A. OVERALL COVER PAGE

Project Title: Small Airway Chronic Obstructive Disease Syndrome Following Exposure to WTC Dust	
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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

SPECIFIC AIMS
The destruction of the World Trade Center (WTC) on September 11, 2001 resulted in the massive release of dust, gas, and fumes with potential acute (dust clouds, debris on 9/11/01) and chronic (resuspended dust and fumes from fires) inhalation for community members ("Survivors"). The presence and persistence of lower respiratory symptoms (LRS) in Survivors and Responders is now well-documented. Although often managed as asthma, findings associated with LRS include abnormal small airways and alveoli (distal lung units) identified in lung pathologic specimens and physiologic measurements (respiratory oscillometry). These studies suggest that inhalation of toxic agents can produce abnormalities in the distal lung unit that result in lower respiratory symptoms. Our most recent preliminary studies suggest that 1) there is incomplete improvement in spirometry and oscillometry measurements over time, and 2) LRS, particularly dyspnea on exertion, persists despite therapy with high dose inhaled corticosteroid (ICS) and long acting β2-agonist (LABA). The involvement of the distal lung units and the incomplete reversibility of symptoms with ICS/LABA are similar to findings in COPD. Thus we can call this the "small Airway Chronic Obstruction Syndrome" (sACOS).

The persistence of LRS and the resulting functional impairment make it imperative to understand the underlying physiologic and biologic mechanisms in order to improve our therapy. Distal lung unit abnormalities can be revealed/exaggerated during rapid breathing (as during exercise), and result in expiratory flow limitation and/or dynamic hyperinflation providing a potential mechanism for exertional dyspnea. To understand the persistent LRS, we propose to: 1) measure functional abnormalities in distal lung units at rest and during exercise; 2) since responses to ICS/LABA are incomplete, determine whether residual reversibility can be elicited with an anti-muscarinic agent; and 3) identify biologic markers associated with LRS that can lead to new interventions. Our overarching hypothesis is that persistent LRS in WTC "Survivors" are associated with abnormal small airways/distal lung units whose dysfunction is amplified during exercise and are associated with biologic correlates of inflammation and remodeling. The present proposal will address a knowledge gap in inhalational lung injury specifically for WTC "Survivors." Understanding the underlying processes of LRS, particularly dyspnea on exertion, has implications for management of WTC exposed populations and wider implications for other inhalation injuries in which distal lung units may be involved.

SA1. Compared with healthy controls, do "Survivors" with persistent LRS have functional abnormalities in their distal lung units that are revealed during exercise? Hypothesis: Exercise testing with evaluation of distal lung units will reveal reversible and irreversible functional abnormalities associated with LRS.
SA1.a To compare resting lung function in "Survivors" with LRS with asymptomatic controls to characterize large and small airway abnormalities that can lead to heterogeneity of airflow. We will measure functional impairment at rest and with increased respiratory frequency (spirometry and oscillometry). To test for structural distal lung unit abnormalities, we will include measures of alveolar membrane abnormalities (DM). To test for a residual reversible component, we will quantify lung function after inhalation of a targeted anti-muscarinic agent.
SA1.b To compare lung function during exercise in "Survivors" with LRS with controls to characterize large and small airway lung mechanics leading to heterogeneity of airflow and exertional dyspnea. Cardiopulmonary exercise testing with oscillometry and diffusion assessments will be performed. Measures include heterogeneity of distal airflow distribution, expiratory flow limitation and dynamic hyperinflation and DM. Reversibility will be assessed by repeat exercise after inhalation of an anti-muscarinic agent.

SA2. Compared to healthy controls, do "Survivors" with LRS have lung and systemic inflammation associated with markers of remodeling? Hypothesis: patients with persistent LRS will have lung and circulating markers of inflammation and airway remodeling similar to those identified in COPD.
SA2.a To compare serum markers of inflammation and remodeling in patients with LRS and controls. We will measure serum markers of inflammation (IL-6, IL-8, CRP, fibrinogen), Th2 inflammation (periostin, eotaxin) and compare levels in patients with persistent LRS compared to controls. To characterize lung remodeling, we will measure recently described markers of remodeling (YKL-40, VEGF, MMPs) in patients with persistent LRS compared to controls.
SA2.b To compare sputum markers of airway remodeling in patients with LRS compared to controls. Because lung markers

may provide information that reflects local responses, we will perform minimally invasive procedures (induced sputum) to obtain lung/airway samples to measure markers of inflammation and remodeling.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

Closeout Document / *Final Progress Report*

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Grant number: **6 U01OH011317-03-01**

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Abstract

Background: The destruction of the World Trade Center Towers (WTC) on September 11, 2001 resulted in massive release of dust, gas, and fumes with potential acute and chronic inhalation for community members ("Survivors"). The presence and persistence of lower respiratory symptoms in Survivors is now well-documented. Although often managed as asthma, findings associated with respiratory symptoms include abnormal small airways and alveoli (i.e. distal lung units) identified in lung pathologic specimens and physiologic measurements. These studies suggest that inhalation of toxic agents can produce abnormalities in the distal lung unit that result in respiratory symptoms. Our prior research indicates that there is incomplete improvement small airway measurements over time and symptoms, particularly exertional dyspnea, persist despite therapy. The involvement of distal lung units with incomplete reversibility of symptoms upon therapy are similar to findings in chronic obstructive pulmonary disease. Thus, we can call this the "small Airway Chronic Obstruction Syndrome" (sACOS).

Rationale: Our overarching hypothesis is that persistent respiratory symptoms in WTC "Survivors" are associated with abnormal small airways whose dysfunction is amplified during exercise and are associated with biologic correlates of inflammation and remodeling. Symptomatic WTC dust exposed community members provide an opportunity to study the role of small airway dysfunction in producing symptoms that persist despite chronic therapy and occur in the setting of normal airflow on spirometry.

Methods: Symptomatic subjects (n=20) with normal airflow on spirometry and asymptomatic controls (n=7) were recruited from the WTC Environmental Health Center. Small airway dysfunction was assessed at rest, during exercise and following exercise using respiratory oscillometry. Testing was repeated following administration of a long acting anti-muscarinic agent to assess whether additional reversibility is demonstrable in these individuals receiving chronic high dose therapy. Induced sputum and blood were obtained for biomarker assessment

Results: Resting oscillometry measurements demonstrated small airway dysfunction in symptomatic subjects despite normal airflow on routine spirometry. Reversibility of these abnormalities was noted after inhalation of an anti-muscarinic agent. Exercise testing reproduced respiratory symptoms in the symptomatic group. Analysis of expiratory airflow during exercise coupled with respiratory oscillometry during and following exercise uncovered several potential explanations for dyspnea including expiratory flow limitation and/or dynamic hyperinflation during exercise, enhanced small airway dysfunction during exercise and small airway hyper-reactivity following exercise. While therapy with a single dose anti-muscarinic agent was effective at improving small airway function at rest, persistent small airway dysfunction and dyspnea was noted during exercise.

