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Distal Airway Function in Symptomatic Subjects With Normal Spirometry Following World Trade Center Dust Exposure*

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Rationale: **Following collapse of the World Trade Center (WTC), individuals reported new-onset respiratory symptoms. Despite symptoms, spirometry often revealed normal airway function. However, bronchial wall thickening and air trapping were seen radiographically in some subjects. We hypothesized that symptomatic individuals following exposure to WTC dust may have functional abnormalities in distal airways not detectable with routine spirometry.**

Methods: **One hundred seventy-four subjects with respiratory symptoms and normal spirometry results were evaluated. Impedance oscillometry (IOS) was performed to determine resistance at 5 Hz, 5 to 20 Hz, and reactance area. Forty-three subjects were also tested for frequency dependence of compliance (FDC). Testing was repeated after bronchodilation.**

Results: **Predominant symptoms included cough (67%) and dyspnea (65%). Despite normal spirometry results, mean resistance at 5 Hz, 5 to 20 Hz, and reactance area were elevated (4.36 ± 0.12 cm H_2O/L/s, 0.86 ± 0.05 cm H_2O/L/s, and 6.12 ± 0.50 cm H_2O/L, respectively) [mean ± SE]. Resistance and reactance normalized after bronchodilation. FDC was present in 37 of 43 individuals with improvement after bronchodilation.**

Conclusions: **Symptomatic individuals with presumed WTC dust/fume exposure and normal spirometry results displayed airway dysfunction based on the following: (1) elevated airway resistance and frequency dependence of resistance determined by IOS; (2) heterogeneity of distal airway function demonstrated by elevated reactance area on oscillometry and FDC; and (3) reversibility of these functional abnormalities to or toward normal following administration of a bronchodilator. Since spirometry results were normal in all subjects, these abnormalities likely reflect dysfunction in airways more distal to those evaluated by spirometry. Examination of distal airway function when spirometry results are normal may be important in the evaluation of subjects exposed to occupational and environmental hazards.** ***(CHEST 2007; 132:1275–1282)***

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Key words: distal airways; environmental exposure; oscillometry; respiratory function tests; World Trade Center disaster

Abbreviations: BMI = body mass index; Cdyn,l = dynamic lung compliance; Cst,l = static lung compliance; DLCO = diffusing capacity of the lung for carbon monoxide; FDC = frequency dependence of compliance; FRC = functional residual capacity; IOS = impedance oscillometry; RV = residual volume; TLC = total lung capacity; V_{50} = airflow at 50% of vital capacity; WTC = World Trade Center

Individuals exposed to the environment in downtown Manhattan following collapse of the World Trade Center (WTC) on September 11, 2001 were exposed to dust, debris, and fumes, and are therefore potentially at risk for development of airway disease. Many individuals have reported new-onset and persistent respiratory symptoms.[1–10] However, the physiologic abnormalities associated with these complaints remained incompletely understood. Herbert et al[9] published data from > 9,000 WTC dust-exposed subjects; 72% had normal spirometry results despite respiratory symptoms. Reibman et al[6] evaluated residents of Lower Manhattan with ongoing WTC dust exposure. Despite new-onset symptoms, no significant difference between exposed and unexposed subjects was identified on spirometry.[6] Studies[1,2] in firefighters following acute high-level exposure to WTC dust demonstrated normal mean values for FEV_1, FVC, and FEV_1/FVC. Despite this, airway disease was suspected because FEV_1 and FVC were reduced compared to pre-September 11, 2001 values. In some subjects, airway disease was identified either by bronchial wall thickening and air trapping on chest radiography, or by bronchial hyperreactivity in response to methacholine,[1,2,5,8] suggesting the presence of functional abnormalities in airways not detected with routine spirometry.

