reversal of FEV_1/FVC than the Severe asthma group ($P < 0.003$).

Residual obstruction after maximal bronchodilation. The nonreversible portion of reduced FEV_1 had components of both air trapping (reduced FVC%Prd) and airflow limitation [reduced (FEV_1/FVC)%Prd], with the airflow limitation component contributing relatively more to the residual reduced FEV_1 [maximal (FEV_1/FVC)%Prd < maximal FVC%Prd; $P < 0.01$] in both the Severe and Nonsevere asthma groups (Table 2). Using a multivariate general linear model, three variables (the Severe asthma classification, male sex, and age) were identified as independent predictors of residual reduction in FEV_1%Prd after maximal bronchodilation (Table 3).

Responsiveness to inhaled methacholine. Methacholine challenge and computation of a PC_{20} FEV_1 were completed for 113 Severe asthma and 321 Nonsevere asthma subjects, all of whom had a prechallenge $FEV_1 \geq 50$%Prd. Within this sub-

Fig. 3. Association between TLC and RV/TLC. Linear regression line is for the pooled severe and nonsevere asthma subjects.
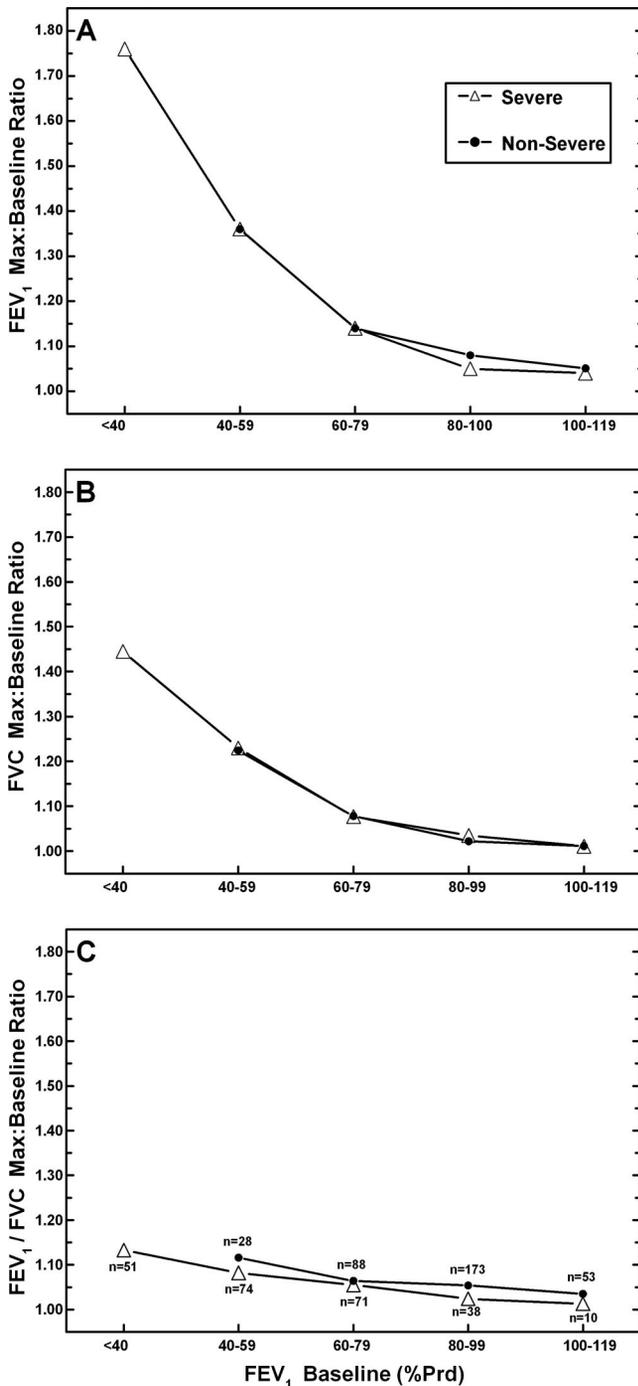
Fig. 5. Reversibility of airway obstruction after maximal bronchodilation (Max) with albuterol, expressed as a fractional change relative to baseline FEV_1 (*A*), FVC (*B*), and FEV_1/FVC (*C*) in severe and nonsevere asthma subjects, plotted against baseline FEV_1%Prd. Each symbol is the group median for subjects in that range of baseline FEV_1; nos. of subjects (*n*) represented by each symbol are indicated.