Conclusions: Several mechanisms for persistent dyspnea were identified in WTC dust exposed patients despite normal spirometry and high-dose therapy. Assessment of small airway function demonstrated that dyspnea may be attributable to either small airway dysfunction at rest and/or exercise induced hyper-reactivity in small airways. Therapy with a single dose long acting anti-muscarinic agent was effective at improving small airway dysfunction at rest but with residual abnormality and persistence of exertional dyspnea. This study highlights that assessment of small airway function in addition to spirometry during exercise can uncover a spectrum of abnormalities that may contribute to unexplained dyspnea.

Section 1 of the Final Progress Report

Significant or Key Findings

Specific Aim 1. Compared with healthy controls, do "Survivors" with persistent LRS have functional abnormalities in their distal lung units that are revealed during exercise? Hypothesis: Exercise testing with evaluation of distal lung units will reveal reversible and irreversible functional abnormalities associated with LRS.

- Specific Aim 1a. To compare resting lung function in "Survivors" with LRS with asymptomatic controls to characterize large and small airway abnormalities that can lead to heterogeneity of airflow.
- Specific Aim 1b. To compare lung function during exercise in "Survivors" with LRS with controls to characterize large and small airway lung mechanics leading to heterogeneity of airflow and exertional dyspnea.

Data from symptomatic subjects uncovered several abnormalities at rest and during exercise that are attributable to small airway dysfunction and may explain the chronic lower respiratory symptoms in these individuals.

- Resting abnormalities include presence of small airway dysfunction in nearly 78% of subjects with positive therapeutic response to a long acting anti-muscarnic agent (LAMA).
- Exercise testing was successful at reproducing patient symptoms and uncovered additional mechanisms for dyspnea related to small airways dysfunction. Abnormalities include expiratory flow limitation during tidal breathing with or without dynamic hyperinflation in 67% of subjects and large or small airway reactivity post exercise in 50% of subjects.
- Reversibility of exercise findings: Patients were re-studied after administration of a LAMA to determine reversibility of the exercise induced abnormalities. There was improvement in small airway function during exercise, but a single dose of medicine did not result in improved symptoms.
- These small airway abnormalities were not apparent in the asymptomatic control group
- Of importance, the small airway abnormalities were demonstrable by oscillometry during tidal breathing, but they were not apparent from spirometry assessment of maximal expiratory airflow during forced exhalation.
- Data presentation: These data were presented as an abstract at the 2020 annual meeting of the American Thoracic Society (held virtually due to COVID-19) and will also be presented at the next semi-annual CDC/NIOSH World Trade Center investigator meeting. A manuscript with detailed description of experimental methods and results is currently being prepared for peer review and publication in a scientific journal

Specific Aim 2. Compared to healthy controls, do "Survivors" with LRS have lung and systemic inflammation associated with markers of remodeling? Hypothesis: patients with persistent LRS will have lung and circulating markers of inflammation and airway remodeling similar to those identified in COPD.

- Specific Aim 2a. To compare serum markers of inflammation and remodeling in patients with LRS and controls.
- Specific Aim 2b. To compare sputum markers of airway remodeling in patients with LRS compared to controls.

Subject recruitment was severely curtailed due to COVID 19 pandemic. Consequently, the study lacks sufficient power to draw inferences regarding biologic mechanisms for the small airway abnormalities observed in specific aim 1. Of note, there was a small group of individuals that did demonstrate elevated eosinophils, which suggests potential for targeted therapy. This will need to be studied in future clinical trials to assess therapeutic efficacy.

Translation of Findings.
The observed findings indicate that monitoring for occupational and/or environmental lung injury should be modified to include assessment of small airway function in addition to routine spirometry. This conclusion is based on the concept that spirometry may identify airway injury as a reduction in lung volume or air flow, however, spirometry can often be normal even in symptomatic patients, particularly when injury is located in the distal airways. Prior data from our program has demonstrated an association between presence of small airway dysfunction and presence of new onset and persistent respiratory symptoms following exposure to inhaled toxins caused by the collapse of the World Trade Center on September 11, 2001. The present study extends these observations by establishing a direct link between exertional dyspnea and simultaneous enhancement of small airway dysfunction. We further demonstrate that these findings may occur despite chronic high dose therapy with ICS and LABA medications. A key finding in the present study is that many individuals demonstrate residual reversibility upon administration of a single dose of a LAMA.

It must be emphasized that the presence and reversibility of these small airway abnormalities were only demonstrable by oscillometry during tidal breathing, but they were not apparent from spirometry assessment of maximal expiratory airflow during forced exhalation. These studies build upon prior histologic and functional evidence for distal airway abnormalities as a manifestation of obstructive lung diseases. Thus, characterization of distal airway injury in addition to standard spirometry is crucial in determination of both optimal medical therapy and assessment of changes over time. Moreover, identification of distal airway injury may be an early marker of disease that may be progressive but may also be amenable to therapy.

Research Outcomes/Impact. It is anticipated that the results of our studies may have impacts on several areas of occupational and environmental respiratory health. First, our data support additional of oscillometry to routine spirometry to monitor for inhalational lung injury in at-risk populations. Our data clearly establish that this change will allow identification of small airway disease at a time point prior to development of impaired airflow on spirometry. Second, the data indicate that therapy for symptomatic patients should consider use of a broad range of medications in addition to ICS and LABA. Lastly, longitudinal monitoring will be enhanced by inclusion of small airway metrics to establish improvement in respiratory health.

Section 2 of the Final Progress Report

SPECIFIC AIMS

The destruction of the World Trade Center (WTC) on September 11, 2001 resulted in the massive release of dust, gas, and fumes with potential acute (dust clouds, debris on 9/11/01) and chronic (resuspended dust and fumes from fires) inhalation for community members ("Survivors"). The presence and persistence of lower respiratory symptoms (LRS) in Survivors and Responders is now well-documented. Although often managed as asthma, findings associated with LRS include abnormal small airways and alveoli (distal lung units) identified in lung pathologic specimens and physiologic measurements (respiratory oscillometry). These studies suggest that inhalation of toxic agents can produce abnormalities in the distal lung unit that result in lower respiratory symptoms. Our most recent preliminary studies suggest that 1) there is incomplete improvement in spirometry and oscillometry measurements over time, and 2) LRS, particularly dyspnea on exertion, persists despite therapy with high dose inhaled corticosteroid (ICS) and long acting β_2-agonist (LABA). The involvement of the distal lung units and the incomplete reversibility of symptoms with ICS/LABA are similar to findings in COPD. Thus we can call this the "**s**mall **A**irway **C**hronic **O**bstruction **S**yndrome" (sACOS).

