Isolated Small Airway Reactivity During Bronchoprovocation as a Mechanism for Respiratory Symptoms in WTC Dust-Exposed Community Members

Kenneth I. Berger, MD,[1,2]* Samantha Kalish, BA,[1] Yongzhao Shao, PhD,[3] Michael Marmor, MD,[3] Angeliki Kazeros, MD,[1] Beno W. Oppenheimer, MD,[1,2] Yinny Chan,[1,2] Joan Reibman, MD,[1] and Roberta M. Goldring, MD[1,2]

Introduction *Small airway dysfunction occurs following WTC dust exposure, but its role in producing symptoms is unclear.*
Methods *Methacholine challenge (MCT) was used to assess the relationship between onset of respiratory symptoms and small airway abnormalities in 166 symptomatic WTC dust-exposed patients. Forced oscillation testing (FOT) and respiratory symptoms were assessed during MCT. FOT parameters included resistance at 5 and 20 Hz (R_5 and R_{20}) and the R_5 minus R_{20} ($R_{5–20}$).*
Results *Baseline spirometry was normal in all (mean FEV_1 100 + 13% predicted, mean FEV_1/FVC 80 + 4%). MCT revealed bronchial hyperreactivity by spirometry in 67 patients. An additional 24 patients became symptomatic despite minimal FEV_1 change (<5%); symptom onset coincided with increased R_5 and $R_{5–20}$ ($P > 0.001$ vs. baseline). The dose–response of FOT (reactivity) was greater compared with subjects that remained asymptomatic ($P < 0.05$).*
Conclusions *FOT during MCT uncovered reactivity in small airways as a mechanism for respiratory symptoms in subjects with inhalational lung injury.* Am. J. Ind. Med. 59:767–776, 2016. © 2016 Wiley Periodicals, Inc.

KEY WORDS: airway physiology; bronchial hyper-reactivity; forced oscillation; methacholine challenge test; respiratory function

INTRODUCTION

The destruction of the World Trade Center (WTC) released massive amounts of dust and fumes into the surrounding environment. Many community members ("Survivors"), as well as rescue and recovery workers, had acute exposure to the dust clouds from the collapsing buildings and/or chronic exposure from re-suspended dust or from fumes produced by fires that burned for months [Lioy et al., 2002; Offenberg et al., 2004; Reibman et al., 2016]. Although only 1–2% of WTC dust consisted of particles <2.5 μm [Lioy et al., 2002], the extremely large mass of material (~10^6 tons) suggested potential for small, as well as large airways exposure to particulate matter. Indoor dust was

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, NYU School of Medicine, New York, New York
[2]Andre Cournand Pulmonary Physiology Laboratory, Bellevue Hospital, New York, New York
[3]Department of Population Health, NYU School of Medicine, New York, New York
*Correspondence to: Kenneth I. Berger, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, NYU School of Medicine, 240 East 38th Street, Room M-15, New York, NY 10016. E-mail: Kenneth.berger@nyumc.org

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composed of a greater concentration of small particles; >50% of particles had diameters <53 μm [Yiin et al., 2004]. Analysis of pathologic specimens as well as induced sputum revealed particles ranging in size from 1 to 50 μm confirming inhalation of particles into the lower airways [Rom et al., 2002; Fireman et al., 2004; Caplan-Shaw et al., 2011; Lippmann et al., 2015].

New onset or worsening and persistent lower respiratory symptoms (LRS) have now been well-described in "Survivors" and "Responders" [Prezant et al., 2002; Salzman et al., 2004; Skloot et al., 2004; Banauch et al., 2005; Reibman et al., 2005, 2009; Herbert et al., 2006; Lin et al., 2007; Farfel et al., 2008; Brackbill et al., 2009; Friedman et al., 2011; Caplan-Shaw et al., 2014; Jordan et al., 2015]. Abnormalities that contribute to LRS have been reported extensively. Importantly, many of these studies suggest involvement of distal lung units (small airways, alveoli). These findings include expiratory computed tomography images demonstrating mosaic attenuation of lung parenchyma suggesting air trapping [Prezant et al., 2002; Mendelson et al., 2007]. In addition, direct evidence for small airway involvement has been reported on histologic evaluation of lung tissue specimens [Caplan-Shaw et al., 2011]. Whereas histologic data are only available in a small number of WTC dust-exposed individuals, evidence for small airway involvement in larger populations is available from physiologic studies using forced oscillation testing (FOT). FOT is a non-invasive test that assess respiratory resistance during tidal breathing; parameters sensitive to small airway function can be derived (e.g., frequency dependence of resistance). Studies in patients in the Bellevue Hospital WTC Environmental Health Center demonstrated abnormal frequency dependence of resistance on FOT measured by impulse oscillometry (IOS) consistent with small airway dysfunction [Oppenheimer et al., 2007; Berger et al., 2013, 2015a,b]. In a separate case–control study of enrollees in the WTC Health Registry, symptomatic community members demonstrated small airway involvement on oscillometry testing as compared to asymptomatic controls [Friedman et al., 2011].