Table 3. *Predictors of persistently reduced FEV_1 (%Prd) after maximal bronchodilation with inhaled albuterol in subjects with asthma*

Variable	Effect on FEV_1%Prd	*P* Value
Severe (vs. Nonsevere) asthma classification	−14.9%Prd	<0.0001
Male (vs. female) sex	−4.6%Prd	0.0015
Age	−0.46%Prd/yr	<0.0001

Effects (least squares mean) and *P*-values were determined using the multiple general linear model. %Prd, percent of predicted value.

(12%) had $PC_{20} > 16$ mg/ml; of those 50 subjects, 15 met the criteria for Severe asthma, and 29 had at least one baseline spirometric variable <80%Prd. Compared with the more responsive subjects, those having $PC_{20} > 16$ mg/ml were significantly older, both at their onset of asthma (median ages 19 vs. 10 yr; $P = 0.0003$) and at the time of enrollment (median ages 42 vs. 34 yr; $P = 0.016$). The subjects with $PC_{20} > 16$ mg/ml also had significantly higher baseline FEV_1%Prd ($P = 0.003$) but did not differ from the more responsive subjects in the FEV_1%Prd measured after maximal bronchodilation ($P > 0.7$). We repeated the analyses of air trapping, lung volumes, reversibility, and residual obstruction with the subjects having $PC_{20} > 16$ mg/ml excluded from the models, confirming that inclusion of these subjects had no influence on the results or conclusions of those analyses.

DISCUSSION

We evaluated a large cohort of subjects classified as having "Severe asthma" or "Nonsevere asthma," applying the concept of partitioning airway obstruction, as measured by FEV_1, into components of airflow limitation (measured as reduced FEV_1/FVC) and air trapping (measured as reduced FVC). We found that air trapping is a prominent group characteristic in Severe asthma during a period of stable disease, not only in those subjects exhibiting severe airflow limitation, but throughout the range of airflow limitation. In contrast, the Nonsevere asthma group had less prominent air trapping, even when
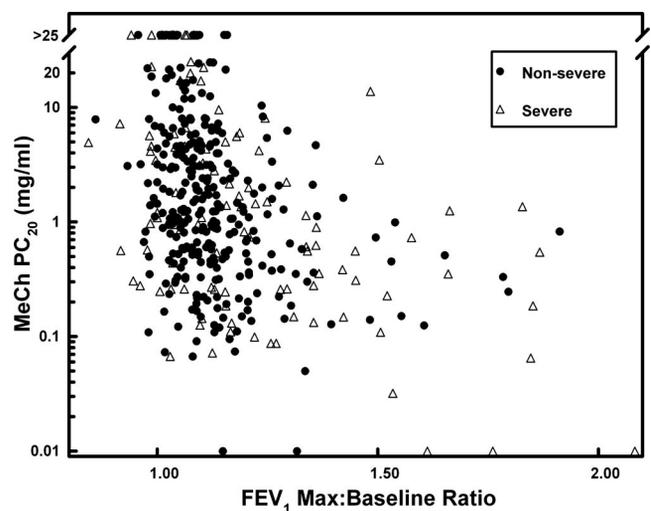

Fig. 6. Methacholine (MeCh) concentration associated with a 20% decrease in FEV_1 (PC_{20}) vs. fractional change in FEV_1 with maximal bronchodilation in severe and nonsevere asthma subjects. The ordinate is scaled as the log for PC_{20}.

group of subjects without severe obstruction at baseline, there was no significant difference in PC_{20} between the Severe asthma and Nonsevere asthma classifications ($P > 0.16$). Methacholine PC_{20} correlated weakly with most of the other measures of airway physiology, the best correlation being with the reversibility of FEV_1 ($r_s = -0.40$; Fig. 6). Of the 434 asthma subjects who completed methacholine challenge, 50