The persistence of LRS and the resulting functional impairment make it imperative to understand the underlying physiologic and biologic mechanisms in order to improve our therapy. Distal lung unit abnormalities can be revealed/exaggerated during rapid breathing (as during exercise), and result in expiratory flow limitation and/or dynamic hyperinflation providing a potential mechanism for exertional dyspnea. To understand the persistent LRS, we propose to: 1) measure functional abnormalities in distal lung units at rest and during exercise; 2) since responses to ICS/LABA are incomplete, determine whether residual reversibility can be elicited with an anti-muscarinic agent; and 3) identify biologic markers associated with LRS that can lead to new interventions. Our overarching hypothesis is that persistent LRS in WTC "Survivors" are associated with abnormal small airways/distal lung units whose dysfunction is amplified during exercise and are associated with biologic correlates of inflammation and remodeling. The present proposal will address a knowledge gap in inhalational lung injury specifically for WTC "Survivors." Understanding the underlying processes of LRS, particularly dyspnea on exertion, has implications for management of WTC exposed populations and wider implications for other inhalation injuries in which distal lung units may be involved.

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SA2.a To compare serum markers of inflammation and remodeling in patients with LRS and controls. We will measure serum markers of inflammation (IL-6, IL-8, CRP, fibrinogen), Th2 inflammation (periostin, eotaxin) and compare levels in patients with persistent LRS compared to controls. To characterize lung remodeling, we will measure recently described markers of remodeling (YKL-40, VEGF, MMPs) in patients with persistent LRS compared to controls.

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BACKGROUND

The destruction of the 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.[1-3] Although 1-2% of outdoor dust consisted of particles <2.5µm,[1] the extremely large mass of material (~1 x106 tons) suggested potential for small, as well as large airways exposure to particulate matter. Indoor dust was composed of a greater concentration of small particles; > 50% of particles had diameters <53µm.[4] Analysis of pathologic specimens as well as induced sputum revealed particles ranging in size from 1 to 50µm confirming inhalation of particles into the lower airways.[5-8]

<u>The Bellevue WTC Environmental Health Center (WTC EHC) and respiratory symptoms:</u> We were the first group to report adverse health effects in local community members.[9,10] In 2005, in response to requests from local community groups, Bellevue Hospital, an affiliate of the New York University School of Medicine and a public hospital in New York City, began a standardized medical program to provide treatment to local workers, residents, and cleanup workers with physical symptoms thought to be associated with WTC exposures.[3,11] The program started as a small community-participatory treatment program, and was subsequently funded by the American Red Cross, followed by the City of New York. In 2008, the Bellevue WTC EHC program received its first Federal funding and two additional treatment sites were added: Elmhurst Hospital and Gouverneur Treatment Center. The WTC EHC was included as the "Center of Excellence" for community members, called "Survivors" under the James Zadroga Health and Compensation Act of 2010.

New onset or worsening and persistent respiratory symptoms have now been well-described in "Survivors" and "Responders."[9,11-22] We, and others suggest an interplay of comorbid mental health symptoms and LRS. However, abnormalities that contribute to LRS have also been reported extensively. Importantly, many of these studies suggest an involvement of small airways or distal lung units (small airways, alveoli). These findings include expiratory computed tomography images demonstrating mosaic attenuation of lung parenchyma suggesting air trapping[12,23] and studies by our group that include:

- demonstration of lung pathology in "Survivors" with a variety of pathologic changes in the small airways and surprising evidence of parenchymal destruction.[6]

- studies of symptomatic community members compared to asymptomatic members enrolled in the WTC Health Registry suggesting distal lung involvement as measured by oscillometry.[22]
- studies in patients in the WTC EHC showing abnormal respiratory oscillometry consistent with abnormal distal lung function.[24-27]

These studies suggest that abnormalities in the distal lung are important components in WTC inhalational lung injury. However, the link between dysfunction in small airways and exertional LRS is by inference and the physiologic mechanisms producing dyspnea remain unexplained.

Persistent LRS and role of distal lung units: Our recent studies during our previous funding periods suggest that spirometry measurements improve in many in the WTC EHC cohort yet LRS remained chronic.[21,28] Our recent preliminary studies show that despite improvement in spirometry, oscillometry measurements remain abnormal.[29] Furthermore, LRS, particularly dyspnea on exertion, persist despite high dose therapy with inhaled corticosteroid (ICS) and long acting β_2-agonist (LABA) (current study in progress). These findings have several implications. We suggest that the combination of the presence of pathologic changes, persistent physiologic abnormalities in the distal lung units, and the incomplete improvement in symptoms with standard asthma therapy, suggest a clinical syndrome similar to COPD. Thus we have called this syndrome in the WTC "Survivors," the "small airway chronic obstruction syndrome" (sACOS). The persistence of LRS and the resulting functional impairment of the WTC-exposed populations makes it imperative to understand the underlying physiologic abnormalities that produce these symptoms to improve our therapy.

Importance of studying patients during exercise: Studies of WTC "Survivors" and "Responders" have been performed at rest, however, most LRS occur with exertion. Exercise assessment can reveal abnormalities in lung mechanics, which may be undetected at rest.[30,31] Abnormalities in different areas of the lung (large and small airways, distal lung units) lead to heterogeneity of airflow, which becomes more pronounced during rapid breathing, as seen during exercise. The resulting expiratory flow limitation and/or dynamic hyperinflation provides a potential mechanism for exertional dyspnea. Alveolar membrane remodeling is an additional abnormality that may contribute to distal lung dysfunction and exertional dyspnea. Lastly, studies with and without bronchodilator can reveal these components of lung physiology and provide potential therapeutic targets. An understanding of mechanisms of heterogeneity of airflow distribution that can occur during exercise is critical because of its association with negative mechanical and sensory consequences.

Importance of studying underlying biology: To date, we have treated most symptomatic WTC EHC and responder patients as if they had "asthma" with inhaled corticosteroids (ICS) and LABAs.[32,33] Despite this treatment, many remain symptomatic.[20,21] Since medication non-adherence is the most common cause of lack of control, our recent study asked whether patients had uncontrolled symptoms despite adherence to high dose ICS/LABA. Our preliminary data suggest that despite monitored use of high dose ICS/LABA, median Asthma Control Test (ACT) scores were unchanged, and less than 30% of the patients had an improvement in symptoms. This absence of improvement may be due to structural changes in the lung, or to a relatively ICS-resistant process – a process more reminiscent of COPD. A heterogeneic inflammatory response has been described for both asthma and COPD, and patients with the asthma-COPD overlap syndrome, and the importance of biologic markers recognized.[34,35] Cluster analyses performed in large asthma cohorts,[36,37] including our own,[38] confirm clinical and biologic heterogeneity. A recent analysis of severe asthma suggests that multidimensional endotyping with a combination of clinical, pathologic and inflammatory parameters can be used to identify clusters, and thus biologic underpinnings.[39] These clusters include those which would be relatively corticosteroid resistant. COPD is also characterized by heterogeneity at the etiologic, mechanistic,

physiologic, and clinical levels. Recent clustering studies in COPD have incorporated biomarkers including C-reactive protein (CRP) and fibrinogen to characterize heterogeneity.[40] Our previous studies in the WTC EHC suggest an association of peripheral eosinophils in some patients with wheezing, and an association of systemic CRP levels with oscillometry measurements, suggesting heterogeneity within this population. We therefore propose to perform measurements of biomarkers of inflammation and remodeling associated with both asthma and COPD to further characterize chronic LRS. The relative resistance to ICS/LABA, the chronicity of symptoms, and the resulting functional impairment of the "Survivors" and "Responders" makes it imperative to understand the underlying biology that produce these symptoms in order to improve our therapy.

