Proposed Study Title: Soluble Intracellular Adhesion Molecule-1 levels in acute ST Elevation Myocardial Infarction.
Submitted by: Charles Perry, MD
Submitted to: I.C.C.R. Faculty
Date: 4/13/07

1. Introduction

Coronary artery disease (CAD) remains the leading cause of death in industrialized nations. It is estimated that the absolute mortality due to CAD will increase as the average age of the population rises.(Braunwald E. N Engl J Med. 1997;337:13609). Evidence suggests that CAD event onset arises from the combination of endothelial dysfunction, inflammation, and platelet reactivity (Corti R et al. J Am Coll Cardiol. 2003;41:7S14S). Research over the past decade has demonstrated the important role of inflammation and the underlying cellular and molecular mechanisms in promoting the formation of atherosclerosis, and subsequent plaque rupture.

Large, population based prospective studies have confirmed that increased levels of inflammatory markers, including high-sensitivity C-reactive protein (hsCRP), interleukin6 (IL6), and soluble intercellular adhesion molecule1 (ICAM1), are associated with an increased risk of incident CAD events (Ridker PM et al. Circulation. 2004;109: IV69). While plasma levels of these markers have been examined in the peripheral blood during acute myocardial infarction [MI], only CRP and IL-6 intra-coronary arterial plasma levels have been examined in the acute ST elevation MI setting. (Corti R et al. J Am Coll Cardiol 2004;282A). It has been shown that coronary artery IL-6 plasma levels at the plaque rupture site are elevated to levels 252% greater than systemic blood samples drawn simultaneously from aortic blood. Plasma levels of hsCRP at the plaque rupture site, however, are significantly decreased up to 12% from aortic blood sample levels. These results may reflect increased local consumption of hsCRP, and in contrast, increased local release of IL-6 at the plaque rupture sites. The findings impact on current concepts of the pathogenesis of plaque rupture and myocardial infarction.

While prior studies have shown that during the acute MI setting, systemic plasma levels of ICAM1 increase only modestly, there have been no studies examining the plasma levels of ICAM1 at plaque rupture site (Pudil R et al.Clin Chim Acta. 1999;1-2: 127-34). Knowledge of the corresponding plasma levels of ICAM1 will also add to the current concepts of the pathogenesis of plaque rupture and MI.

2. Hypothesis

The central hypothesis is that plasma levels of ICAM1 will be significantly different from plasma levels in contemporaneously drawn aortic blood samples.

3. Methods

a. Conceptual and Operational Definitions

The study will measure arterial plasma levels of ICAM1 drawn from STEMI patients' aorta and infarct related artery at the plaque rupture site at the time of percutaneous coronary intervention [i.e. after stent deployment]. Blood samples from controls, patients presenting to Columbia's catheterization laboratory for staged PCI, will also be drawn. A 15 cc sample of blood will be aspirated from the coronary artery at the time of stent deployment. The catheter will next be retracted to the Aortic arch, flushed with 20 cc of normal saline, and a second 15 cc blood sample of will then be drawn from the aorta. The first 10 cc of each blood sample will be discarded, and the remaining 4-5 cc transferred to an EDTA tube. Tubes will be labeled and personal patient information will be de-identified from samples in accordance with good clinical practice standards and HIPAA regulation. Samples will then be given to research associate (RA), who will centrifuge samples, extract plasma using standard commercial pipettes, divide the remaining plasma samples into aliquots, and store them at -80 C. Once ready to be assayed, the aliquots will be thawed, and the inflammatory marker ICAM1 will be assayed using commercially available ELISA kits.

b. Study Design

The study is a prospective case-control design. Patients in the acute STEMI group will both serve as their own controls [i.e. intracoronary blood will be compared to aortic blood] and will also be compared against control groups [i.e. intracoronary plasma levels in patients with acute STEMI will be compared against those with staged PCI patients]. Levels of inflammatory marker ICAM1 in all of these patients will be examined. The study will seek to enroll consecutive patients that are identified to the hospital's acute MI pager carried by the cardiology fellow and staged PCI patients using the catheterization laboratory daily schedule. Specific inclusion and exclusion criteria are detailed below.

c. Statistical Procedures and Sample Size

- Paired t-test: Intra-patient comparison of aortic and coronary plasma levels.
    - Peak systemic levels in patients with acute STEMI are 330 with standard deviation of 169 ng/ml. In order to detect a 10% difference with a power of 85%, it is necessary to enroll 211 subjects.
- Unpaired t-test: Inter-patient comparison of intracoronary plasma levels between controls and STEMI patients.
    - Using above values, to detect 10% difference with a power of 85%, it is necessary to enroll 425 patients.

4. Subject Selection

<u>Inclusion criteria for STEMI patients:</u>

1) Acute ST Elevation MI including all three of the below:
    - History of chest pain > 30 minutes and within 180 minutes of stent placement.
    - ST elevations > 2 mm in at least 2 geographically colocated leads in the admission EKG, no greater than 90 minutes prior to procedure.
    - Visualization of thrombosis in infarct related artery on angiography
2) Age > 45 years-old

Inclusion criteria for staged PCI patients: Patients presenting for elective primary or staged PCI for known stenosis in epicardial artery thought secondary to CAD.

Exclusion Criteria for both Patient Populations:

1) STEMI determined secondary to coronary artery spasm or chronic total occlusion
2) Crack or cocaine use
3) Thrombolytic therapy received during concurrent admission
4) Connective tissue disease, advanced liver disease, or renal failure,
5) Malignant disease
6) Infectious disease
7) Inflammatory disease

5. Confidentiality of Study Data:

Participants will be identified by number rather than by name. All data will be stored in a locked, secure facility. Names will not be stored with data. Specifically, names will not be stored with the questionnaires or frozen blood samples. All data will eventually be stored in a computerized database. Individual subjects will be identifiable by number and not by name. Only research personnel listed on this study will have the coding key that relates the name to number. The Principal Investigator will be responsible for ensuring that the confidentiality of the data is maintained at all times. These data will be obtained specifically for research purposes.

6. Potential Risks

There are no additional risks that this study poses above the procedural risks associated with catheterization.

7. Potential Benefits

There are no direct benefits to participants. Importance of the knowledge to be gained and elucidation of the complex mechanisms between inflammation and acute MI are examples of general benefits of this study. In light of the anticipated knowledge to be derived from the study, the minimal risks to participants appear reasonable.

8. Alternatives

The alternative to participating in the study would be to not participate.

9. Compensation:

There will be no compensation offered for participation.

10. Cost:

Include but not limited to RA salary, 26 gold top tubes, access and use of centrifuge, freezer access, ELISA assay, computer with SAS software acess, and costs associated with manuscript submission.