Spirometry is an imperfect diagnostic tool for detection of distal airway disease.[11] Because of their large total cross-sectional area, the distal airways are largely ignored by typical pulmonary function testing and have been labeled the *silent zone* of the lung.[12,13] Frequency dependence of compliance (FDC) is an accepted tool to evaluate distal airway function[14]; however, the requirement for esophageal manometry has limited its application. Forced oscillation is a noninvasive test that has been proposed to evaluate distal airway function.[15] Forced oscillation has been demonstrated to differentiate healthy subjects from patients with respiratory complaints by identifying increased distal airway resistance not detected by spirometry.[16,17]

This study tested the hypothesis that subjects with self-reported respiratory symptoms following exposure to WTC dust may have functional abnormalities in the distal airways that are not detectable with routine spirometry. Data were retrospectively analyzed from 174 subjects with normal spirometry results and ongoing unexplained respiratory symptoms who underwent specialized evaluation of distal airway function. This study was approved by the institutional review boards of the New York University School of Medicine and Bellevue Hospital.

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Methods and Materials

Data from subjects referred to the New York University/Bellevue Hospital Pulmonary Function Laboratory for evaluation of respiratory symptoms following exposure to WTC dust were retrospectively analyzed. Subjects were referred from outpatient clinics including the Bellevue Hospital WTC Treatment Program. One hundred seventy-four subjects with normal spirometry results were included. Six exposure scenarios were defined: initial dust cloud, dust cleanup, involvement in rescue/recovery, residence near the WTC site, employment near the WTC site, and a group with unspecified exposure. Testing included spirometry and impedance oscillometry (IOS) in all subjects and esophageal manometry in 43 of 174 subjects. Lung volumes were assessed by plethysmography in 102 individuals, and diffusing capacity of the lung for carbon monoxide (DLCO) was assessed in 67 individuals.

Spirometry

Spirometry was performed in accord with American Thoracic Society/European Respiratory Society standards (Vmax; SensorMedics; Yorba Linda, CA).[18] Data collected included FEV_1, FVC, FEV_1/FVC, expiratory reserve volume, and instantaneous flow rates at 50% of vital capacity (V_{50}). Normal spirometry results were defined as FEV_1 and FVC $> 80\%$ of predicted[19] and $FEV_1/FVC \geq 77\%$. This high cutoff value for FEV_1/FVC was specifically chosen to ensure that subjects with mild large airway disease were excluded from the study.

IOS

IOS was measured (Jaeger Impulse Oscillation System; Jaeger USA; Yorba Linda, CA) with patients in the seated position during tidal breathing while firmly supporting their cheeks with their hands. A minimum of three trials, each lasting 30 s, were performed. Studies were performed before inhalation (n = 174) and after inhalation of albuterol (n = 131). Data from reproducible tests (variability < 10%) were analyzed.

Oscillometry data included a global measure of airway resistance (resistance at an oscillating frequency of 5 Hz), frequency dependence of resistance (the fall in resistance from 5 to 20 Hz), and a marker of heterogeneity of distal airway function (reactance area). Reactance area was calculated as the area under the reactance curve from 5 Hz to the resonant frequency.

Data are presented as raw data and are compared to an upper limit of normal selected from prior publications.[10,15–17,20–23] An upper limit of normal for resistance at 5 Hz (3.8 cm H_2O/L/s) was chosen to approximate the 95% confidence interval (mean plus 2 SDs). Although a single value for an upper limit of normal was selected for all subjects, this value is a conservative estimate because it approximates 150% of previously published mean values for resistance in normal subjects.[10,15–17,20–23] A conservative upper limit of normal for resistance at 5 to 20 Hz was chosen at 0.76 cm H_2O/L/s. For reactance area, there are limited published normative data[10,15]; a conservative upper limit of normal of 3.6 cm H_2O/L/s was selected. Data obtained in our laboratory in 20 asymptomatic nonsmoking subjects without a history of lung disease and in whom spirometry results were within normal limits fell below these upper limits of normal and did not respond to bronchodilation.