Impact of the study: Our proposal addresses several areas of interest cited within the relevant program announcement (PAR-16-098) and one of the broad research goals of the Zadroga Act, i.e., "Diagnosing WTC related health conditions for which there has been diagnostic uncertainty." The project further qualifies for consideration because it investigates two of the major areas of interest listed in the PAR: (1) "identifying phenotypes and biomarkers"; and (2) "improve diagnosis and treatment activities." Finally, our proposal addresses one of the "relevant diseases or conditions" listed in the PAR, namely respiratory diseases

This study uses the infrastructure developed for other studies funded by CDC NIOSH to describe the nature of WTC dust induced lung disease. The proposal capitalizes on the complimentary academic fields of the investigators with expertise in clinical and translational studies, pulmonary physiology and biostatistics. The study expands upon our longstanding collaboration that has resulted in 16 published manuscripts in WTC dust exposed cohorts[6,9,11,24-26,28,41,42] including 4 in preparation or submitted;[21,29,43,44] some of these have resulted from an additional collaboration with the NYC Department of Health.[20,22,45] These studies have highlighted the interaction of environmental insult with damage to the distal lung units. The current study addresses a problem that results in significant impairment and will improve our ability to manage this impairment. The use of measurements in multiple domains, including standard patient reported outcomes and lung function, measures of lung mechanics during exercise, and biomarkers of systemic and lung inflammation will allow for multidimensional analyses with potential to reveal new targets for intervention. The assessment with long acting antimuscarinic agents may provide rationale for an additional therapeutic approach for these patients. It is anticipated that the results of this study will be useful to respiratory health physicians caring for both "Survivors" and "Responders" and that the results of these studies will have implications to diagnosis and management of a broader population of patients with airway diseases (asthma, COPD, and inhalational / environmental injury).

Rigor and transparency:

Rigor or existing data on which this study is based:

The preliminary data and basis for the current hypothesis is robust and reflected in all WTC exposed populations. Specifically, small airway dysfunction has been directly demonstrated using OSCILLOMETRY in survivors and enrollees in the WTC Health Registry.[22,24,26] In addition, indirect evidence for small airway dysfunction has been demonstrated by air trapping on expiratory computed tomography and parallel reduction in FEV_1 and FVC in the responder population including the New York City firefighters.[12,14,23] In addition, persistence of symptoms and functional abnormality despite therapy has been demonstrated in all of above populations.[20,45,46] Lastly, the relationship between abnormal lung mechanics during exercise and exertional dyspnea is well established in obstructive lung diseases.[30,31,46]

Rigorous experimental design:
The experimental design for physiologic assessment uses well established tools that are applied in a novel manner to specifically relate the onset of symptoms to the simultaneous underlying physiologic abnormality. In addition, selection of patients without evidence for large airway obstruction on baseline spirometry (i.e. normal FEV_1/FVC) allows attribution of exercise induced abnormalities to the distal lung. Lastly, although the level of exertion will, by definition, be dependent on patient effort, the primary physiologic endpoints are obtained during tidal breathing and are independent of patient effort.

Consideration of relevant biological variables:
Data suggest that multiple inflammatory / remodeling pathways may be active in WTC exposed individuals. Response to bronchodilator, presence of bronchial hyper-reactivity and improvement with therapy prescribed per current asthma guidelines contrast with absence of elevated FeNO and association of peripheral eosinophils in only a subset of WTC EHC patients, presence of elevated CRP, and alveolar destruction on histologic evaluation.[6,12,24,25,28,41,42] Thus, the proposed experimental design will investigate airway and systemic inflammation and evaluate inflammatory pathways of COPD as well as those involved in the type 2 immune response. Evaluation will include both systemic (blood) and intrapulmonary inflammation (induced sputum).

INNOVATION
This proposal is anticipated to have a broad impact on diagnosis and management of toxic inhalation induced chronic airway injury and has numerous areas of innovation:

- The concept of sACOS, or a syndrome with areas of distal lung unit abnormalities resulting from inhalational injury that lead to persistent LRS is a novel concept. Characterization of this syndrome will have important implications for WTC-exposed patients as well as enhance understanding of inhalational lung injury in response to other toxic agents.
- Selection of patients without evidence for large airway obstruction on baseline spirometry (normal FEV_1/FVC) allows attribution of oscillometry and D_M abnormalities to the distal lung.
- The evaluation of dyspnea with the use of exercise studies with measurements of distal lung unit function during constant work is timely and novel.[46,47] These studies will allow us to understand the relationship of physiologic abnormalities to the dyspnea described by these patients, and will identify areas that need to be targeted (small airway/distal lung units, reversible components).
- Use of respiratory studies with increased rates of breathing concurrent with exercise studies will allow evaluation of these two techniques, with potential for future development of the use of rapid breathing at rest to elicit OSCILLOMETRY response as a surrogate for exercise response. This would have significant clinical implications for diagnosis and evaluation of treatment for this as well as other populations.
- The evaluation of distal lung unit function in response to an anti-muscarinic agent is novel in this population and may provide rationale for addition of this agent in the management of these patients.
- Finally, the evaluation of chronic small airway/distal unit abnormalities in combination with systemic and respiratory biomarkers of both asthma and COPD is novel. Identifying inflammatory pathways such as those seen in COPD vs. asthma will allow for targeted therapy in this population.

METHODS

SA1. Compared with healthy controls, do "Survivors" with persistent LRS have functional abnormalities in their distal lung units that are revealed during exercise?

Rationale: The persistence of LRS in the WTC-exposed populations is a significant problem. Heterogeneity of airflow, which can be undetected by spirometry, but which becomes more pronounced during rapid breathing such as that seen with exercise, can result in expiratory flow limitation and/or dynamic lung hyperinflation leading to dyspnea on exertion. Prior studies demonstrating abnormalities in the distal lung units have been obtained at rest when symptoms are not present; thus, the link between dysfunction in small airways and exertional LRS is by inference and additional physiologic abnormalities may be revealed by exercise. Indeed, a recent pediatric study reported that baseline oscillometry measurements were not associated with severity of exercise induced bronchospasm.[48] In this proposal, the link between abnormal distal lung units and LRS will be characterized using physiologic studies of lung mechanics that extend beyond standard spirometry and our previous oscillometry evaluation. Data will be analyzed to more fully characterize both the reversible component of small airway function, as well as irreversible physiologic abnormalities.

Hypothesis: Exercise testing with evaluation of distal lung units will reveal reversible and irreversible functional abnormalities associated with LRS.

Goals: To characterize the role of distal lung unit abnormalities in DOE using a constant work rate test (CWRET) with measures of heterogeneity of airflow, expiratory flow limitation, dynamic hyperinflation, and alveolar membrane diffusion.