These studies suggest that small airway abnormalities are important components of WTC inhalational lung injury. However, the link between dysfunction in small airways and LRS is by inference since patients are usually asymptomatic at the time that testing is performed in the laboratory. Bronchial provocation testing with methacholine provides an opportunity to study the relationship between onset of LRS and small airway dysfunction since the predominant effect of methacholine has been demonstrated on small as compared with large airways [Pimmel et al., 1981; Ohrui et al., 1992; King et al., 2005; Tgavalekos et al., 2005; Segal et al., 2011; Beretta et al., 2014]. Therefore, the present study uses spirometry and FOT data obtained during routine methacholine challenge testing to evaluate the direct link between development of LRS and simultaneous development of small airway dysfunction. We hypothesized that distal airway dysfunction may be associated with onset of methacholine-induced symptoms even in subjects without significant spirometric response.

METHODS

This study retrospectively analyzed data from 166 subjects who were referred for methacholine testing from the WTC Environmental Health Center for evaluation of unexplained persistent LRS (cough, dyspnea, wheeze). All subjects had reported exposure to dust from the World Trade Center disaster site with subsequent development of new onset and persistent respiratory symptoms. All subjects demonstrated normal baseline spirometry [Hankinson et al., 1999]. These subjects were tested using a standardized clinical testing protocol, implemented June 2007, that utilized simultaneous measurement of respiratory resistance by oscillometry [Segal et al., 2011]. Data were analyzed from patients who gave consent for entry in a registry approved by our Institutional Review Board.

Methacholine Challenge Testing

Methacholine challenge testing (MCT) was performed in accord with American Thoracic Society (ATS) recommendations [Crapo et al., 2000]. The laboratory protocol required that the ratio between the forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) was greater than 0.7 on the baseline spirometry in order to proceed with the MCT. Increasing doses of methacholine were administered with a 2-min tidal breathing protocol up to a maximum dose of 16 mg/ml. Spirometry and respiratory symptoms (cough, dyspnea, chest tightness, or wheeze) were assessed after each dose of methacholine. The degree of bronchial hyperreactivity (BHR) was determined by the calculated provocative concentration that resulted in a 20% fall in FEV_1 (PC20) [Crapo et al., 2000]. The presence of bronchial hyperreactivity was defined based on ATS recommendations as a $PC20 < 4$ mg/ml. Subjects were instructed to abstain from using short acting β2-agonists for 12 hr, long acting β2-agonists for 48 hr, anti cholinergics for 24 hr, and inhaled corticosteroids for 14 days prior to testing [Crapo et al., 2000]. There were no subjects treated with theophylline or leukotriene antagonists.

FOT was added to the MCT in all subjects. The protocol was designed to assess the relationship between both respiratory symptoms and BHR to FOT abnormalities. Accordingly, FOT was assessed at baseline and at the lowest methacholine dose that resulted in either development of a respiratory symptom or a 20% reduction in FEV_1. For subjects that did not meet these endpoints, FOT was repeated following the 4 mg/ml dose.

Spirometry was performed (Vmax; Carefusion) in accordance with ATS/European Respiratory Society (ERS) recommendations [Miller et al., 2005]. FOT was performed with the Jaeger Impulse Oscillation System (Jaeger, Yorba Linda, CA) during tidal breathing with support of the cheeks. Resistance was calculated from airflow and pressure oscillations between frequencies of 5–35 Hz. Parameters included resistance at oscillation frequencies of 20 Hz (R_{20}) and 5 Hz (R_5) and frequency dependence of resistance calculated as change in resistance between 5 and 20 Hz (R_{5-20}) as a measure of small airway function. Only data from trials with constant tidal volume were analyzed. The volume time tracings were inspected to ensure that there were no pauses suggestive of glottis closure and that there was no leak around the mouthpiece [Bikov et al., 2015]. Since FOT analyzes 150 impulses over a 30-s measurement, coherence >0.7 at 5 Hz and >0.85 at 10 Hz were required [Miller and Pimmel, 1983; Komarow et al., 2011; Berger et al., 2013, 2015a]. Conservative upper limits of normal (ULN) were selected that approximate 150% of mean data in normal subjects [Skloot et al., 2004; Goldman et al., 2005; Berger et al., 2013, 2015b]. Data obtained in our laboratory in 80 asymptomatic nonsmoking subjects with normal spirometry and without lung disease fell within these limits. In addition, the values for the selected upper limits of normal agree with estimates based on recent publications of normative FOT data [Newbury et al., 2008; Oostveen et al., 2013].

