Collagen Degradation Products As Biomarkers Of Disease Progression In Emphysema

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A. Study Purpose and Rationale

The overall prevalence of smoking has continued to trend downward since 1940. However, the prevalence amongst certain demographic groups has steadily continued to rise over the past thirty years, predominantly represented by women and adolescents (1). As well, those groups of individuals who have quit smoking are still at risk for, or are suffering from, smoking related mortality. The risk factors which predispose certain individuals and not others to development of COPD or lung cancer are not well understood. However, it is known that, approximately one-third of smokers will develop symptoms of chronic bronchitis without evidence of reduced lung function (2). Fifteen percent of all smokers develop reduced function and parenchymal destruction consistent with emphysema.

Emphysema remains clinically silent for many years with the progressive decline in respiratory function not being apparent until greater than 50-60% of predicted normal pulmonary function is lost. Studies employing the use of high resolution computed tomography (HRCT) in smokers without any evidence of respiratory compromise, symptomatically or by spirometry, demonstrate mild parenchymal changes consistent with inflammation (3). It has been proposed that HRCT may represent a means to detect early, subclinical COPD, therefore, allowing the physician and patient to modify behaviors which predispose the patient to further parenchymal inflammation and destruction. However, the relatively small percentage of patients who ultimately develop emphysema, in combination with the lack of treatment other than smoking cessation to halt disease progression make HRCT an unacceptable screening tool for COPD.

The pathogenesis of emphysema has been extensively studied over many years. The widely accepted protease/antiprotease model of parenchymal destruction has been validated in both animal and human studies. The well known model of alpha- I antiprotease deficiency causing emphysema in nonsmoking humans has promoted the role of elastin destruction as the central defect in the development of emphysema. D'Armiento et al (4) demonstrated in transgenic mice constituently expressing collagenase collagen degradation and pulmonary parenchymal destruction consistent with emphysema. Dalai et al (5) demonstrated the presence of collagenase in 22 of 23 surgical patients with emphysema undergoing lung volume reduction surgery and in 0 of 8 patients without emphysema. In this same group of patients with emphysema and collagenase expression there was no detectable elastase expression(7). In a study of brochoalveolar lavage (BAL) fluid by Finlay et al (8) upregulation of collagenolytic enzymes was clearly demonstrated.

Other than smoking cessation and symptomatic treatment (i.e. bronchodilator, supplemental oxygen, surgical lung volume reduction) there is currently no therapy available to halt the progression of this disease process. Based on the scientific data indicating a central role for a degradative enzyme as the mediator of tissue destruction protease inhibitors against elastase, c6llagenase, and other tissue and inflammatory degradative enzymes are being developed. There are many associated with the development of protease inhibitors as a therapy for emphysema, one of which is how to follow and measure a therapeutic response (6). It takes many years for the progression of detectable clinical disease as measured by spirometry or radiograph. As well, an apparent lack of progression on these studies over a short course of time cannot be interpreted as a clinical response. Studies looking for a serum or urinary marker specific for lung parenchyma degradation have provided some evidence for urinary desmosine as a biomarker of elastin destruction, however, elastin is found throughout the body and tissue specificity of a urinary marker cannot be determined (6,7). Additionally, the aforementioned data suggest collagenase and collagen degradation may significantly contribute to the destruction seen in emphysema.

In an effort to demonstrate and characterize a sensitive and specific biomarker for pulmonary collagen degradation, the proposed study will assay the BAL fluid of patients, with emphysema for collagen degradation products. Therefore, from the data of Dalal and Finlay the hypothesis is collagen degradation products in the BAL fluid of patients with emphysema will be elevated. Once characterized as a blomarker of disease activity and progression, collagen degradation products can be followed after the institution of protease inhibitor therapy and used to assess clinical response to protease inhibition.

B. Study Design and Statistical Analysis

The study will be a cohort analysis of patients with emphysema as determined by clinical symptoms and spirometry referred to Columbia Presbyterian to undergo open lung volume reduction surgery. Only those patients medically cleared and accepted to undergo surgery having completed the informed consent process and not having met any of the exclusion criteria would undergo intraoperative BAL. Two major exclusion criteria in addition to routine pre-operative cardiac screening are: 1. Any prior history of adverse reaction to bronchoscopy including but not limited to bronchospasm, arrhythmia, pneumothorax, or pulmonary hemorrhage. 2. Any recent febrile illness, current leukocytosis, acute infiltrate on chest radiograph, or pre-operative sputum culture with significant overgrowth of an organism other than routine commensal flora.

Based on the data of Dalal et al (5) demonstrating a greater than 95% prevalence of upregulation of collagenase in patients with emphysema and less than 1% amongst controls, ten patients would be required to yield a study with a power of 80% and a p-value of less than .0 1 on Student's T-test

C. Study Procedures and Risks

Preoperatively, those patient's referred for open lung volume reduction surgery and recommended by Drs. Schulman and M. Ginsburg will be interviewed and complete informed consent. After having been medically cleared and accepted for open lung volume reduction surgery, the patient will complete full pulmonary function tests, including resting arterial blood gas to assess baseline functional capacity and severity of disease. These studies will be performed as per the Pulmonary Diagnostics Lab routine protocol. Intraoperatively, after induction with general anesthesia and endotracheal intubatlon as per the anesthesiology team, the patient will be oxygenated to maintain an oxygen saturation of greater than 96%. Those patients with saturation on supplemental oxygen persistently below 92% or a greater than 5% drop in oxygen saturation from the preoperative baseline will not undergo BAL. BAL in these patients will not be performed to avoid potential confounding effect bypoxemia may have in data analysis, as well as, eliminating further risk of hypoxic insult during lavage.

Once the patient is intubated and evidenced not to have hypoxemia, a flexible fiberoptic bronchoscope will be introduced via the endotracheal tube to the level of the carina. After visualization of the carina the scope will be advanced to the lingual and right middle lobe respectively, wedged at a subsegemental bronchus, and 20 ml of 37 degree sterile normal saline will be infused and aspirated twice per region yielding a total of 80 of lavage fluid for both right and left sides. The total length of time anticipated for the procedure is fifteen minutes (9). There will be continuous monitoring of oxygen saturation, heart rate, and blood pressure as per anesthesiology. Hypoxemia will be managed with supplemental oxygen sufficient to raise the saturation above 96% or maintain the patient's preoperative baseline saturation. Subsequently, patient's will undergo open lung volume reduction surgery as per Dr. Ginsburg. No further postoperative procedures are required for the purpose of our study.

The BAL fluid will be transported within one hour and stored at -70 degrees. Samples will be assayed using a standard commercial assay for Type I fibrillar collagen cross-link degradation products (Osteomark by Ostex - Seattle, Wash.). As estimated by the statistical analysis, ten patients will be required for a statistically significant results. It is anticipated that this number of patients can be assayed in one year's time.

The potential risks associated with BAL are infrequent and minor, the most common being post-lavage fever and pneumonitis seen in less than 3% of patients (9). Other risks associated with BAL include bronchospasm, laryngospasm, hypoxemia, arrhythmia, pneumonia, pneumothorax, and hemorrhage. In our proposed patient population these risks are partially compensated for by endotracheal intubation, and are superseded by the risks associated with general anesthesia and open lung volume reduction surgery.

D. Costs and Compensation

There will be no additional cost to the patient outside what is charged for their surgical procedure. There will be no compensation provided to study subjects.

References

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