Preliminary data for Specific Aim 1:

Persistence of LRS: Our analysis of the WTC EHC cohort suggests persistent LRS, which remain uncontrolled in many of our patients. In a recent analysis, > 60% of 944 WTC EHC patients with complete spirometry and oscillometry data, continued to report severe LRS at monitoring (Caplan-Shaw unpublished data). We are currently completing a CDC-NIOSH funded study to characterize LRS after 3 month treatment with high dose ICS/LABA including measures of resting lung function and vocal cord dysfunction. Data from the 66 patients enrolled to date were analyzed. Despite adherence to ICS/LABA, median ACT score is unchanged and only 11 patients developed improvement in LRS (>3 point increase ACT).

Involvement of distal lung unit: We showed abnormal oscillometry measurements in the WTC exposed population[24] and subsequently demonstrated abnormalities in oscillometry measurements in the WTC Registry associated with both WTC exposures and symptoms.[22,45] More recently, we showed an association of abnormal oscillometry measurements in the WTC EHC population associated with both presence and severity of LRS.[26] In the interim analysis of our ongoing study, we suggest that despite therapy, most patients (68%) had abnormal small airway function as measured by oscillometry and 35% had persistent hyperreactivity as measured by a methacholine challenge test (PC20 < 8). Our preliminary study of the WTC EHC cohort also suggests that although longitudinal analysis suggested overall improvement in spirometry,[28] oscillometry measurements remain abnormal in most.[29] Moreover, we have shown that measures of oscillometry, specifically, reactance area (AX) a measure of airflow heterogeneity, is increased with increased respiratory rate in patients with distal airway disease.[49] Taken together, these studies point to the presence of abnormalities in the distal lung that remain abnormal despite standard therapy and may be detected with respiratory maneuvers.

Cardiopulmonary exercise testing (CPET): Dyspnea and exercise limitation can also be produced by an increased peripheral airway resistance. This effect has been shown to occur in response to breathing cold dry air and to hyperventilation, as occurs during exercise.[50,51] Decreased exercise capacity in asthma subjects with normal FEV_1 is correlated with tidal flow limitation and dynamic hyperinflation rather than changes in FEV_1, compatible with small airway collapse in absence of large airway changes.[52] Using increased respiratory rate as a surrogate for exercise, we showed that measures of oscillometry increased with respiratory rate in patients with frequency dependence of compliance.[49] Expiratory flow limitation accompanies hyperinflation in patients with diseases such as COPD[30] and recent European Respiratory Society Statements reviewed measurement properties of commonly used exercise tests in patients with chronic respiratory diseases and recommended the use of the Constant Work-Rate Exercise test (CWRET) for evaluation of dyspnea.[47,53] These studies highlight the importance of exercise studies for the characterization of mechanisms of dyspnea.

Experimental plan for Specific Aim 1.

We propose to study WTC EHC patients with persistent LRS (n = 40) and compare findings to an asymptomatic control WTC EHC population (n = 20). Recruitment will include additional subjects (total n = 75) to account for expected dropout. Briefly, patients from the WTC EHC will be defined as having persistent LRS based on chart review and the presence of LRS on study V1 including dyspnea on exertion in the preceding month, an ACT score < 20, use of ICS/LABA, and normal spirometry. Detailed inclusion/exclusion criteria are shown (Table 1). A scheme for the study protocol is shown in Fig. 1 and Table 2. The scheme includes baseline values, including questionnaires assessing multiple domains of symptom severity and frequency, quality of life and functional status used for asthma and COPD studies.

Table 1. Inclusion / Exclusion criteria

Inclusion Criteria for sACOS	**Inclusion Criteria for Control**
Age ≥ 18 years Onset of LRS after 9/11/01 ACT <20 on Monitoring ACT < 20 on V1 FEV_1 > 70% predicted on Monitoring Using ICS/LABA at Fluticasone equivalent > 250/50 bid Normal chest radiograph Provides informed consent	Age ≥ 18 years Absence of LRS ACT <20 on screening ACT < 20 on V1 FEV_1 > 70% predicted No ICS/LABA/LAMA Provides informed consent
Exclusion Criteria for sACOS	**Exclusion Criteria for Control**
Current tobacco use > 10 p-y tobacco Unstable cardiac disease Uncontrolled HTN, DM Musculosketal inability to exercise LAMA use in past 2 weeks Using oral corticosteroid Any other pulmonary disease including sarcoidosis, ILD Pregnancy / plans to become pregnant, lactation History of narrow angle glaucoma	Current tobacco use > 10 p-y tobacco Unstable cardiac disease Uncontrolled HTN, DM Musculosketal inability to exercise Using ICS/LABA/SABA/LAMA/LAMA Using oral corticosteroid Any other pulmonary disease including sarcoidosis, ILD Pregnancy / plans to become pregnant, lactation History of narrow angle glaucoma

Table2. Schedule of assessments

	V1	V2	V3	V4
Consent	X			
Inclusion / exclusion	X			
Physical exam	X			
ECG	X			
Questionnaires				
ACT	X			
SF12	X			
ASUI	X			
CCQ	X			
MMRC	X			
Blood	X			
Pre LAMA resting studies				
Spirometry	X			
OSCILLOMETRY	X			
IC	X			
Plethysmography	X			
D_LCO	X X			
D_LNO				
Post LAMA resting studies				
Spirometry	X			
OSCILLOMETRY	X			
IC	X			
Plethysmography	X			
D_LCO	X X			
D_LNO				
Incremental CPET (AT)		X		
Pre LAMA CWRET*			X	
Post LAMA CWRET*			X	
Sputum induction				X

* Borg scale, oscillometry, tidal flow rates, D_LNO

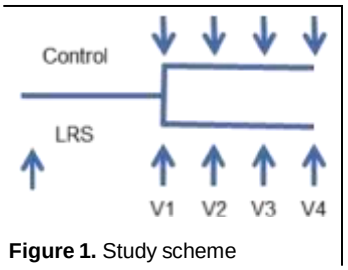

Figure 1. Study scheme

SA1.a To compare resting lung function in "Survivors" with LRS with asymptomatic controls to characterize large and small airway abnormalities that can lead to heterogeneity of airflow. The scheme of studies for this aim is shown in Table 3. To test for functional impairment we will measure spirometry and oscillometry (R_5, R_{5-20}, AX) at rest and with increased respiratory frequency to mimic respiratory patterns during exercise.[49] Spirometry will be performed according to ATS criteria and normal values based on NHANES.[54] Oscillometry will be performed with Impulse oscillation (Jaeger) as per current recomendations.[55] To test for structural distal lung unit abnormalities, we will measure D_LCO with additional measurement of alveolar membrane diffusion (D_M) using nitric oxide diffusion (D_LNO).[56,57] Finally, to test whether abnormalities in lung function have a residual reversible component, we will repeat studies after inhalation of Tiotropium (Spiriva Respimat; 2.5 micrograms). Repeat studies will be performed after 2 hours based on Tiotropium pharmacokinetics.[58] Tiotropium is a specific antagonist of muscarinic receptors with relative specificity for M1, M3 receptor and thus targets a pathway that differs from ICS/LABA.