FEV_1/FVC was $<75\%$Prd. Although elevated RV/TLC has been reported previously as a group characteristic of adults with severe asthma (41), and associated with persistent airway obstruction in severe asthma (4, 40), this is the first study to show the predilection of severe asthma for air trapping over the entire range of airflow limitation. In the present study, had the air trapping occurred only in the presence of moderate-severe airflow limitation, or in a pattern relative to airflow limitation that was consistent in Severe and Nonsevere asthma classifications, we would interpret that as evidence that Severe asthma represents a more severe manifestation of the general pathophysiology that causes airway obstruction in the population of asthma. However, the data instead show a statistically and physiologically significant shift of the study population classified as Severe asthma toward more air trapping at all levels of airflow limitation—these results suggest that there may be a pathophysiological process present commonly in severe asthma that contributes to air trapping.

A strength of this study is the large number of subjects with severe asthma. Lacking distinguishing biomarkers or other precise definitions of asthma phenotypes, the consensus definition of refractory asthma employed for this study focused on identifying asthma that is incompletely controlled despite intensive treatment. While the definition may result in the inclusion of multiple phenotypes of difficult asthma, as well as some subjects who are misclassified because of inaccuracies of reported treatments, histories or diagnoses, the Severe asthma cohort does include a large number of subjects with difficult asthma that will ensure a group analysis that is meaningful even in the presence of a small number of misclassified subjects and outliers. The present study found strong associations of the Severe asthma classification with some physiological variables, illustrating that, although imprecise, the definition was sufficient to identify an asthma subgroup with an identifiable pattern of airway obstruction.

Partitioning FEV_1. Central to our analysis of spirometry measurements is the concept of partitioning the FEV_1 into components of airflow limitation and air trapping, and we have presented a novel approach for doing this in a quantitative manner. *Equation 4* and Fig. 1 show that $FEV_1\%$Prd is linked quantitatively to the product of $FVC\%$Prd and $(FEV_1/FVC)\%$Prd and may be treated as a dependent variable based on those quantities. *Equation 7* further shows that any fractional change measured in FEV_1 may be partitioned quantitatively into the concomitant fractional changes of FVC and FEV_1/FVC ratio. The significance of these relationships is that FVC and FEV_1/FVC may be altered differentially, and a systematic change in one of these quantities relative to the other could discern an underlying difference in pathophysiology that would not be apparent from the FEV_1.

FVC is determined by TLC and by the fraction of TLC that can be exhaled forcibly, so $FEV_1\%$Prd will be reduced if either TLC is reduced (smaller than predicted lung size or restrictive disease), or if exhaled volume is reduced (air trapping). Air trapping in this context is inclusive of all causes of reduced exhaled volume, including airway premature closure/near closure, dynamic airway compression, and reduced expiratory muscle strength. The spirometry procedures evoked maximal inspiratory and expiratory efforts from the subjects, with ATS standard end-of-test criteria (at least 6-s maximal expiratory effort). While severely obstructed subjects often did not meet

the zero-flow criterion within the time that they could sustain a maximal expiratory effort, the reduced FVC was accepted as an indicator of air trapping, as the subjects were indeed unable to exhale more volume voluntarily. The random variability of TLC%Prd within the cohort (Fig. 3) probably accounts for some of the random variability in FVC%Prd as a function of (RV/TLC)%Prd (Fig. 4), and in addition, we have shown that there is a nonrandom increase in TLC associated with air trapping (Fig. 3) that reduces the magnitude of the deviation from predicted FVC relative to the deviation from predicted RV. However, as shown in Fig. 4, FVC%Prd does correlate well with (RV/TLC)%Prd despite the variability in TLC and thus is valid as an indicator for air trapping in an asthma population.