Analysis of Respiratory Symptoms During Methacholine Challenge Test

Respiratory symptoms were assessed in all subjects throughout the protocol [Crapo et al., 2000]. The presence or absence of LRS was documented after each methacholine dose in all subjects and, if present, the specific symptom was recorded (cough, dyspnea, chest tightness). In addition, subjects were asked whether the symptom that developed during the MCT was similar to their chronic symptom. Lastly, the resolution of symptoms at the end of the MCT was confirmed in all subjects following administration of bronchodilator.

Data Analysis

Data were summarized either as mean ± standard error (SE) or standard deviation (SD), as indicated. Data for change in FOT parameters in response to methacholine are presented as absolute numeric change to allow analysis of the relative contribution of changes in R_{20} and R_{5-20} to the observed change in R_5. Differences between groups were assessed utilizing a Student's *t*-test or Mann–Whitney U-test for data that were not normally distributed. Analyses were performed utilizing SPSS for Windows version 20.0.

RESULTS

Baseline Data

Subject characteristics for the 166 patients are illustrated in Table I. Mean age was 48 years (range 13–91). Fifty-two percent were female. Prior history of smoking was reported by 29% with 2% reporting current smoking. Predominant symptoms were dyspnea and cough. By design, all patients demonstrated $FEV_1/FVC > 0.70$. Baseline FEV_1 ranged from 72 to 132% of the predicted value. There was minimal evidence for small airway dysfunction on baseline spirometry as only 11 patients (<7%) demonstrated an abnormality in expiratory airflow measured at 50% of the vital capacity.

Figure 1 illustrates baseline oscillometric parameters. Baseline FOT parameters are plotted for each patient as a function of their baseline FEV_1. The dashed lines indicate the upper limits of normal for each FOT parameter. Mean values for oscillometry parameters were elevated above the upper limits of normal ($R_5 = 4.30 \pm 1.44$, $R_{20} = 3.52 \pm 1.06$, $R_{5-20} = 0.78 \pm 0.64$ cmH2O/L/s; mean ± standard deviation). Analysis of individual data demonstrated that

TABLE I. Patient Characteristics

Age (yr)	48 ± 12
Sex (M/F)	80/86
BMI (kg/m^2)	29 ± 5
Smoking history	
Never	69%
Past	29%
Current	2%
Baseline symptoms[a]	
Dyspnea	62%
Cough	48%
Wheeze	14%
Other	28%
Baseline spirometry	
FVC (% predicted)	104 ± 14
FEV_1 (% predicted)	100 ± 13
FEV_1/FVC (%)	80 ± 4

Data are expressed as mean ± SD unless otherwise specified.
BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.
[a]The sum is >100% since symptoms are not mutually exclusive.