SA1.b To compare lung function during exercise in "Survivors" with LRS with controls to characterize large and small airway lung mechanics leading to heterogeneity of airflow and exertional dyspnea. Using cardiopulmonary exercise testing (CPET), we will assess oscillometry measures of heterogeneity of distal airflow in addition to expiratory flow limitation and dynamic hyperinflation. An outline of the studies proposed is shown above (Table 3). Briefly, an incremental exercise test (IET) will be performed at V2 to obtain each patient's peak exercise capacity (VO_2 max), heart rate, and anaerobic threshold (AT) to be used for reference for subsequent studies. Constant work rate test (CWRET) will be performed on a separate day (V3), according to recent recommendations.[46] A low intensity CWRET (bicycle) will be performed at 40 watts to standardize the external workload across all patients. Subsequently, as per ERS recommendations, we will obtain a high intensity CWRET (10% below AT).[46,47]

Measurements to be obtained during low and high intensity CWRET are shown in Table 3 and include: 1) dyspnea as assessed by the Borg scale; 2) oscillometry with measurement of reactance area (AX) to assess for peripheral heterogeneity; 3) inspiratory capacity (IC) as a measure of dynamic hyperinflation[59]; 4) flow rates during tidal breathing to assess for expiratory flow limitation[59]; and 5) D_LNO and D_M to evaluate the contribution of structural distal lung unit abnormalities.

In addition, serial spirometry and oscillometry will be performed every 3 minutes after cessation of exercise for a total of 15 minutes to evaluate for residual exercise induced large and small airway hyper-reactivity. To test whether exertional abnormalities in lung function have an untreated reversible component, we will quantify exercise measurements before and after inhalation of a targeted anti-muscarinic agent.

SA2. Compared to healthy controls, do "Survivors" with LRS have lung and systemic inflammation associated with markers of remodeling?

Rationale: Little is known about the ongoing inflammatory or remodeling processes associated with chronic LRS in the WTC-exposed population. The absence of elevated FeNO and association of peripheral eosinophils in only a subset of WTC EHC patients suggest that a type 2-eosinophilic mediated process may not be the predominant inflammatory process driving the chronic LRS. The presence of elevated CRP associated with

small airway abnormalities detected with OSCILLOMETRY suggest a process analogous to COPD. As such, we propose to build upon our previous studies and to investigate airway and systemic inflammation and evaluate inflammatory pathways of COPD as well as pathways involved in the type 2 immune response. Both lung derived samples (sputum) and systemic samples (blood) will be used for analysis.

Hypothesis: Patients with WTC-related persistent LRS will have increased lung and circulating markers of inflammation and airway remodeling similar to those identified in COPD.

Goals: To perform studies of induced sputum and blood with biomarkers associated with inflammation and remodeling for analysis of combined clinical, physiologic and inflammatory parameters in multidimentional phenotyping.

Preliminary data for Specific Aim 2.

Little is known about the underlying biologic mechanisms associated with chronic LRS in WTC-exposed populations. Studies in firefighters described biomarkers that predict progression of lung function.[53] We reported an association of peripheral eosinophils with a subset of WTC EHC patients with wheezing,[41] and systemic CRP levels associated physiologic changes in the distal lung units.[42] Our recent studies performed with the NYC DOH WTC Registry[49] support the absence of an eosinophilic process in most, and our preliminary data from our previous study fail to show elevated FeNO or peripheral eosinophils. Thus we suggest a COPD rather than asthma-like inflammatory/remodeling process. Although studies of blood markers of inflammation can be revealing, they may not directly reflect inflammatory processes in the lung. The use of induced sputum, where one can measure RNA, or secreted proteins in the supernatant, has enhanced our understanding of asthma and COPD. Obtaining induced sputum samples is relatively easy for a patient and minimally invasive, and thus a useful tool to use in this population.[32,61,62] Using induced sputum with enrichment of rare cell types (bronchial epithelial cells and dendritic cells), we recently reported upregulation of genes for type 2 cytokines, thymic stromal lymphopoietin and IL-33 in bronchial epithelial cells, with concomitant upregulation of their targets in dendritic cells.[63] We now propose whole sputum analysis and blood analysis for an expanded panel of type 2 and neutrophilic markers. In addition, because we suggest irreversible changes in distal lung units, consistent with remodeling, we will include markers associated with remodeling and toxic injury.

Table 3. Blood and sputum markers

	Blood	Sputum
Eosinophilic / Type 2		
Eosinophils	X	X
Eotaxin-1	X	X
Periostin	X	X
Eosinophilic cationic		X
Total / allergen specific	X	
IL-5		X
sST2	X	X
Inflammatory		
CRP	X	
IL-6	X	X
IL-8	X	
Fibrinogen	X	
IL-1, IL-1RA		X
Neutrophil elastase		X
Myeloperoxidase		X
Remodeling MMP-1		
MMP-2	X	X
MMP-7	X	X
MMP-8	X X	X
MMP-9	X	X
MMP-12	X X	X
YKL-40	X	X
VEGF		X
Lung derived		
SP-D	X	X
Club Cell 16 (CC16) CCL-18	X	X
	X	X
Oxidative damage 8-isoprostane		X
Apoptosis HMG81		
IL-33		X
CCL2	X	X
CXCL8		X
CXCL1		X
CCL5		X
		X

SA2.a To compare serum markers of inflammation and remodeling in patients with LRS and controls. We will measure serum markers in patients with persistent LRS compared to controls (Table 3). Markers will include those associated with inflammation (IL-6, IL-8, CRP, fibrinogen), type 2 inflammation (periostin, eotaxin) and recently described markers of remodeling (YKL-40, VEGF, MMPs). Blood markers of interest include, but are

not limited, to those shown in Table 4. Blood will be obtained at V1, coagulated, centrifuged (4°C), and serum removed and stored in aliquots (-80°C) until analysis. Serum/plasma markers will be measured using cytokine bead array (Luminex's xMAP® assays) when available (e.g. MMPs, IL1 family members, IL-8, 13), or defined enzymelinked immunosorbent assays as necessary (e.g. IL-6, VEGF, YKL-40, periostin, sST2).