FDC

Forty-three subjects underwent esophageal manometry to assess for FDC.[14] Esophageal manometry was performed utilizing an esophageal balloon (Ackrad Labs, Cooper Surgical Company; Turnbull, CT) positioned in the distal third of the esophagus.[24] Static lung compliance (Cst,1) was measured after two inspiratory capacity maneuvers by periodically occluding the airway during exhalation from total lung capacity (TLC) to functional residual capacity (FRC). Dynamic compliance (Cdyn,1) was determined at increasing respiratory frequencies and expressed as a ratio to the Cst,l. Constancy of Cdyn,1 during successive breaths at each frequency provided evidence that changes in FRC did not affect the results.[25] Breath-by-breath data were analyzed to calculate Cdyn,1 by multiple linear regression of the equation of motion.[26] While there is no clear-cut normal range for FDC, a Cdyn,l/Cst,l < 0.80 at a respiratory rate of 60 breaths/min was chosen because it likely reflects peripheral heterogeneity beyond that expected in a normal population of this age.[14,25]

Statistical Analysis

Data were summarized as mean ± SD or SE. Differences in measures between groups were assessed utilizing a Student *t* test or Mann-Whitney *U* test. Statistical significance was set at $p < 0.05$. Analysis was performed utilizing statistical software (SPSS for Windows, version 13.0; SPSS; Chicago, IL). Data were analyzed for the entire cohort, and analyses were repeated after excluding subjects with history of smoking, obesity (body mass index [BMI] > 30 kg/m^2), and/or prior lung disease.

Table 1—*Clinical Characteristics (n = 174)*

Characteristics	Data
Age, yr*	44 ± 10
Male gender, %	57
Current smokers, %	3
Past smokers, %	20
Associated disease, %	
Asthma history	7
Allergic rhinitis	27
Obesity	
BMI > 30 kg/m^2 and < 35 kg/m^2	21
BMI > 35 kg/m^2	9
Exposure history, No. of subjects†	
Dust cloud	13
Rescue/recovery worker	15
Cleanup worker	83
Work near WTC	34
Residence near WTC	35
Unspecified	14
Symptoms, %‡	
Cough	67
Dyspnea	65
Wheeze	30
Chest tightness	38

*Mean ± SD.
†Sum is > 174 because categories are not mutually exclusive.
‡Sum is > 100% because categories are not mutually exclusive.

Results

Table 1 shows the demographic characteristics of the 174 subjects. Mean age was 44 ± 10 years. A history of asthma prior to September 11, 2001 was reported in 7%. Exposure to WTC dust varied and included exposure during cleanup activities (50%) or due to work or residence in the vicinity of the WTC (40%). All subjects were symptomatic; predominant symptoms included cough and dyspnea, and to a lesser extent wheezing and chest tightness.

Spirometry

Data from pulmonary function testing are shown in Table 2. By design, all subjects had normal large airway function on spirometry as assessed by FEV_1 and FEV_1/FVC (mean values: FEV_1, 99.3 ± 13.3% of predicted; FEV_1/FVC, 83.5 ± 4.0%). The mean value for V_{50} was within the normal range (110.0 ± 27.3%). Spirometric parameters demonstrated < 5% change after inhaled albuterol. When measured, lung volumes and DLCO were within normal limits. Although mean residual volume (RV)/TLC was within normal limits, approximately 33% of the subjects demonstrated elevated values (> 0.35).

IOS

The mean value for resistance at 5 Hz was elevated (4.36 ± 0.12 cm H_2O/L/s; upper limit of normal, 3.8 cm H_2O/L/s), suggesting airway disease despite normal FEV_1 and FEV_1/FVC. Similarly, frequency dependence of resistance (resistance at 5 to 20 Hz) was observed (0.86 ± 0.05 cm H_2O/L/s; upper limit of normal, 0.76 cm H_2O/L/s). In addition, airway heterogeneity was identified by an increased reactance area (6.12 ± 0.50 cm H_2O/L/s; upper limit of normal, 3.6 cm H_2O/L/s). These elevated mean values for IOS parameters reflected abnormalities in 68% of the 174 subjects. When IOS data were analyzed by exposure category, no statistically significant differences were noted for any of the exposure groups (Table 3). Of importance, IOS data were statistically unchanged when subjects with a history of smoking, obesity (BMI > 30 kg/m^2), or prior lung disease were excluded from analysis.