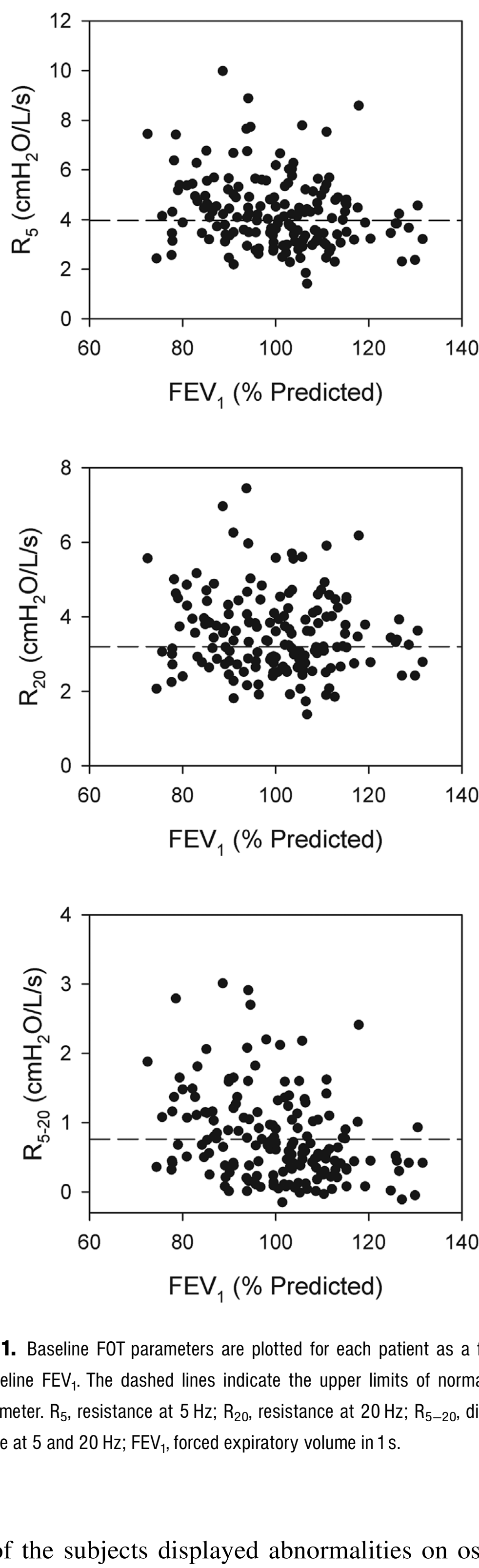

FIGURE 1. Baseline FOT parameters are plotted for each patient as a function of their baseline FEV_1. The dashed lines indicate the upper limits of normal for each FOT parameter. R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, difference in resistance at 5 and 20 Hz; FEV_1, forced expiratory volume in 1 s.

55% of the subjects displayed abnormalities on oscillometry evaluation despite absence of airway obstruction on baseline spirometry (i.e., $FEV_1/FVC > 0.7$). The severity of the oscillometric abnormalities did not relate to history of smoking.

Spirometry Response to Methacholine

BHR was defined as a calculated PC20 < 4 mg/ml, in accord with ATS guidelines. A total of 67/166 subjects demonstrated BHR in response to methacholine, providing a potential mechanism for their chronic LRS related to large airway hyper-reactivity. Respiratory symptoms remained unexplained in the remaining 99 subjects who did not demonstrate BHR. The PC20 was greater than 16 mg/ml in the majority of these latter subjects (n = 78); the remaining 21 subjects were classified as borderline BHR based on PC20 values between 4 and 16 mg/ml.

FOT Response to Methacholine

Figure 2 relates the change in oscillometric parameters to the simultaneous change in FEV_1 during the MCT. Based on the testing protocol, oscillometry was performed when specific conditions were met to allow for assessment of respiratory symptoms and assessment of the relationship between FOT and BHR. Data are plotted for each subject at the maximum dose of methacholine where both FOT and spirometry data were available (range 0.0625–4 mg/ml).

The top graph of Figure 2 shows the relationship between changes in FEV_1 and changes in FOT resistance, as assessed by R_5. The change in FEV_1 varied widely (range +6 to −50%). For subjects who demonstrated a decrease in expiratory airflow (>20% decline in FEV_1), there was a concomitant increase in FOT measures of resistance (R_5) that varied from −1.08 to +12.19 $cmH_2O/l/s$. However, changes in R_5 of similar magnitude (range −2.11 to +8.73 $cmH_2O/l/s$) were noted even in subjects with <20% decrease in FEV_1, including subjects with minimal or no change in FEV_1. On average, the change in R_5 in response to methacholine for the entire cohort was 2.48 ± 2.03 $cmH_2O/L/s$ (dotted line).

The middle and bottom graphs of Figure 2 show similar data that relates the change in R_{20} and R_{5-20} to the simultaneous change in FEV_1 during the methacholine challenge test. The increased R_5 observed in response to methacholine was primarily attributable to increased frequency dependence (R_{5-20}) rather than increased R_{20} (mean change 1.80 ± 1.51 vs. 0.68 ± 0.93 $cmH_2O/L/s$, respectively), compatible with predominant small airway reactivity in response to methacholine. Increased frequency dependence was noted even in patients with minimal change in FEV_1.

Assessment of Respiratory Symptoms During Methacholine Challenge Test

Respiratory symptoms during MCT were noted in 108/166 subjects; the remaining subjects remained asymptomatic at methacholine doses up to 16 mg/ml. In 67 (62%)

