1.a. Full Title: Lung Function, Asthma, and Coronary Heart Disease (CHD) Severity: the Atherosclerosis Risk in Communities Study.

b. Abbreviated Title: Lung Function and MI Severity.

2. Writing Group:
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3. Timeline: Data analysis: 7/1/05 – 7/31/05
   First draft completed: 8/31/05
4. Rationale:

Laboratory studies show that chronic inflammation, particularly inflammation associated with the presence of mast cells, is an important component in the pathogenesis of asthma and may be an important component of the pathogenesis of cardiovascular disease (CVD). In this study we propose to explore the association between the presence and severity of asthma, lung function, and the severity of myocardial infarction (MI).

Laboratory and clinical studies have shown that in asthma eosinophils and lymphocytes infiltrate the lung, releasing Th2-paradigm cytokines and upregulating mast cells. Mast cell activation and the release of mast cell products such as tryptase, histamine, and leukotrienes results in inflammation of the airways and bronchospasm/bronchoconstriction. Reduced Forced Expiratory Volume in the first second of exhalation (FEV1) indicates inflammation-induced airways obstruction. Persistently decreased FEV1 can indicate ongoing asthmatic inflammation.

Animal studies have shown that mast cell activation and concurrent mast cell-mediated inflammation may have a role in the incidence, severity, and outcome of CHD. Activated mast cells may participate in the weakening and rupture of atherosclerotic plaques by secreting heparin proteoglycans and chymase, which have been shown in vitro to inhibit proliferation of smooth muscle cells (SMC) and reduce their ability to produce collagen, leading to plaque instability.(1) Mast cells are also thought to play a critical role in post-injury (post-MI) remodeling. Degranulation of mast cells in normal rat hearts results in the production of multiple cytokines, chemokines, and proinflammatory mediators. Two studies, one in rat hearts and one in dog hearts showed that a major mast cell product, chymase, can activate matrix metalloproteinases (2,3) which then induce marked degradation of interstitial fibrillar collagen, and increase ventricular dilatation.(3) In another study, wild type mice and mast-cell knock-out mice were challenged with systolic pressure overload. Decompensated hypertrophy, perivascular fibrosis, and upregulation of mast cell chymase were seen in wild type mice, but not in knock-out mice. Left ventricular function was preserved in knock-out mice. Treatment with tranilast, a mast-cell stabilizing agent, prevented evolution to heart failure.(4) TNF-alpha, a pro-inflammatory cytokine, is thought to play a role in post-injury remodeling. In the study by Gilles et al, release of TNF-alpha in reperfused hearts was inhibited in hearts treated with mast cell stabilizing agents such as ketotifen and cromoglycate.(5)
No clinical data are available to show a direct association between mast cell-induced inflammation and CVD/CHD. However, indirect support comes from observational study data showing a relationship between reduced lung function and/or the presence and severity of asthma, and CHD outcomes (incidence, death). In a cohort study of CVD outcomes in Swedish men, low FVC was associated with higher levels of inflammation-sensitive plasma proteins and increased incidences of MI and CVD death, in both smokers and nonsmokers.\(^6\) In the ARIC cohort, Shroeder et al showed that reduced lung function (especially severe reduction in FEV1) is associated with incident CHD, when controlled for smoking status.\(^7\) Similarly, in the Baltimore Longitudinal Study of Aging, cardiac mortality increased with increasing quintile of FEV1 decline (RR = 2.92 – 5.13). These results were independent of other traditional risk factors, smoking status, and initial predicted FEV1.\(^8\) A Canadian database study suggested that individuals with asthma on asthma therapy have a decreased incidence of myocardial infarction compared with participants with asthma who were not on therapy. This effect was seen prominently in participants with severe asthma.\(^9\) In the ARIC cohort, Schanen et al found an increased risk of stroke, but not CHD, in participants with ever asthma, current asthma, or asthma symptoms.\(^10\)

These observational studies addressed the incidence of myocardial infarction and CHD mortality as outcome measures, but did not study severity of infarction in terms of the amount of myocardial damage or the extent of post-infarction left ventricular dysfunction. Additionally, data on treatment of asthma and severity of MI is restricted to one study from a largely Caucasian population. Asthma is treated with oral and inhaled corticosteroids, leukotriene modifying agents, and inhaled beta-agonist bronchodilators. Identifying a lesser degree of MI severity in participants who are treated for asthma as compared with those who are not, would support the association between mast cell-induced inflammation and MI.