Table 2—*Pulmonary Function Results (n = 174)**

Variables	Data
FEV_1, % predicted	99.3 ± 13.3
FVC, % predicted	99.2 ± 13.7
FEV_1/FVC	83.5 ± 4.0
V_{50}, % predicted	110.0 ± 27.3
FRC, % predicted (n = 102)	84.1 ± 18.2
RV/TLC, % (n = 102)	32.9 ± 7.2
TLC, % predicted (n = 102)	97.4 ± 12.1
DLCO, % predicted (n = 67)	96.0 ± 17.5

*Data are presented as mean ± SD.

Table 3—*IOS Results by Exposure Categories**

Variables	Dust Cloud	Cleanup	Rescue/Recovery	Resident	Worker	Unspecified
Resistance at 5 Hz, cm $H_2O/L/s$	4.34 ± 0.47	4.63 ± 0.18	3.87 ± 0.39	3.99 ± 0.27	4.51 ± 0.27	3.84 ± 0.20
Resistance at 5 to 20 Hz, cm $H_2O/L/s$	0.81 ± 0.16	1.01 ± 0.08	0.71 ± 0.18	0.69 ± 0.10	0.85 ± 0.12	0.64 ± 0.07
Reactance area, cm H_2O/L	4.57 ± 1.19	7.61 ± 0.81	4.20 ± 1.58	4.60 ± 0.82	6.32 ± 1.19	3.64 ± 0.63

*Data are presented as mean ± SE; p = not significant for difference between groups.

The effect of bronchodilator on IOS parameters was tested in 131 of 174 individuals (Fig 1). Resistance at 5 Hz, frequency dependence of resistance, and reactance area decreased significantly. The mean value for resistance at 5 Hz returned to normal (3.70 ± 0.11 cm $H_2O/L/s$, $p < 0.001$, compared with prebronchodilator values), as did the frequency dependence of resistance and reactance area (0.67 ± 0.04 cm $H_2O/L/s$, $p < 0.001$; and 3.53 ± 0.30 cm H_2O/L, $p < 0.001$, compared with prebronchodilator values, respectively). Also illustrated are data obtained in 20 normal subjects who were within the normal range and showed no response to bronchodilator.

FDC

Lung compliance was measured in 43 of the above subjects. Cst,l was normal (0.22 ± 0.06 L/cm H_2O) in all subjects, indicating normal static lung mechanics. Figure 2 illustrates Cdyn,l/Cst,l plotted at progressively increasing respiratory rates before and after administration of albuterol. The mean value for Cdyn,l/Cst,l decreased with increasing breathing frequency (0.80 ± 0.03 at 20 breaths/min, 0.74 ± 0.02 at 40 breaths/min, and 0.67 ± 0.02 at 60 breaths/min). Abnormal values for Cdyn,l/Cst,l at 60 breaths/min were noted in 37 of 43 subjects, consistent with functional abnormality in the distal airways. Following bronchodilator administration, a consistent improvement in Cdyn,l/Cst,l was observed at all respiratory rates ($p < 0.001$ for 40 breaths/min and 60 breaths/min), indicating reversibility. Mean Cdyn,l/Cst,l returned to normal at respiratory rates of 20 breaths/min and 40 breaths/min; despite this improvement, there was persistence of abnormal values at a respiratory rate of 60 breaths/min in 27 subjects.

Relationship Between IOS and FDC

Figure 3 examines the relationship between IOS parameters and lung compliance measurements. Subjects were classified into two groups based on presence or absence of FDC. Six individuals did not have FDC; mean values for resistance at 5 Hz, frequency dependence of resistance, and reactance area were within normal limits in these individuals (3.71 ± 0.39 cm $H_2O/L/s$, 0.46 ± 0.12 cm $H_2O/L/s$, and 1.80 ± 0.42 cm H_2O/L, respectively). In contrast, 37 of 43 subjects who had FDC demonstrated elevated values for resistance at 5 Hz and frequency dependence of resistance (4.62 ± 0.22 cm $H_2O/L/s$ and 0.99 ± 0.11 cm $H_2O/L/s$, respectively), although this did not achieve statistical significance when compared to the group without FDC. Reactance area was also elevated in the subjects with FDC (6.96 ± 0.89 cm H_2O/L) and did achieve statistical significance despite the small number of subjects in the FDC-negative group. Moreover, when individual data were analyzed, all 22 subjects who demonstrated elevated values for reactance area also had FDC. Following bronchodilator administration, the normal IOS values in the FDC-negative group remained unchanged. The elevated IOS values in the FDC-positive group were bronchodilator responsive in the majority of subjects, and the mean values returned to the upper limit of normal.