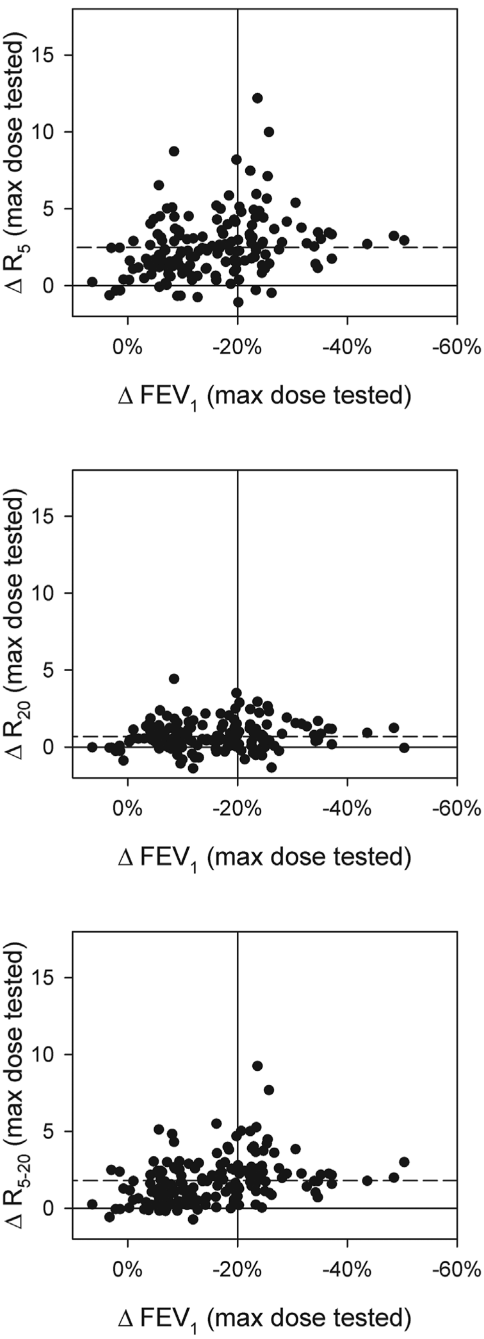

FIGURE 2. The change in FOT parameters observed during MCT is plotted for each patient as a function of corresponding change in FEV_1. The dashed lines indicate the average change in each FOT parameter. R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, difference in resistance at 5 and 20 Hz.

of the subjects who developed respiratory symptoms, the symptoms were associated with BHR as measured by spirometry. Of importance, 24 subjects were identified where the respiratory symptom was unexplained by spirometry since FEV_1 changed minimally (<5%) at the onset of symptoms. Symptoms occurred at variable methacholine dose in these 24 subjects (range 0.0625–4 mg/ml). The most common symptoms reported were chest tightness in 15 subjects, cough in 13 subjects, and dyspnea in 6 subjects. When questioned, 16 subjects confirmed that the symptom that developed during the

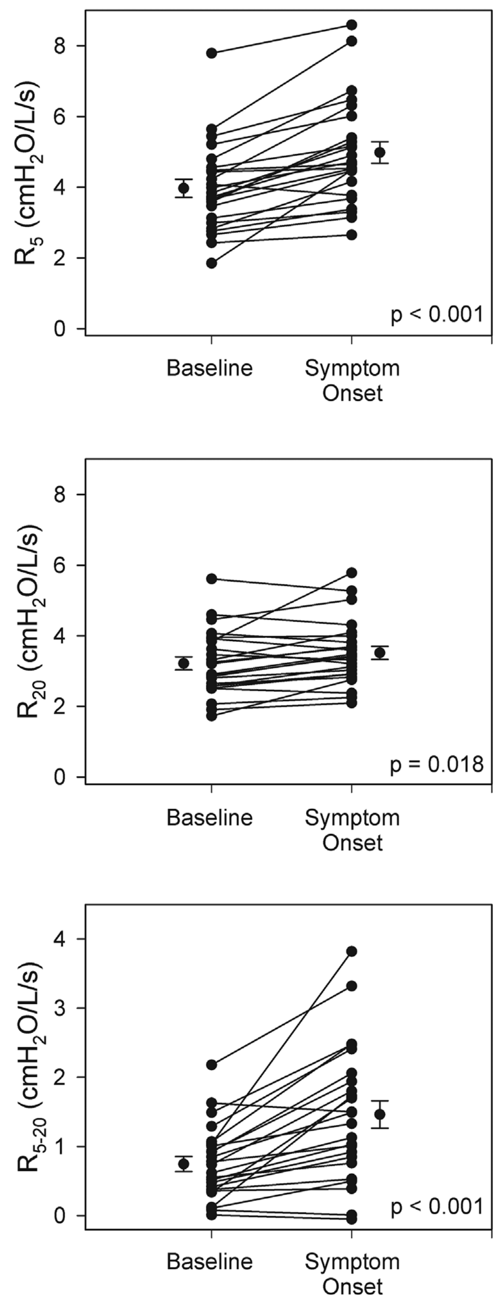

FIGURE 3. FOT parameters are plotted for the 24 subjects that developed respiratory symptoms without change in FEV_1 during MCT. Data are shown for the baseline value and the value noted at the onset of symptoms. The mean values ± SE are also plotted. R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, difference in resistance at 5 and 20 Hz.

MCT was similar to their chronic symptom. Analysis of spirometry data in these subjects revealed that 22/24 tested negative for BHR despite development of respiratory symptoms during the MCT.