From *Eq. 4* it can be reasoned that any change in $FEV_1\%$Prd not associated with a change in FVC%Prd (air trapping or alterations in TLC) must be associated with a change in $(FEV_1/FVC)\%$Prd. This ratio represents the fraction of the total forced expired volume that is exhaled in the first second of the maneuver, and thus is sensitive to pathology that reduces maximal airflow, and is an indicator of airflow limitation. A high correlation between FEV_1/FVC ratio and large airway diameter measured with high-resolution computed tomography suggests that this variable is sensitive to changes in the caliber of central airways (3). Because FVC is the denominator of FEV_1/FVC, the ratio is affected by variability in FVC; for example, the ratio may be increased artifactually if the FVC measurement is terminated before achieving a true RV (35), and thus partitioning of FEV_1 requires a maximal expiratory effort to be interpretable. However, we would argue that an FVC obtained with a maximal effort represents the available expiratory volume, and the fraction of that volume expired in the first second can reveal meaningful information about airflow limitation. FVC%Prd and $(FEV_1/FVC)\%$Prd have considerable independence with one another within the asthma population ($R^2 = 0.10$ for the SARP subjects) , and Fig. 5 shows that marked increases in FVC with bronchodilation typically are accompanied by increases, not decreases, in the FEV_1/FVC ratio. These data suggest that the two variables are affected differentially by underlying pathophysiology, despite having some predictable dependencies. Thus, for the purposes of partitioning the $FEV_1\%$Prd into components that may reflect different aspects of asthma pathophysiology, the use of FVC%Prd and $(FEV_1/FVC)\%$Prd is mathematically sound, and the physiological interpretation of these variables as broad indicators of air trapping and airflow limitation is valid.

Air trapping. The RV is determined primarily by expiratory muscle strength relative to chest wall recoil in young persons with healthy airways, and by airway closure in older persons and in persons having airway pathology or reduced lung elastic recoil (24). The air trapping in asthma is associated with airway closure or near closure (17, 22, 25), but the mechanisms and the sites of airway closure are not well understood. Small airways appear to be the location of ventilatory heterogeneity in asthma (42), and exhibit increases in peripheral airflow resistance of severalfold even in asymptomatic asthma subjects who have normal FEV_1 (45). Using the wedged bronchoscope method, subjects with nonsevere asthma were noted to have slightly elevated plateau pressures during cessation of airflow, indicating that there was complete closure of collateral pathways distal to the bronchoscope occurring at higher pressures

than those measured in subjects with normal airways (20, 23), and in subjects with nocturnal asthma, there was a marked increase in plateau pressures at 4:00 AM compared with 4:00 PM (23); these studies provide direct evidence that closure occurs in the distal airways during baseline conditions in subjects with asthma, and worsens during nocturnal asthma. It follows that severe asthma with measurable air trapping could be a manifestation of a pathophysiological process that increases closure of collateral pathways or of more proximal sites in the airways, either by exacerbating the tendency to closure that is already present in nonsevere asthma, or by introducing additional pathology that is additive or interactive with that found in nonsevere asthma.

Airway closure occurs as a fluid meniscus that forms over the lumen when a critical airway diameter relative to the volume of fluid lining the lumen is reached (16, 21, 27, 43); thus, any process that increases intraluminal fluid volume or that favors airway narrowing would promote closure. Airway smooth muscle contraction favors airway narrowing and closure, and the marked improvement in FVC after β-agonist treatment in the Severe asthma group in the present study suggests a contribution of this mechanism. An inflammatory process in the small airways (51) also could contribute to airway closure, both by interfering with surfactant activity (19, 44), resulting in airway narrowing due to increased surface tension, and by increasing the volume of intraluminal material (16). The marked heterogeneity in airway obstruction observed in severe asthma (8, 25) suggests a patchy pattern of pathology that would be consistent with foci of inflammation. A force that opposes small airway narrowing and closure is airway-parenchymal coupling, which is a bronchodilating force obtained from the tethering effect of lung elastic recoil transmitted to the airway adventitial walls (9, 26). Reduction of airway-parenchymal coupling, due either to reduced lung elastic recoil or to an uncoupling of the tethering force from the airway lumen, could be a contributing factor to air trapping in asthma (11, 14, 18, 28, 52). One consequence of reduced airway-parenchymal coupling may be dynamic airway closure during a forced expiration, which has been observed as a reduced FVC:slow vital capacity ratio in some persons with severe asthma (50).