Discussion

The present study investigated airway function in a cohort of subjects with new-onset respiratory symptoms after reported exposure to WTC dust/fumes in whom spirometry results were within normal limits. This cohort was specially selected because of reported exposure to WTC dust and were therefore potentially at risk for development of airway disease. Despite normal spirometry results, airway dysfunction was demonstrated based on the following: (1) elevated airway resistance and frequency dependence of resistance as determined by IOS; (2) heterogeneity of distal airway function as demonstrated by both elevated reactance area on oscillometry and FDC; and (3) reversibility of these functional abnormalities to or toward normal following administration of bronchodilator. Since spirometry results were normal in all subjects, these abnormalities likely reflect dysfunction in airways more distal to those evaluated by spirometry.

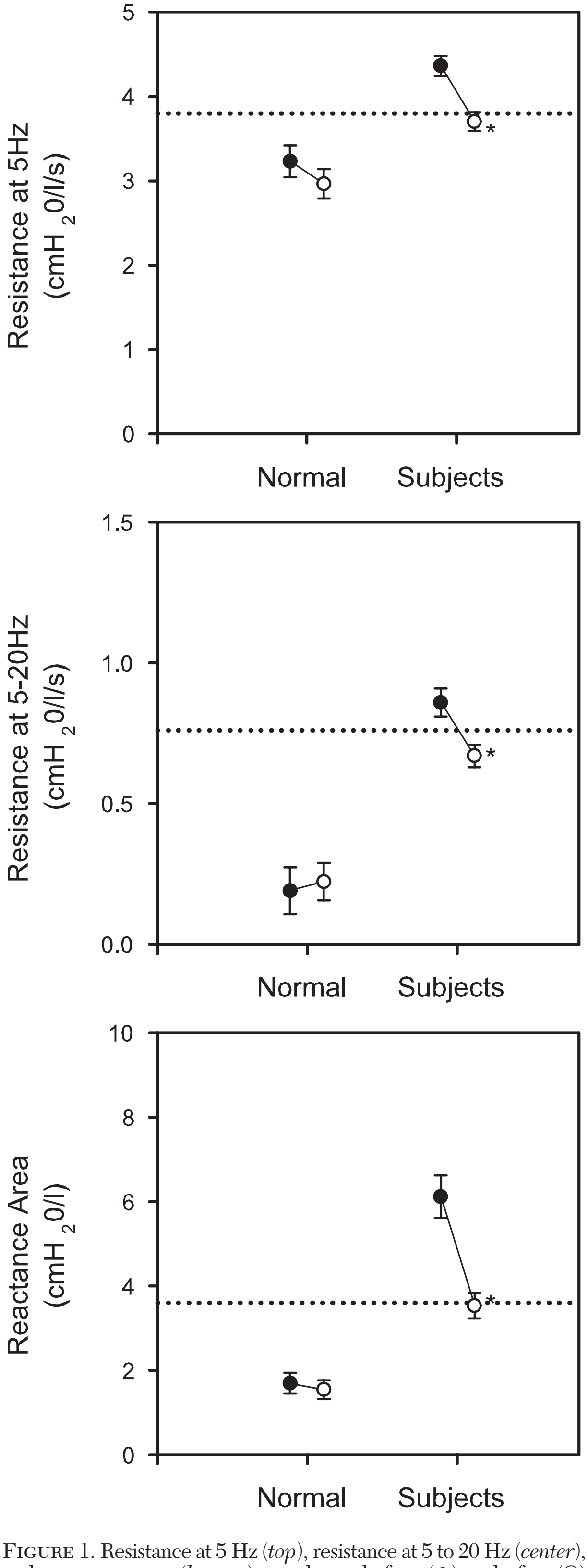

FIGURE 1. Resistance at 5 Hz (*top*), resistance at 5 to 20 Hz (*center*), and reactance area (*bottom*) are shown before (●) and after (○) bronchodilator therapy. The dotted line represents the published upper limit of normal for each parameter. Values are mean ± SE. Statistically significant changes after bronchodilator compared with baseline are illustrated as $^*p < 0.001$. Following bronchodilator administration, mean values for resistance at 5 Hz, frequency dependence of resistance, and reactance area returned to normal.