Figure 3 illustrates the change in oscillometric parameters from baseline to symptom onset in these 24 subjects whose respiratory symptoms during MCT were not associated with changes in spirometry. Paired comparison revealed a significant increase in R_5 at the onset of symptoms (top panel); the average increase in R_5 was 1.01 ± 0.77 $cmH_2O/L/s$. This increase in R_5 was predominately due to increased frequency dependence (R_{5-20}) rather than to increased R_{20} (0.72 ± 0.68 vs. 0.30 ± 0.52 $cmH_2O/L/s$, respectively). In contrast, assessment of mid-expiratory airflow rates demonstrated minimal change in these individuals despite onset of symptoms (mean % change $-4.9 \pm 1.7\%$), highlighting the limitation of spirometry in identifying small airway dysfunction.

The changes in oscillometric parameters were observed at methacholine doses that varied between subjects. To account for the variable methacholine dose, the data were expressed as percent change in oscillometric parameters per unit methacholine dose. This calculation provides a continuous value that reflects the degree of reactivity for each oscillometry parameter. Figure 4 shows the relationship between degree of reactivity and development of respiratory symptoms. The 24 subjects who developed respiratory symptoms with minimal change in FEV_1 are compared with 11 subjects who remained asymptomatic with a similar change in FEV_1 at the 4 mg/ml methacholine dose. Subjects who remained asymptomatic during MCT demonstrated minimal reactivity for each of the oscillometry parameters. In contrast, development of symptoms was associated with enhanced reactivity of R_5 ($P < 0.05$), despite lack of change in FEV_1. This increased reactivity was attributable to increased reactivity of R_{5-20} rather than R_{20}, compatible with predominant site of action in the small airways. Of these subjects who developed symptoms with enhanced small airway reactivity, the majority (22/24) had negative methacholine tests, as assessed by the change in FEV_1 at the 4 mg/ml methacholine dose.

Response to Bronchodilator

Figure 5 illustrates the change of oscillometric parameters during MCT and its reversal following bronchodilator administration in the 24 subjects that developed LRS with minimal change in FEV_1. All oscillometric parameters returned to baseline following bronchodilator administration. Reversal of oscillometric parameters to baseline was associated with resolution of the methacholine-induced respiratory symptoms in all subjects.

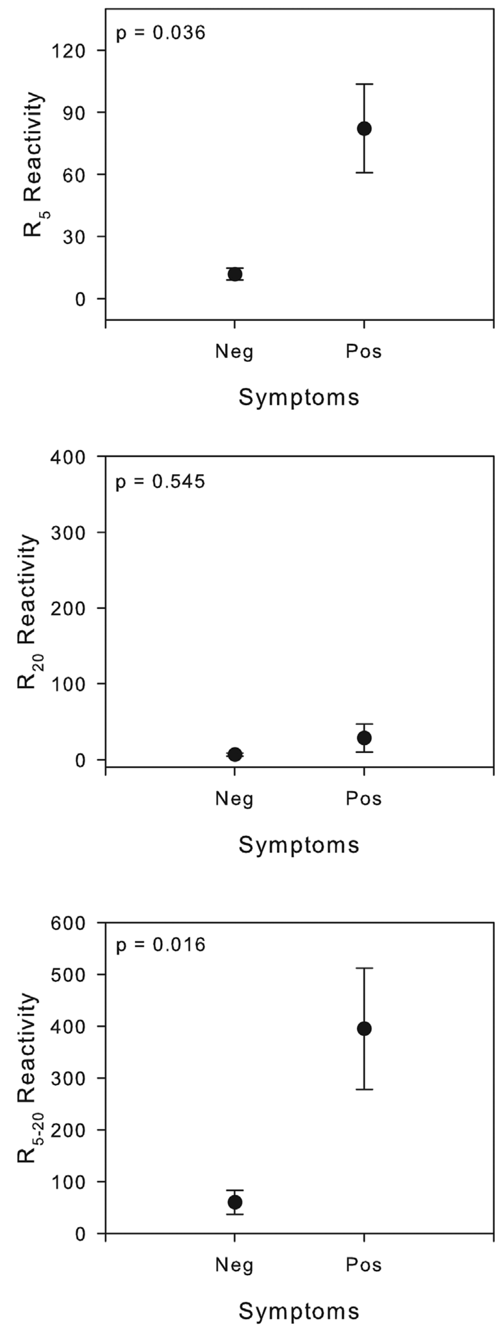

FIGURE 4. Reactivity of FOT parameters is plotted. Mean values $\pm$ SE from 11 subjects that remained asymptomatic with minimal change in FEV_1 at the 4 mg/ml methacholine dose are compared with data from the 24 subjects that developed respiratory symptoms during MCT with similar change in FEV_1. R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, difference in resistance at 5 and 20 Hz.

