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Pregnancy associated plasma protein-A and risk stratification of patients presenting with chest pain in the emergency department

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Abstract

Background: The aim of this study was to evaluate the clinical utility of serum pregnancy associated plasma protein-A (PAPP-A) levels in assisting triage of an intermediate to high-risk patient presenting with chest pain in the Emergency Department and no definite evidence of an acute coronary syndrome.
Methods: Serum levels of PAPP-A were measured in 59 patients presenting with chest pain to the Emergency Department. The patients were independently grouped according to the presence of acute coronary syndromes or the absence thereof.
Results: In a multivariate model that corrected for age, sex, type of chest pain, number of risk factors, history of coronary artery disease, troponin levels, and non-specific ECG changes, PAPP-A levels were still predictive of a final diagnosis of acute coronary syndrome in patients presenting with chest pain to the Emergency Department (Odds Ratio, 2.093; 95th confidence intervals, 1.037–4.224; $p=0.039$).
Conclusions: Elevated serum PAPP-A levels were predictive of a diagnosis of acute coronary syndrome in intermediate- to high-risk patients presenting to the Emergency Department with chest pain and no definite evidence of an acute coronary syndrome. Thus, serum PAPP-A may be valuable as an adjunct, minimally invasive marker to improve risk stratification in chest pain patients.
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Keywords: Pregnancy-associated plasma protein A; Chest pain; Emergency Department

1. Introduction

Chest pain is second only to abdominal pain as the most common reason for Emergency Department visits in the United States, making up 5.4% of all visits in 2000 [1]. While it has multiple causes, the most clinically important are the acute coronary syndromes, which must be differentiated from non-cardiac causes [2]. The ability to accurately triage chest pain patients in the Emergency Department remains elusive and is most challenging in patients with intermediate- to high-risk profiles and no definitive evidence of an acute coronary syndrome.

Current blood-based markers such as the troponin and creatine kinase-MB reflect myocardial injury and are thus secondary phenomena and not necessarily elevated in unstable angina or early myocardial infarction [3–5]. A circulating marker that would reflect unstable plaque in coronary arteries could provide additional and powerful diagnostic information for patients with acute coronary

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syndromes. Such a marker would also improve risk stratification in chest pain patients and might identify those at risk for future acute coronary syndromes.

Serum levels of pregnancy associated plasma protein-A (PAPP-A), a recently identified metalloproteinase in the insulin-like growth factor system [6], were demonstrated to be elevated in men and women with proven unstable angina or acute myocardial infarction [7]. In another study, circulating PAPP-A was found to be a strong independent predictor of ischemic cardiac events and need for revascularization in patients with acute coronary syndromes whose troponin was negative [8]. Therefore, the current study was designed to assess whether there is an additive diagnostic value of measuring circulating PAPP-A levels to the known clinical information and laboratory tests available to Emergency Department physicians when evaluating a patient with chest pain of at least intermediate risk and no definitive diagnosis of an acute coronary syndrome.

2. Methods

2.1. Patients and design

The study consisted of patients presenting with chest pain to the Emergency Department at St. Mary's Hospital, Rochester, MN. One hundred and six patients accepted to participate in the study and gave informed consent. Blood was drawn and sent for analysis. After completion of the medical evaluation, the paper records of these 106 patients were reviewed. Patient history, cardiac risk factors, electrocardiogram (ECG), stress test results, coronary angiogram results and laboratory values for serum troponin were abstracted.

Patients of intermediate to high likelihood of having a significant coronary event at presentation to the emergency department were eligible for the study while patients with a definite acute coronary syndrome at presentation or very low likelihood of a significant coronary event were excluded. Accordingly, patients with one or more risk factors for coronary atherosclerosis regardless of the character of the chest pain and patients with atypical or typical chest pain were included. There were 59 patients that met these inclusion criteria and subsequently formed the study population. Excluded patients were (1) patients with non-cardiac chest pain and no risk factor who were considered very unlikely to have an acute coronary syndrome (18 patients); (2) patients with ST elevation myocardial infarction or dynamic electrocardiographic ST segment changes ≥ 0.5 mm from baseline (4 patients); (3) patients with a positive initial troponin T (13 patients); (4) patients with significant renal dysfunction and serum creatinine >1.8 mg/dL (5 patients); (5) patients with acute or chronic inflammatory diseases (7 patients); (6) and pregnant patients (none). This protocol was approved by the Mayo Clinic Institutional Review Board.

After reviewing the records of the complete evaluation that included a stress test and/or a coronary angiogram, a final diagnosis of the presence or absence of an acute coronary syndrome (ACS) was made. Patients were grouped independently by 2 reviewers (AAE and AED) who were blinded to the PAPP-A results. Acute coronary syndromes were defined as patients with a positive troponin T on subsequent blood draws, a positive treadmill stress test with Duke score ≤ 5, an imaging stress test with new areas of myocardial involvement, or "active" coronary artery disease (ulceration, thrombus) shown by subsequent coronary arteriography. All other patients who did not meet the above criteria for an ACS were considered to have non-cardiac chest pain.

2.2. Definitions

History of coronary artery disease was considered present in patients with a prior positive stress test, positive coronary angiogram, previous myocardial infarction or coronary revascularization procedure.

Coronary artery disease (CAD) risk factors, as outlined by the National Cholesterol Program (NCEP), were age, gender, family history of disease, smoking, hypertension, diabetes mellitus, and hyperlipidemia [9]. The later five risk factors were collapsed into one variable (risk factor number, 0 to 5) reflecting the presence or absence of each one of them.

Chest pain was considered typical if it met these 3 characteristics: (1) retrosternal; (2) precipitated by effort or stress; and (3) relieved by rest or nitroglycerin. Chest pain was considered atypical if it met any 2 characteristics and non-cardiac if it met only 1 characteristic.

The glomerular filtration rate was estimated with the use of the Modified Diet in Renal Disease (MDRD) equation [10]. A troponin $T>0.03$ ng/mL was considered positive.

2.3. Serum assays for PAPP-A

Blood samples were taken by venipuncture on admission to the Emergency Department. Serum PAPP-A levels were determined by Ultra-sensitive PAPP-A ELISA kits kindly provided by Diagnostic Systems Laboratories, Inc. (Webster, TX). In view of the fact that circulating ACS-related PAPP-A is different from circulating pregnancy-related PAPP-A in that it is not complexed with proMBP [11], the test used in our study was developed and validated for non-pregnancy applications and uses different antibodies that specifically recognize epitopes on PAPP-A and not the pro-form of eosinophil major basic protein. Minimum sensitivity is 0.24 mIU/L, with intra- and inter-assay coefficients of variation of 4.7% and 4.2%, respectively. All patient samples were run together for the assay by a technician who was blinded to the ACS status of the patients.

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