Subtle markers such as reduction in airflow at mid-lung volume and/or elevated RV/TLC suggest the presence of airways dysfunction.[27–29] These markers may be interpreted as indicators of distal airway dysfunction in the setting of normal large airway function.[14,28,30] Reduction of mid-expiratory flow rate was observed in < 10% of subjects, and RV/TLC was elevated in approximately 33% of subjects. Even when these subtle markers were normal, distal dysfunction could be identified by IOS testing, highlighting the limitations of routine pulmonary function testing for identification of distal airway abnormality.

Airway function has been previously evaluated by oscillometry in WTC dust-exposed ironworkers with normal spirometry results, but abnormalities were identified only in smokers.[10] The present study extends these observations by demonstration of abnormal airway function even after exclusion of subjects with history of smoking, preexisting lung disease, and obesity. The specific anatomic levels of the tracheobronchial tree identified as abnormal based on IOS testing have not been clearly established.[31] However, the pattern of abnormality observed in the present study is compatible with distal airway abnormality based on theoretical considerations.[15,31,32] Resistance at 5 Hz is a global measure that evaluates abnormalities throughout the tracheobronchial tree.[15,32,33] Additionally, frequency dependence of resistance in the 5- to 20-Hz range has been shown to reflect increased resistance and/or heterogeneity of distal airway mechanics.[17,20,34,35] In the present study, spirometry results were normal in all subjects, suggesting that the elevated resistance at 5 Hz probably reflects abnormality in distal airways. In support of this hypothesis, subjects also manifested frequency dependence of resistance, elevated reactance area, and FDC confirming heterogeneity of distal airway mechanics.

This study provided an opportunity to compare oscillometric findings to FDC, the traditional marker of distal airway heterogeneity. Grimby et al[33] and Otis et al[36] hypothesized that heterogeneity of distal airway function would be reflected in both FDC detected by esophageal manometry and frequency dependence of resistance detected by IOS. In addition, Lutchen et al[37,38] demonstrated, based on modeling studies, that heterogeneity of distal airway mechanics produces a frequency dependent increase in lung elastance (a determinant of reactance), providing the rationale for evaluating the relationship between reactance area and FDC performed in the

The graph includes data obtained from the 20 normal subjects studied in our laboratory; in this subgroup, the observed changes after bronchodilation were small and not statistically significant.