DISCUSSION

This study evaluated the relationship between measures of large and small airway function and development of respiratory symptoms in a cohort of patients referred from a

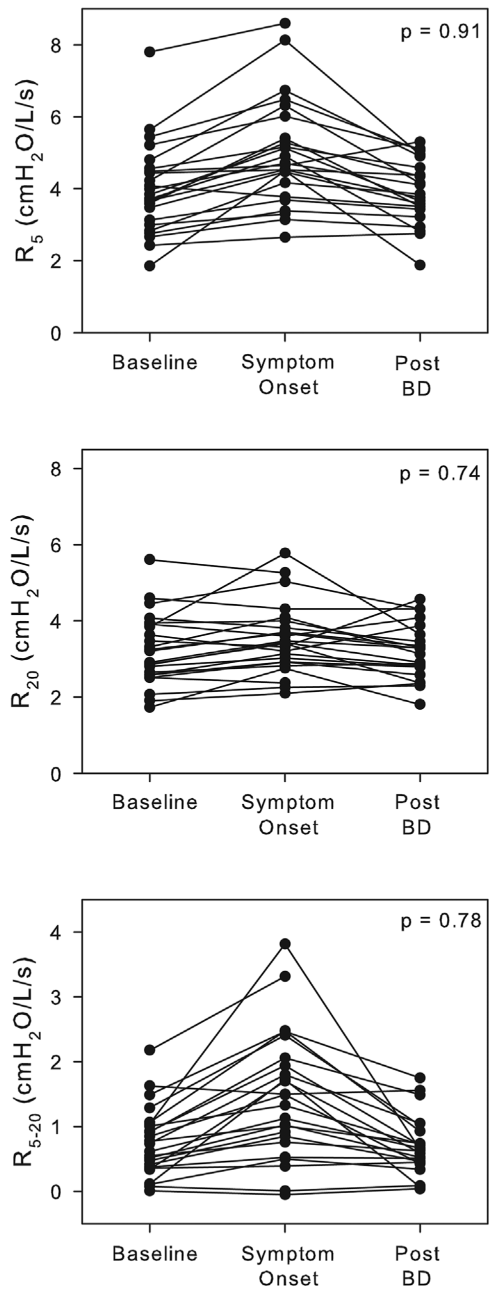

FIGURE 5. FOT parameters are plotted for the 24 subjects that developed respiratory symptoms without change in FEV_1 during MCT. Data are shown for the baseline value, the value noted at the onset of symptoms, and the value noted post bronchodilator (Post BD). The *P* values reflect comparison between baseline and post BD data. R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, difference in resistance at 5 and 20 Hz.

WTC treatment program for evaluation of chronic unexplained respiratory symptoms. Methacholine challenge testing was used to elicit functional changes in subjects with history of exposure to WTC dust. The data demonstrated that many patients developed large airway abnormalities during bronchoprovocation that were associated with lower respiratory symptoms. Importantly, a cohort of the patients developed abnormal FOT measures of small airway function (R_{5-20}) that coincided with development of respiratory symptoms in the absence of BHR and even in the absence of change in FEV_1. Reversal with bronchodilator administration reinforced the link between symptoms and small airway dysfunction. These findings suggest that dysfunction isolated to the small airways may provide an explanation for chronic respiratory symptoms. This study highlights the disparity between proximal and distal airway behavior, which has implications in the identification of disease and evaluation of chronic respiratory symptoms when spirometry is normal.

In the present study, we used methacholine as a provocative agent to explicitly demonstrate a link between simultaneous development of small airway dysfunction and development of LRS. The rationale for this approach is based on accumulated evidence that small airways are the primary site of abnormality during methacholine inhalation. Studies using a wedged bronchoscope demonstrated a direct effect of methacholine and histamine on small airway resistance [Wagner et al., 1990, 1998; Kaminsky et al., 2004]. However, since the drugs were delivered using a using wedged bronchoscope the contribution of large airways was not assessed. Confirmation that the predominant effect of methacholine is a change in peripheral, rather than central, resistance was obtained using a wedged micromanometer into a distal airway [Ohrui et al., 1992]. Whole lung measurements confirmed the peripheral site of action of methacholine using numerous techniques including air trapping as assessed by spirometry [Chapman et al., 2008], and peripheral ventilation defects using imaging [Tgavalekos et al., 2005], and FOT [Pimmel et al., 1981; King et al., 2005; Beretta et al., 2014].

