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Evaluation of Gastroesophageal Reflux and Restrictive Lung Disease: MESA Lung Study

A. Study Purpose and Rationale

Restrictive lung disease refers to a category of lung disease characterized by stiff lungs causing incomplete expansion. There are many different types of restrictive lung disease, with the final common pathway resulting in fibrosis and scarring of the lung parenchyma. Specific causes of restrictive lung disease include asbestos exposure, radiation exposure, medications such as amiodarone and bleomycin, autoimmune diseases such as rheumatoid arthritis, as well as a number of idiopathic causes. The most common type of restrictive disease without a known cause is idiopathic pulmonary fibrosis (IPF). IPF is most common in men over the age of fifty, is 1.5 times more common in men, and affects ten to fifteen per one hundred thousand people.[1] There is usually a long asymptomatic phase prior to presentation, with the most common presenting symptom being chronic progressive shortness of breath. Diagnosis of the disease is often made based on clinical criteria, requiring all four major criteria: exclusion of other interstitial lung disease, restriction on pulmonary function tests, bibasilar reticular changes on chest CT (without significant ground-glass opacities), and bronchoalveolar lavage not supportive of alternative diagnosis, and also three out of four minor criteria: age over fifty, insidious conset, duration of symptoms more than three months, and bibasilar inspiratory crackles.[2] If performed, surgical lung biopsy shows usual interstitial pneumonia, characterized by areas of interstitial fibrosis with proliferation of fibroblasts ("fibroblastic foci") and eventual distortion of the normal lung structure ("honeycombing). Compared to other types of interstitial lung disease, there is a marked absence of interstitial inflammation.[3]

IPF has a poor prognosis, with median survival less than three years after diagnosis. No treatments have been found to significantly improve survival, except for lung transplantation.[1] However, many patients either do not qualify for lung transplantation due to older age or comorbidities, or they die on the transplant list. Additionally, survival after lung transplant is only 50-60% at five years, which is not much more favorable. There have been studies to evaluate possible causes of idiopathic pulmonary fibrosis. The most recent hypothesis suggests the pathogenesis is a process of sequential lung injury, with inflammation and aberrant wound healing that results in scarring and fibrosis.[2] A few risk factors which have been associated with IPF include smoking, environmental exposures such as metal and wood dust, chronic aspiration, medications, infections, as well as genetic predispositions.[2]

Gastroesophageal reflux disease (GERD) provides a potential mechanism for chronic inflammation and lung injury, leading to pulmonary fibrosis. One study compared the rates of proximal GERD as measured by esophageal pH monitoring between patients with IPF and controls with other forms of interstitial lung disease. They found GERD in

89% of 17 patients with IPF compared to 50% of their controls.[4] A separate study also found a high prevalence of GERD, present in 87% of 65 patients with IPF.[5] A third study evaluated patients with IPF who were referred for lung transplant evaluation, and found GERD in 67% of 30 patients.[6] Although not all of these studies evaluated controls, the general prevalence in the US is estimated to be 10-20%.[7] All of these studies have evaluated patients with a diagnosis IPF, but none have studied the prevalence of GERD in patients with only a restrictive lung disease pattern on pulmonary function tests.

My hypothesis is that GERD is causally related to the pathogenesis of IPF. The primary aim of this study is to determine if GERD is associated with restrictive lung disease, at the time of MESA Lung PFTs. The secondary aims of this study are to determine if restrictive lung disease in the MESA cohort is associated with any symptoms by questionnaire, and to follow patients with restrictive lung disease over time for the development of IPF in order to determine if there is any association between GERD and the future development of IPF.

B. Methods

Study Design:

This will be a retrospective cohort study including subjects already enrolled in the Multi-Ethnic Study of Atherosclerosis. The cohort consists of 6,814 subjects who were enrolled at six field centers representing areas of ethnic diversity across the United States (Columbia University, Johns Hopkins University, Northwestern University, University of Minnesota, University of California – Los Angeles, and Wake Forest University). The dataset from their first examination that was completed in 2003 includes information on demographics, anthropomorphics, socioeconomic status, medical conditions, medication use, and physical activity. An ancillary study, MESA Lung, performed pulmonary function tests (PFTs) on approximately 60% (4,000) of these subjects and also administered a more detailed questionnaire on respiratory symptoms.

The subjects included in this study will be those subjects with a restrictive lung disease pattern by pulmonary function testing. This is defined as having a forced ventilatory capacity less than the lower limit of normal for their age, sex and ethnicity. Additionally, it excludes those patients with advanced obstructive lung disease where the ratio of forced expiratory volume in one second to the forced vital capacity is reduced. Controls will be patients in the MESA Lung cohort with normal pulmonary function testing, chosen at a rate of 2 controls for each subject and matched for age, gender, ethnicity, BMI and smoking status. The independent variable of interest in this study will be those patients taking proton pump inhibitors (PPIs) or H2 blockers, which is the best approximation of symptomatic GERD in this study. While there are errors inherent in this design, such as missing a large number of patients with asymptomatic reflux or including patients who may be on PPIs or H2 blockers for peptic ulcer disease, this is the best measure of GERD that has been collected in this population. Additionally, the use of a symptomatic questionnaire has been shown to be an inaccurate way to diagnose GERD, compared to the gold standard of esophageal pH monitoring. For example, in one recent study of patients with IPF, 35% of those without typical symptoms were found to have

GERD, and 29% of those with typical symptoms were found to not have GERD with esophageal pH monitoring.[5]

Power Analysis:
This is a comparison of two groups in the proportion of subjects taking a PPI or H2 blocker. Given the known size of the two groups, the study will be powered to detect a 10% difference in the proportion of subjects taking PPIs or H2 blockers, assuming 80% power and an alpha of 0.05.

Statistical Analysis:
The subjects and controls will be matched for age, gender, ethnicity, BMI and smoking status. These and other possible confounders will be compared across the two groups using chi square testing. The outcome of interest is the prevalence of being on a PPI or H2 blocker, and will be tested across the two groups using chi square testing.

C. Study Procedures

There are no additional procedures being performed on these patients.

D. Study Drugs

There are no drugs being used in this study.

E. Medical Device

There are no medical devices being used in this study.

F. Study Questionnaires

There are no additional questionnaires needed for this study.

G. Study Subjects

Inclusion criteria: all subjects in the MESA Lung cohort with a restrictive pattern on PFTS, and 2:1 nested controls matched for age, gender, ethnicity, BMI, and smoking.

Exclusion criteria: presence of obstructive lung disease on PFTs.

H. Recruitment of Subjects

There is no need to recruit additional subjects for this study.

I. Confidentiality of Study Data

All study data is without personal identifiers.

J. Potential Conflict of Interest

There are no potential conflicts of interest on the part of the investigators.

K. Location of the Study:

The study has already been conducted at the six field centers mentioned above.

L. Potential Risks

There are no additional risks to subjects.

M. Potential Benefits

There are no benefits to subjects participating in the study.

N. Alternative Therapies: N/A

O. Compensation to Subjects: N/A

P. Cost to Subjects: N/A

Q. Minors as Research Subjects: N/A

R. Radiation or Radioactive Substances: N/A

References:

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