SA2.b To compare sputum markers of airway remodeling in patients with LRS compared to controls. Because blood markers may not reflect lung processes, we will perform minimally invasive procedures (induced sputum) to obtain lung/airway samples to measure markers of inflammation and remodeling between cases and controls. Patients will undergo sputum induction at V4 following pretreatment with albuterol (360 mcg) and repeat spirometry. Sputum will be obtained using 3% hypertonic saline (20 min) with peak flow monitored every 4min.[64] Subjects will cough sputum into a cup. Samples will immediately be processed with removal of sputum plugs, dilution with phosphate buffered saline (30 min, 4°C), followed by centrifugation and resuspension in 1% dithiothreitol. Sputum will be filtered (70 µm), cell count and viability performed, and cytospin slides generated for cell differentials. Samples will be centrifuged and cell pellets and supernatants removed. RNA will be isolated from cell pellets (Qiagen RNeasy Mini column). Resulting RNA preparations will be used in custom qPCR arrays using appropriate primers for select targets. Gene expression will be normalized to a housekeeping gene (GAPDH). Supernatants will be used for protein analysis with Luminex's xMAP® assays or defined ELISAs. Relevant targets of interest are shown in Table 3. Genes and proteins associated with type 2 and non type 2 inflammation and those associated with lung remodeling will be analyzed.

RESULTS

Specific Aim 1. Compared with healthy controls, do "Survivors" with persistent LRS have functional abnormalities in their distal lung units that are revealed during exercise? Hypothesis: Exercise testing with evaluation of distal lung units will reveal reversible and irreversible functional abnormalities associated with LRS.

Specific Aim 1a. To compare resting lung function in "Survivors" with LRS with asymptomatic controls to characterize large and small airway abnormalities that can lead to heterogeneity of airflow.

Resting measurements uncovered presence of small airway dysfunction in symptomatic subjects despite chronic high dose inhaled corticosteroid (ICS) and long acting β-agonist (LABA) therapy. Small airway dysfunction was assessed by oscillometry measurement of frequency dependence of resistance (FDR). Prior studies indicate that FDR is a marker of non-uniform distribution of airflow within the distal lung that correlates with frequency dependence of compliance, the "gold standard" assessment for small airway disease. Specifically, symptomatic subjects demonstrated greater FDR at rest as compared with asymptomatic controls (R_{5-20} = 1.36±0.73 vs. 0.82±0.53 $cmH_2O/[L/s]$; p=0.048). When data from individual subjects were analyzed, 72% of the symptomatic subjects had values above the upper limit of normal; of these individuals, 38% demonstrated reversibility after inhalation of a long acting anti-muscarinic (LAMA) agent (ΔFDR ≥0.56 $cmH_2O/L/s$) with one subject returning to normal. Of importance, these small airway abnormalities were demonstrable by oscillometry during tidal breathing, but they were not apparent from spirometry assessment of maximal expiratory airflow during forced exhalation.

Specific Aim 1b. To compare lung function during exercise in "Survivors" with LRS with controls to characterize large and small airway lung mechanics leading to heterogeneity of airflow and exertional dyspnea.

Exercise testing was successful at reproducing patient symptoms and uncovered additional mechanisms for dyspnea related to small airways dysfunction. Assessments included:

- Measurement of tidal expiratory airflow during incremental exercise
- Assessment of small airway hyper-reactivity following cessation of incremental exercise
- Assessment of small airway function during steady state exercise with assessment of reversibility post inhalation of a LAMA

Tidal expiratory airflow during incremental exercise
All subjects underwent assessment of tidal flow vs. volume curves during exercise to identify expiratory flow limitation during tidal breathing and/or dynamic hyperinflation. Both of these abnormalities have been well established as potential etiologies for exertional dyspnea in subjects with chronic obstructive pulmonary disease. In the asymptomatic control group, all subjects demonstrated normal tidal airflow without evidence for either expiratory flow limitation or dynamic hyperinflation. In contrast, 67% of the symptomatic subjects demonstrated one or both of these abnormalities. These abnormalities were associated with development of exertional dyspnea, ass assessed by the Borg scale. Specifically, the control group reported no dyspnea at rest (Borg scale = 0 ± 0) with minimal increment during exercise (Borg scale = 1.5 ± 1.0). In contrast, the sympotmatic subjects demonstrated both greater dyspnea at rest with a larger increment during exercise (rest Borg scale = 1.4 ± 1.5; exercise Borg scale = 4.2 ± 2.3; $p < 0.05$ for both vs. control).

Small airway hyper-reactivity following cessation of incremental exercise
All subjects underwent assessment of exercise induced large and small airway hyper-reactivity using spirometry and oscillometry obtained immediately following exercise and at 3 minute intervals for a total of 15 minutes. In the control group there was no evidence for exercise induced airway hyper-reactivity. In contrast, in the symptomatic group post exercise spirometry and oscillometry uncovered 12 subjects (60%) with airway hyper-reactivity; in 3 individuals exercise-induced bronchoconstriction was demonstrated FEV_1 criteria coupled with increased FDR=1.56±1.6 $cmH_2O/[L/s]$ and in 9 symptomatic subjects increased FDR=0.80±0.69 $cmH_2O/[L/s]$ was observed despite minimal decline in post exercise FEV_1 (-3.8±2.8%). The increase in Borg dyspnea score in these individuals with post exercise hyper-reactivity identified by either FEV_1 or FDR was higher than observations in asymptomatic controls (3.7±2.1 vs. 1.5±1.0, *p*=0.01).

Small airway function during steady state exercise and with assessment of reversibility post LAMA inhalation
Small airway function was directly assessed during steady state exercise at low workload (40 Watts) in all subjects. While augmentation of small airway dysfunction was noted in the symptomatic group, the degree of abnormality was minimal, likely reflecting to low workload (rest and exercise FDR = 1.14±0.93 and 1.24±0.76 $cmH_2O/[L/s]$). Following administration of LAMA there was improvement in FDR at both rest and during exercise (1.0±0.84 and 1.0±0.70 $cmH_2O/[L/s]$). These was no improvement in either resting or exertional dyspnea scores associated with these small changes in FDR.

Specific Aim 2. Compared to healthy controls, do “Survivors” with LRS have lung and systemic inflammation associated with markers of remodeling? Hypothesis: patients with persistent LRS will have lung and circulating markers of inflammation and airway remodeling similar to those identified in COPD.

- Specific Aim 2a. To compare serum markers of inflammation and remodeling in patients with LRS and controls.

- Specific Aim 2b. To compare sputum markers of airway remodeling in patients with LRS compared to controls.

Subject recruitment was severely curtailed due to COVID 19 pandemic. Consequently, the study lacks sufficient power to draw inferences regarding biologic mechanisms for the small airway abnormalities observed in specific aim 1. Of note, there was a small group of individuals that did demonstrate elevated eosinophils; all of these subjects also demonstrated exercise induced small airway hyper-reactivity, which suggests potential for targeted therapy. This will need to be studied in future clinical trials to assess therapeutic efficacy.

CONCLUSIONS

This study evaluated small airway function at rest and during exercise to uncover mechanisms for exertional dyspnea that persists despite high dose chronic therapy and despite presence of normal airflow on spirometry. The data demonstrated: 1) Small airway dysfunction was present at rest in persistently symptomatic subjects to a degree that was more pronounced as compared with an asymptomatic control group; 2) Despite chronic ICS/LABA therapy, residual reversibility of the small airway dysfunction was demonstrable following inhalation of a LAMA; 3) Exertional dyspnea was reproduced during exercise in symptomatic patients testing to a degree that was more pronounced as compared with an asymptomatic control group; 4) numerous mechanisms for exertional dyspnea were uncovered by specific assessment of small airway function during and following exercise including expiratory flow limitation during tidal breathing, dynamic hyperinflation and small airway hyper-reactivity.