We observed increases in TLC and FRC associated with increases in RV, consistent with the studies of Brown and colleagues (3). Analogous to the fractional changes in FVC relative to changes in RV with bronchodilation that were reported in the study of Brown et al. (3), we found that the volume differences between measured baseline FVC and predicted FVC were, on average, only about two-thirds the volume differences between measured baseline and predicted RV, supporting their argument that an increase in TLC helps to preserve vital capacity in the presence of air trapping. However, in contrast to the study of Brown et al. (3), we found no association between the postmaximal bronchodilation FEV_1/FVC ratio and the deviation in baseline FVC from its predicted value relative to the deviation in baseline RV from its predicted value. Although the Severe asthma group in our study had more air trapping (both reduced FVC and increased RV) compared with the Nonsevere asthma group, the associated increases in TLC were similar for the two groups for a given level of air trapping (Fig. 3).

Reversibility and hyperresponsiveness. In addition to the strong association with air trapping, the Severe asthma classi-

fication also was an independent predictor of persistent airway obstruction after maximal bronchodilation with β-agonist. Age and male sex also were identified as independent predictors of persistent obstruction, in agreement with previous studies of subjects with severe asthma (4, 40). In addition to age, long duration of asthma in an elderly population has been identified as a risk factor for persistent airflow limitation after bronchodilation (5). If maximal expiratory airflow is determined by airway conductance and lung elastic recoil (30, 36), then persistent airflow limitation after relaxing smooth muscle must be related to other factors causing airway narrowing/closure and/or reduced elastic recoil. The postbronchodilator FEV_1/FVC correlates strongly with large airway luminal diameter measured with high-resolution computed tomography (3), suggesting that airway narrowing due to thickening of the airway wall via inflammation or remodeling may contribute to postbronchodilator airflow limitation. Reduction of luminal area due to accumulation of mucous secretions or inflammatory exudates also would be expected to cause reduced airway conductance that would not be reversed rapidly with bronchodilators. Reduced lung elastic recoil has been observed commonly in persons with stable asthma, including young adults with relatively short durations of asthma diagnosis, and in the absence of emphysema that could be detected by high-resolution computed tomography or by reduced carbon monoxide diffusion capacity (11, 12, 29, 52). In these subjects a large proportion of the airflow limitation could be attributed to reduced lung elastic recoil (11, 12, 29). Thus the persistent airflow limitation after maximal bronchodilation is more prominent in the Severe asthma group and likely is associated with both reduced lung elastic recoil and reduced airway caliber.

Responsiveness of FEV_1 to inhaled methacholine correlated with the change in FEV_1 after maximal bronchodilation, but responsiveness correlated only weakly with other measures of airway physiology, and 12% of the subjects with asthma who completed methacholine challenge had a $PC_{20} > 16$ mg/ml, which is generally considered to be in the nonasthma range (7). One reason for the weak correlation with other physiology variables is that subjects with more severe baseline airway obstruction were excluded from methacholine challenge, thus truncating the range of physiological variables available for comparison. Although subjects withheld bronchodilator therapy before methacholine challenge, their maintenance inhaled corticosteroid therapy would be expected to increase methacholine PC_{20} by 1 to 2 doubling concentrations (37, 47), which could reverse mild hyperresponsiveness. Also, the dosimeter method (7) used in SARP for methacholine challenge involves repeated deep breaths, which may reduce responsiveness to methacholine compared with the tidal breathing method in some subjects with asthma (6), potentially shifting the PC_{20} of a subject with mild hyperresponsiveness into the normal range. It is possible that some of the nonhyperresponsive subjects did not have asthma, although more than half had at least one spirometric variable <80% predicted, suggesting baseline airflow limitation. Further evaluation of methacholine responsiveness relative to other characteristics and biomarkers being measured in the SARP cohort may provide insight regarding the utility of methacholine PC_{20} for the identification of asthma subgroups.

In conclusion, the group of persons meeting the consensus definition criteria for Severe asthma was distinguished physi-

ologically by more prominent air trapping relative to the level of airflow limitation, and more prominently reduced FEV_1 after maximal bronchodilation, compared with subjects with Nonsevere asthma. The presence of these differences over the ranges of $(FEV_1/FVC)\%Prd$ and age suggest that they reflect an underlying pathology that is present in persons with severe asthma, and not simply the extremes of the general asthma population.

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