5. Main Hypothesis/Study Questions:

The aim of this study is to describe and model the relationship between lung function and MI severity and (separately) between asthma and MI severity, adjusting for other CVD risk factors.
1) Hypothesis: Lung function at baseline is inversely correlated with MI severity.
2) Hypothesis: Participants with a decline in lung function (FEV1 decline > 10% between first clinic visit and second clinic visit) have more severe MI than those without FEV1 decline.
3) Hypothesis: Participants with asthma have more severe MI than participants without asthma.
4) Hypothesis: In asthmatics, persistently low FEV1 (two consecutive FEV1 <80%) is associated with more severe MI.
5) Hypothesis: Participants with treated asthma have less severe MI than untreated asthmatics.

In examining each of the above hypotheses, MI severity will be assessed in 2 ways:
   a) using a number of clinical, hemodynamic, EKG, and biochemical markers (correlated individually with the predictor variable)(11)(12)
   b) using a composite index of severity, the modified PREDICT score(13)

These measures of MI severity, and the categories for asthma and lung function, are described below.

6. Data (variables, time window, source, inclusions/exclusions):

Inclusion
All participants in the ARIC database, data from visits 1 through 4, 1987 to 1998, who are never smokers. White and African-American only. STUDY WILL BE RESTRICTED TO NEVER SMOKERS.

Exclusion
Participants with missing FVC/FEV1 data, asthma status not known, smoking status not known, race not known, prevalent CVD (CHD and/or stroke) at baseline or CVD status not known, prevalent chronic bronchitis at baseline.
Outcome variables:
Individual markers of myocardial infarction severity, as described and used in (11) and (12):
   a) SBP <100 mm Hg
   b) Abnormal pulse rate
   c) ST-segment elevation
   d) Initial Q wave
   e) New Q wave
   f) Diagnostic EKG
   g) Abnormal enzymes (CK-MB, troponin)
   h) Cardiogenic shock
   i) CHF
   j) Peak CK ratio (mean, SE)

Composite index of MI severity, as described and used in (13):
   a) Modified PREDICT score

Predictor variables:
1) Lung function will be categorized in three groups, adjusted for age, ethnicity, and gender:
   FEV1 ≥80%, FEV < 80% but ≥60%, FEV1 <60%.
   2) Asthma status yes (ever/current) or no: based on self-report at baseline.

Covariates / potential confounding variables:
1) Sociodemographic information:
   a) Age: years
   b) Gender: male, female
   c) Race: white, African-American
   d) Study center

2) Cardiovascular risk factors:
   a) Diabetes: FBG ≥126 mg/dl (xxx mmol/L), NFBG ≥200 mg/dl (xxx mmol/L), self-report of physician diagnosis, or self-report of hypoglycemic treatment
b) Hypertension: SBP ≥140 mmHg, DBP ≥90 mmHg, or self-report of antihypertensive medication use

c) LDL-cholesterol: mg/dl

d) HDL-cholesterol: mg/dl

e) Physical activity: yes (self-report of exercise or playing sports) or no

f) BMI: weight (kg) / height (m)^2

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes X No

8.a. Will the DNA data be used in this manuscript? _____ Yes ___X No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X__ Yes _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

The studies by Schroeder (7) and Schanen (10) are the closest ARIC publications.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes ___X No

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.
Reference List