The observed findings indicate that monitoring for occupational and/or environmental lung injury should be modified to include assessment of small airway function in addition to routine spirometry. This conclusion is based on the concept that spirometry may identify airway injury as a reduction in lung volume or air flow, however, spirometry can often be normal even in symptomatic patients, particularly when injury is located in the distal airways. Prior data from our program has demonstrated an association between presence of small airway dysfunction and presence of new onset and persistent respiratory symptoms following exposure to inhaled toxins caused by the collapse of the World Trade Center on September 11, 2001. The present study extends these observations by establishing a direct link between exertional dyspnea and simultaneous enhancement of small airway dysfunction. We further demonstrate that these findings may occur despite chronic high dose therapy with ICS and LABA medications. A key finding in the present study is that many individuals demonstrate residual reversibility upon administration of a single dose of a LAMA.

It must be emphasized that the presence and reversibility of these small airway abnormalities were only demonstrable by oscillometry during tidal breathing, but they were not apparent from spirometry assessment of maximal expiratory airflow during forced exhalation. These studies build upon prior histologic and functional evidence for distal airway abnormalities as a manifestation of obstructive lung diseases. Thus, characterization of distal airway injury in addition to standard spirometry is crucial in determination of both optimal medical therapy and assessment of changes over time. Moreover, identification of distal airway injury may be an early marker of disease that may be progressive but may also be amenable to therapy.

It is anticipated that the results of our studies may have impacts on several areas of occupational and environmental respiratory health. First, our data support additional of oscillometry to routine spirometry to

monitor for inhalational lung injury in at-risk populations. Our data clearly establish that this change will allow identification of small airway disease at a time point prior to development of impaired airflow on spirometry. Second, the data indicate that therapy for symptomatic patients should consider use of a broad range of medications in addition to ICS and LABA. Lastly, longitudinal monitoring will be enhanced by inclusion of small airway metrics to establish improvement in respiratory health.

PUBLICATIONS

Kwok B, Goldring RM, Oppenheimer BW, Bohart I, Pehlivan S, Durmus N, Gloeggler P, Reibman J, Berger KI. Identification of mechanisms for persistent unexplained lower respiratory symptoms using rest and exercise assessment of small airway function. Am J Respir Crit Care Med 2020; 201:A2992.

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B.2 (SACOS Award Closeout document final.pdf)

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Berger KI, Kalish S, Shao Y, Marmor M, Kazeros A, Oppenheimer BW, Chan Y, Reibman J, Goldring RM. Isolated small airway reactivity during bronchoprovocation as a mechanism for respiratory symptoms in WTC dust-exposed community members. American journal of industrial medicine. 2016 September;59(9):767-76. PubMed PMID: 27582479; DOI: 10.1002/ajim.22639.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
BERGEK01	Y	BERGER, KENNETH I	MD	PD/PI	1.0	0.0	0.0			NA
REIBMJ01	Y	REIBMAN, JOAN	MD	PD/PI	1.0	0.0	0.0			NA

Glossary of acronyms:

S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

It is anticipated that the results of our studies may have impacts on several areas of occupational and environmental respiratory health. First, our data support additional of oscillometry to routine spirometry to monitor for inhalational lung injury in at-risk populations. Our data clearly establish that this change will allow identification of small airway disease at a time point prior to development of impaired airflow on spirometry. Second, the data indicate that therapy for symptomatic patients should consider use of a broad range of medications in addition to ICS and LABA. Lastly, longitudinal monitoring will be enhanced by inclusion of small airway metrics to establish improvement in respiratory health.

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
Cumulative Inclusion Enrollment Report.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Small Airway Chronic Obstructive Disease Syndrome Following Exposure to WTC Dust

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native										**0**
Asian	1									**1**
Native Hawaiian or Other Pacific Islander										**0**
Black or African American	4	3			3					**10**
White	1	8		1	1					**11**
More Than One Race										**0**
Unknown or Not Reported				2	3					**5**
Total	**6**	**11**	**0**	**3**	**7**	**0**	**0**	**0**	**0**	**27**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

CONCLUSIONS
This study evaluated small airway function at rest and during exercise to uncover mechanisms for exertional dyspnea that persists despite high dose chronic therapy and despite presence of normal airflow on spirometry. The data demonstrated: 1) Small airway dysfunction was present at rest in persistently symptomatic subjects to a degree that was more pronounced as compared with an asymptomatic control group; 2) Despite chronic ICS/LABA therapy, residual reversibility of the small airway dysfunction was demonstrable following inhalation of a LAMA; 3) Exertional dyspnea was reproduced during exercise in symptomatic patients testing to a degree that was more pronounced as compared with an asymptomatic control group; 4) numerous mechanisms for exertional dyspnea were uncovered by specific assessment of small airway function during and following exercise including expiratory flow limitation during tidal breathing, dynamic hyperinflation and small airway hyper-reactivity.

The observed findings indicate that monitoring for occupational and/or environmental lung injury should be modified to include assessment of small airway function in addition to routine spirometry. This conclusion is based on the concept that spirometry may identify airway injury as a reduction in lung volume or air flow, however, spirometry can often be normal even in symptomatic patients, particularly when injury is located in the distal airways. Prior data from our program has demonstrated an association between presence of small airway dysfunction and presence of new onset and persistent respiratory symptoms following exposure to inhaled toxins caused by the collapse of the World Trade Center on September 11, 2001. The present study extends these observations by establishing a direct link between exertional dyspnea and simultaneous enhancement of small airway dysfunction. We further demonstrate that these findings may occur despite chronic high dose therapy with ICS and LABA medications. A key finding in the present study is that many individuals demonstrate residual reversibility upon administration of a single dose of a LAMA.

It must be emphasized that the presence and reversibility of these small airway abnormalities were only demonstrable by oscillometry during tidal breathing, but they were not apparent from spirometry assessment of maximal expiratory airflow during forced exhalation. These studies build upon prior histologic and functional evidence for distal airway abnormalities as a manifestation of obstructive lung diseases. Thus, characterization of distal airway injury in addition to standard spirometry is crucial in determination of both optimal medical therapy and assessment of changes over time. Moreover, identification of distal airway injury may be an early marker of disease that may be progressive but may also be amenable to therapy.

It is anticipated that the results of our studies may have impacts on several areas of occupational and environmental respiratory health. First, our data support additional of oscillometry to routine spirometry to monitor for inhalational lung injury in at-risk populations. Our data clearly establish that this change will allow identification of small airway disease at a time point prior to development of impaired airflow on spirometry. Second, the data indicate that therapy for symptomatic patients should consider use of a broad range of medications in addition to ICS and LABA. Lastly, longitudinal monitoring will be enhanced by inclusion of small airway metrics to establish improvement in respiratory health.