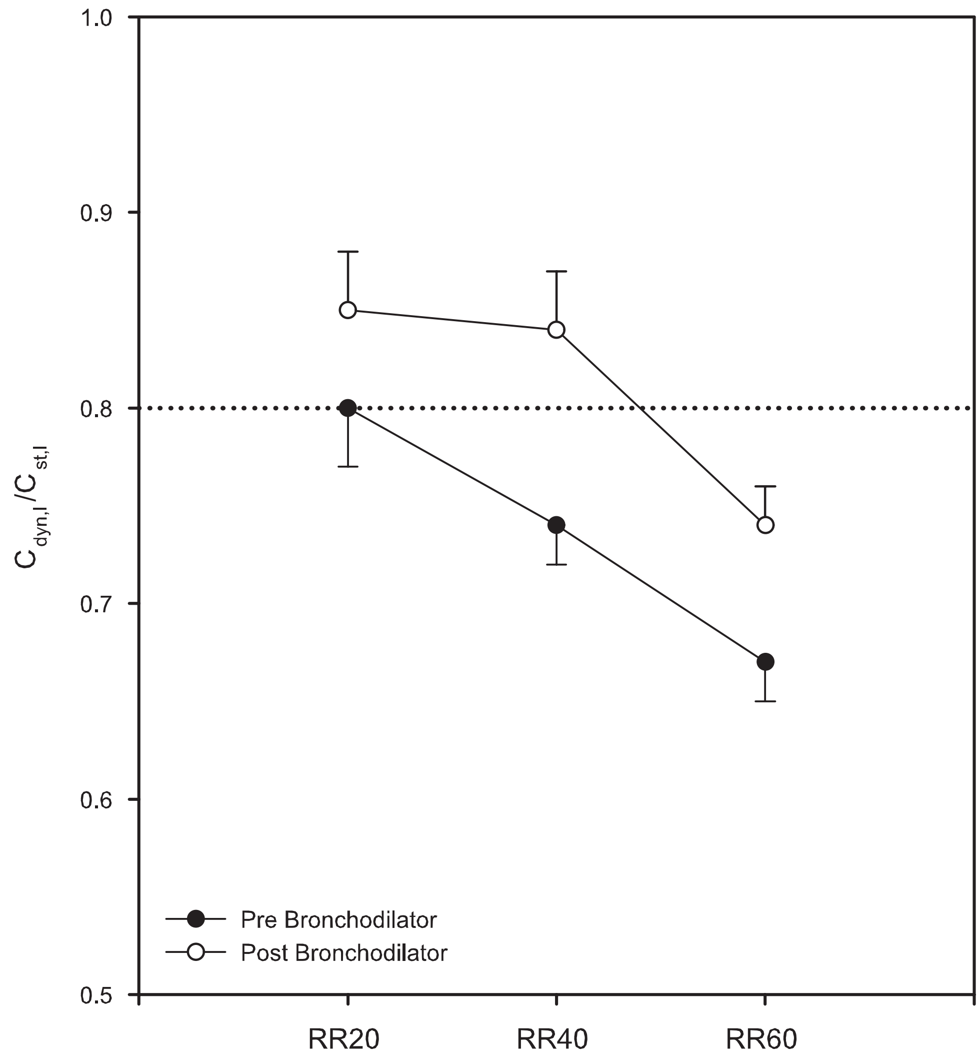

FIGURE 2. Cdyn,1, expressed as percentage of Cst,l, is plotted at each increasing respiratory frequency. Data are shown before (●) and after (○) bronchodilator therapy. The dotted line represents the published lower limit of normal for Cdyn,1/Cst,l at 60 breaths/min (RR60). Values are mean ± SE. The majority of individuals exhibited a decrease in Cdyn,1/Cst,l with increasing breathing frequencies that improved with bronchodilator administration. RR20 = 20 breaths/min; RR40 = 40 breaths/min.

present study. In accord with these considerations, mean values for frequency dependence of resistance and reactance area were elevated in the subjects with FDC compared to subjects without FDC, reinforcing the hypothesis that distal airway function was abnormal in the subjects of the present study. However, when individual data were analyzed, FDC was still observed in some subjects with normal IOS data, suggesting that although they are both tests of distal airway function, FDC may be a more sensitive marker. The sensitivity of IOS may be increased by evaluation of resistance and reactance at lower oscillation frequencies,[38] but this remains to be further explored.

Bronchodilator responsiveness was demonstrated in all tests of distal airway function, including frequency dependence of resistance and peripheral airway heterogeneity as determined by reactance area and FDC. However, despite bronchodilator responsiveness, these tests did not correct to normal in all subjects. This may indicate either poor medication distribution to the distal airways,[39] residual bronchoconstriction, or potential structural abnormalities in the distal airways. Histologic and physiologic evaluation has demonstrated isolated distal airway abnormalities in patients with history of smoking and/or following environmental/occupational exposure to inhaled toxins.[25,27,40]

The relationship between the airway abnormality demonstrated in the present study and WTC dust exposure cannot be definitively determined. Most subjects were previously asymptomatic, sug-