The clinical relevance of small airway dysfunction for development of respiratory symptoms during MCT has been assessed in numerous studies. Initial observations demonstrated that changes in FOT parameters reflecting small airway function precede and are more sensitive than spirometry variables for the detection of bronchoconstriction [Vink et al., 2003]. Subsequently, Mansur et al. [2008] and van der Wiel et al. [2013] demonstrated that symptoms during MCT are more tightly correlated with FOT measures that reflect small airway function than with spirometry. Of note, a significant drop in FEV_1 was observed in these studies and, therefore, a contribution from large airway dysfunction cannot be excluded. Review of data from our laboratory identified a group of patients that developed LRS and abnormal FOT (R_5 and R_{5-20}) during MCT in absence of change in spirometry [Segal et al., 2011]. Since FEV_1 remained unchanged in these patients, the FOT abnormalities can only be attributed to changes in small airway function. The present study extends these data in a larger cohort of patients with potential for inhalational lung injury by demonstrating enhanced small airway reactivity as compared with subjects that remained asymptomatic during MCT. Furthermore, attribution of LRS to isolated small airway reactivity is supported by demonstration that the methacholine-induced symptom reproduced the chronic symptom in the majority of subjects. Reversibility of both symptoms and small airway dysfunction following inhalation of β-agonist provides additional support for this conclusion. The observed reactivity suggests the possibility of persistent small airway inflammation. Although this was not evaluated in the present study, persistent pulmonary and systemic inflammation in patients enrolled in the Bellevue Hospital WTC Environmental Health Center has been demonstrated in other studies [Kazeros et al., 2013, 2015].

The results of the present study have clinical implications with respect to diagnosis of airway hyper-reactivity. The presence of bronchial hyper-reactivity during MCT is defined by the change in FEV_1 [Crapo et al., 2000]. However, whereas the distal airways may be an important site of action for MCT, measurement of FEV_1 may be relatively insensitive to changes in airway caliber in the lung periphery [Mead, 1970]. Accordingly, numerous studies have demonstrated enhanced sensitivity of FOT parameters for detection of bronchoconstriction and development of LRS during MCT [Vink et al., 2003; Mansur et al., 2008; van der Wiel et al., 2013]. Of particular interest is the observation, in the present study, that symptoms can be explained by reactivity in small airways even in subjects who test negative for bronchial hyper-reactivity by conventional spirometric criteria. These findings indicate a role for evaluation of distal airway behavior when spirometry changes minimally in response to methacholine and extends prior observations from this laboratory demonstrating a role for FOT in evaluation of symptomatic subjects when spirometry is normal [Oppenheimer et al., 2007; Berger et al., 2010, 2015b].

A factor to be considered in evaluation of the present study is the interpretation of FOT data in the setting of induced bronchoconstriction. Since FOT assesses the entire respiratory system, abnormalities cannot be assumed to reflect changes in airway mechanics per se. In the present study, the pattern of abnormality was an increase in resistance assessed at slow oscillating frequencies (R_5 and R_{5-20}) with minimal change in high frequency resistance (R_{20}). While this pattern is frequently attributed to non-uniformities in the distribution of ventilation across distal airways (i.e., "parallel non-uniformity), additional explanations are possible. Non-uniformity of airflow can also occur within larger and smaller airways in series producing a similar FOT pattern. Although this may explain simultaneous change in FEV_1 during MCT, it cannot explain symptoms in the subgroup of subjects with isolated abnormalities in FOT parameters. An additional explanation for increased R_5 and R_{5-20} is alterations in tissue properties and resistance. While this factor cannot be excluded in the present study, direct assessment of intrabronchial airway resistance demonstrates that the predominant pharmacologic effect is confined to the peripheral airways [Ohrui et al., 1992]. Lastly, increased upper airway shunt may have contributed to the observed data [Peslin and Fredberg, 1986]; however, the most plausible mechanism for this effect would be as a consequence of increased downstream impedance (e.g., increased airway resistance). These considerations, when coupled with absent change in FEV_1 in many subjects and reversal of findings and symptoms with bronchodilator, suggest that the predominant abnormality induced by methacholine in the present study was an increase in small airway resistance.

In summary, addition of FOT to methacholine challenge testing uncovered reactivity in small airways as a mechanism for chronic respiratory symptoms in a population of subjects with potential for inhalational lung injury following exposure to WTC dust. Although the data do not confirm that the airway injury was sustained as a direct result of exposure to WTC dust, the simultaneous development of symptoms and small airway dysfunction provides a location for disease and a potential target for therapy. Identification of a threshold using oscillometry to define hyperreactivity in the distal airways would require further study. Nevertheless, for a given patient the temporal correlation between development of symptoms and small airway reactivity defines the clinical relevance of this approach to a given individual with persistent and unexplained respiratory symptoms.

AUTHORS' CONTRIBUTIONS

KB, BO, JR, RG contributed to conception or design of the work. All authors contributed to acquisition, analysis, or interpretation of data for the work. All authors contributed to drafting the work or revising it critically for important intellectual content. All authors contributed to final approval of the version to be published. KB, JR, RG contributed to agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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INSTITUTION AND ETHICS APPROVAL AND INFORMED CONSENT

Data were analyzed from patients who gave written consent for entry in a registry approved by the Institutional

Review Board of the New York University School of Medicine (IRB number 06-1).

DISCLOSURE (AUTHORS)

The authors declare no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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