

Specific Aims:

The goals of this research are to determine the prevalence and natural history of tracheomalacia (TM) in COPD and to establish the role of a novel CT method in guiding therapy and assessing response to intervention. This work will also have a broader impact upon the understanding of the contribution of expiratory central airway collapse to the morbidity of chronic obstructive pulmonary disease (COPD).

Acquired tracheomalacia (TM), a condition defined by excessive expiratory collapse of the trachea due to weakness of the airway walls and/or supporting cartilage, is a common but often overlooked cause of chronic cough that is associated with a variety of risk factors, most notably COPD.¹⁻⁴ **Over 1 million adults with COPD in the U.S. are estimated to have TM, but the precise prevalence of this condition and range of severity are unknown.**⁵⁻⁷ As COPD is responsible for greater than 30 billion dollars in annual healthcare expenditure in the U.S.,⁸ research regarding the contribution of tracheomalacia to the overall morbidity of this condition is indicated.

There is compelling evidence that TM is a widely underdiagnosed condition that can cause significant respiratory morbidity if left untreated.⁹⁻²⁰ Thus, there is a need for an effective, noninvasive test to improve its detection. As stent placement or tracheoplasty can effectively treat severely symptomatic cases, there is a need to establish guidelines for intervention.²¹⁻²⁵ Although a diagnostic criterion of > 50% expiratory reduction in the tracheal lumen is widely accepted, the normal range of forced expiratory tracheal collapse among healthy volunteers has been shown to exceed this value.^{26, 27} Thus, there is a need for a more rigorous criterion.

Our preliminary data show that paired inspiratory-dynamic expiratory CT is a highly accurate, noninvasive method for assessing expiratory tracheal collapse, with similar accuracy to bronchoscopy.²⁸ Using CT, we plan to establish normative data in order to define a more rigorous diagnostic criterion. We will apply this new criterion to assess the prevalence of TM among patients with COPD. We will determine physiological and clinical correlates of TM by comparing the results of pulmonary function tests, physiological testing, assessment of adaptive behaviors such as pursed-lip breathing and expiratory glottal narrowing, exercise testing, and respiratory questionnaire data between COPD patients with and without TM. We will determine the natural history of TM by following less symptomatic patients over several years. Finally, we plan to identify specific characteristics that are predictive of a positive response to intervention for severely symptomatic TM.

Specific Aim 1: Determine the prevalence of tracheomalacia among patients with COPD.

Hypothesis: Patients who meet standard criteria for COPD will demonstrate a wide range of expiratory tracheal collapse. Approximately 20 to 30% of patients will meet criteria for tracheomalacia.

We will test this hypothesis by first creating a rigorous criterion for diagnosing TM based upon paired inspiratory-dynamic expiratory CT data from a group of 50 healthy volunteers with normal pulmonary function. CT will then be performed in 125 COPD patients in order to determine the prevalence of TM in this population.

Specific Aim 2: Assess physiological and clinical correlates of tracheomalacia in patients with COPD.

Hypothesis: Among patients with COPD, there are distinguishable clinical and physiological parameters at rest and/or during exercise that will help to predict the presence of TM. We plan to test this hypothesis by comparing the results of key parameters including PFT's, 6MWT, clinical observation for use of adaptive behaviors such as pursed lip breathing, respiratory questionnaires, quantitative CT analysis, and physiological testing to the severity of forced expiratory central airway collapse among COPD patients. Participants with TM will also undergo functional bronchoscopy with pressure measurements.

Specific Aim 3: Determine the natural history of tracheomalacia in the absence of treatment among subjects who are asymptomatic or mildly symptomatic. **Hypothesis: Tracheomalacia is progressive in COPD, and the change in percentage expiratory tracheal collapse at CT will correlate with changes in symptoms and functional impairment.** We plan to test this hypothesis by correlating the change in expiratory collapse at CT over time with the same key parameters in Aim 2.

Specific Aim 4 (exploratory): Determine longitudinal changes in key parameters in participants with severely symptomatic tracheomalacia undergoing invasive and minimally invasive treatment.

Hypothesis: Severity of pre-intervention expiratory CT collapse and use of adaptive respiratory behaviors will be predictive of a positive response to therapy. We plan to test this hypothesis by comparing key parameters between subsets of participants with and without positive response to intervention.