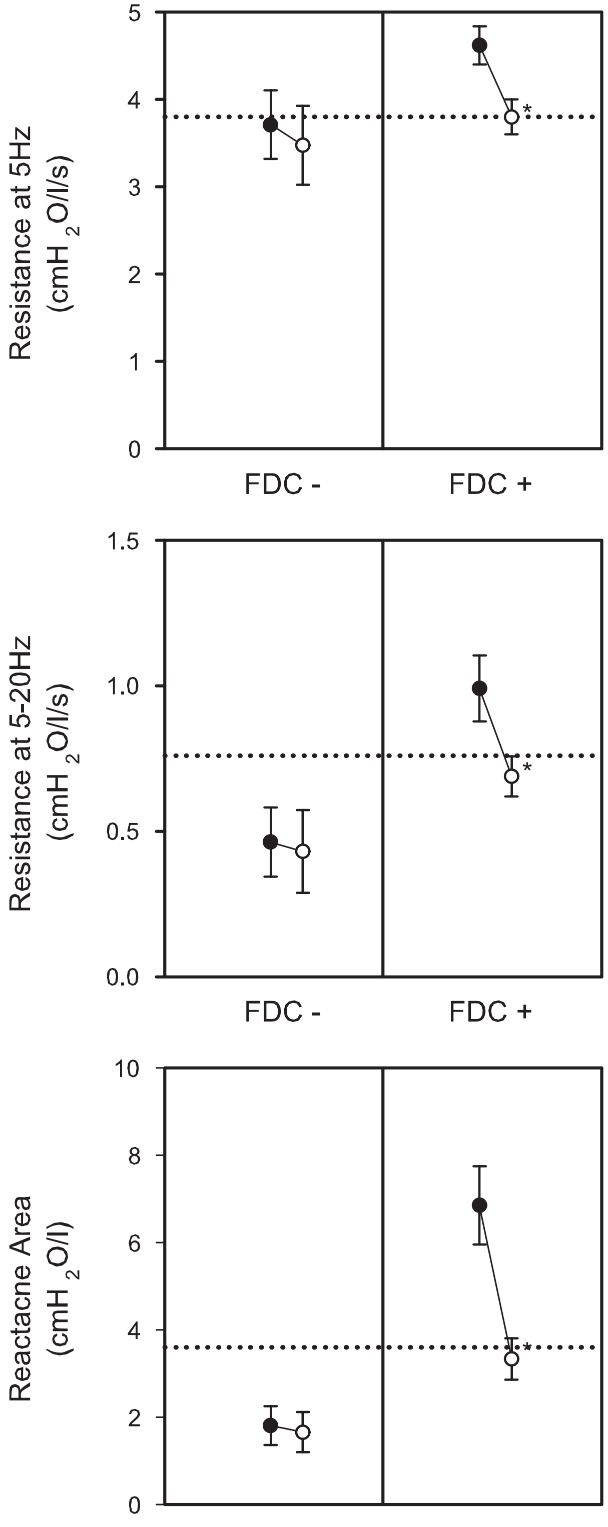

FIGURE 3. Resistance at 5 Hz (*top*), resistance at 5 to 20 Hz (*center*), and reactance area (*bottom*) and their response to bronchodilator (● = before bronchodilator; ○ = after bronchodilator) are shown for subjects without FDC (n = 6) or with FDC (n = 37). Values are mean ± SE. Reactance area distinguished these two groups ($p < 0.02$). Statistically significant changes after bronchodilation compared with baseline are illustrated as $^*p < 0.001$.

gesting causality; however, the absence of preexisting lung disease was determined only by subject report. In addition, exposure assessment could not be accurately quantified in these subjects because this study retrospectively evaluated residents and workers of lower Manhattan with ongoing exposure over weeks to months. Use of respiratory protective devices in this cohort was unlikely, and sporadic use could not be quantified. These factors may contribute to the inability to distinguish exposure categories by physiologic data. Therefore, uncertainty remains about the relationship of the functional abnormalities of the present study to the respiratory symptoms and exposure; histologic evaluation may provide objective data linking WTC dust exposure to a disease process. The present study highlights the importance of examining distal airway function in subjects who present with symptoms suggestive of airways disease but have normal spirometry results.

Examination of distal airway function when spirometry results and thus large-airway function are normal has identified abnormalities in asthmatic patients and smokers.[23,25,41] This study suggests its potential importance in the evaluation of subjects exposed to occupational and environmental hazards.

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