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New predictor of acute coronary syndrome :

Ischemia modified albumin versus cardiac troponin –I in patient with acute chest pain

Thesis
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LIST OF ABBREVIATIONS

ABSU	Absorbance unit
ACS	Acute coronary syndrome
ACB	Albumin cobalt binding assay
ACC	The American College of Cardiology
ALB	Albumin
ALT	Alanine Aminotransferase
AMI	Acute myocardial infarction
AST	Aspartate Aminotransferase
AUC	Area under curve
BNP	Brain-type natriuretic peptide
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CCU	Coronary care unit
CD40L	CD ٤٠ ligand
CK	Creatine kinase
CK MB	Creatine kinase MB fraction
CRP	C- reactive protein
CtnI	Cardiac tropnin I
DTT	Dithiothreitol
CTnT	Cardiac troponin T
ECM	Extra cellular matrix
ECG	Electrocardiogram

ED	Emergency department
EIA	Enzyme immunoassay
ELISA	Enzyme linked immunsorbant assay
ESC	European Society of Cardiology
FDA	Food and drug administration
GP	Glycogen phosphorylase
HDL-C	High density lipoprotein- cholesterol
hs CRP	High sensitivity C-reactive protein
HAS	Human serum albumin
IEMA	Immunoenzymometric assay
IGF-1	Insulin-like growth factor-١
IHD	Ischemic heart disease
IL-6	Interleukin – ٦
IMA	Ischemia modified albumin
LD	Lactate dehydroogenase
LDL-C	Low density lipoprotein- cholesterol
MetS	Metabolic syndrome
MMPs	Matrix metalloproteinases
MPO	Myeloperoxidase
N	Number
NCEP-ATP III	National cholesterol education program and adult treatment panel III
NAD	β-nicotinamide adenine dinucleotide
NADH	Reduced β-nicotinamide adenine dinucleotide
NO	Nitric oxide
NPV	Negative predictive value
NSTEACS	Non ST elevation acute coronary syndrome
NSTEMI	Non ST elevation myocardial infarction
NT-proBNP	amino- teminal fragment of pro BNP
PAPP-A	Pregnancy Associated Plasma Protein-A
PCI	Percutaneous coronary intervention
PDGF	Platelet derived growth factor
PE	Pulmonary embolism

PTCA	Percutaneous transluminal coronary angioplasty
ROC	Recevier operating characteristic curve
sCD40L	Soluble CD٤٠ ligand
SD	Standard deviation
SMA	Superior mesenteric artery
STEMI	ST elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TNFα	Tumor necrosis factorα
UA	Unstable angina

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Introduction

Cardiovascular diseases are presently the leading causes of death in industrialized countries and expected to become so in developing countries by ٢٠٢٠. Heart diseases include silent ischemia, stable angina pectoris, unstable angina, myocardial infarction, heart failure, and sudden death. Patients with chest pain represent a very large proportion of all acute medical hospitalizations in the world. Distinguishing those with acute coronary syndrome (ACS) within the very large proportion with suspected cardiac pain represents a diagnostic challenge. Among these, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. The chest pain is the main clinical presentation of ACS. In spite of modern treatment, the rates of death, MI, and re-admission of patients with ACS remain high.*(*Murray CJ, et al.,٢٠٠٨*)*.

The admission ECG, however, fails to identify many of the patients who experience cardiac event during the early follow-up periods. During the past years, novel sensitive biomarkers for detecting minimal myocardial injury have been developed. Myoglobin has been shown to reach peak values early after the

onset of symptoms. Also , creatinin kinase (CK-MB) mass appears In blood relatively early after the onset of symptoms *(hamm et al.,1994)*

An elevated cardiac troponin I(cTnI) or cardiac troponin-T (cTnT) in patients admitted with chest pain and ST-segment elevation identifies a subgroup of patients (STEMI)with worse short and long-term prognosis(Matetzky et al.,٢٠٠٠)

The use of biomarkers for the identification of suspected acute coronary syndromes depends on the presence of myonecrosis as surrogate indicator for myocardial ischemia .However , many patients have myocardial ischemia in absence of myonecrosis , and markers such as myoglobin ,CK-MB ,and troponins,

although mainstay for the diagnosis of acute cardiac myonecrosis thus are limited for the confident exclusion of coronary ischemia (unstable angina).Furthermore, the release of these markers is time –dependant ;an initial negative results do not exclude the presence of MI. Therefore, a rapidly detectable , highly sensitive marker for myocardial ischemia would be desirable to identify patients with only ischemia and those early in the course of acute myocardial infarction without the evidence of myonecrosis yet .For such a marker to be useful , it should be accompanied by a high negative predictor value *(anwaruddin et al.,2005)*

The N-terminal region of Human Serum Albumin (HAS)(Asprgin-Alanin-Histidin-Lysin) binds the transition metals CoII nd Nill.Synthetic peptides with the first ٢+/-١٢amino acids of the HAS sequence demonstrated that the first three amino acids Asprgin ,Alanin, Histidin are essential for strong binding of cobalt.

Modification of the N-terminal peptide of HAS by way of N-acetylation or the deletion of one or more amino acids resulted in no binding of cobalt .Because the degradation of the susceptible , specific transition metal binding site of HAS may account for the decreased cobalt binding observed during

ischemic events , an assay that detects this reduced binding could be useful in diagnosis of ischemia *(Bar et al.,2001).*
Ischemia modified albumin is highly sensitive for diagnosis of myocardial ischemia in patients presenting with acute chest pain(Sinha et al.,٢٠٠٤). As myocardial ischemia produces lower binding capacity for cobalt to albumin which leads to the development of this new marker (*Liyan et al., 2008*).
Ischemia modified albumin, as measured by the albumin cobalt binding (ACB) assay, has been cleared by the Food and Drug Administration (FDA) United States of America as a possible early indicator of myocardial ischemia (*Govender et al., 2008*).

Aim of study

The aim of this study is to validate ischemia modified albumin(IMA) or Albumin Cobalt Binding(ABC) assay to determine if it will provide a diagnosis and an earlier rule-out of acute coronary syndromes in patients with acute chest pain and its sensitivity compared with cardiac troponin-I

I) ACUTE CORONARY SYNDROME

This is an umbrella term used to cover any group of clinical symptoms compatible with acute myocardial ischemia. Acute myocardial ischemia is chest pain due to insufficient blood supply to the heart muscle that results from coronary artery disease .

Patients who have symptoms of acute myocardial ischemia and are given an electrocardiogram (ECG or EKG) may or may not have an ST elevation. Most patients who have ST-segment elevation will ultimately develop a Q-wave acute myocardial infarction (heart attack). (The Q-wave describes another part of an ECG graph.) Patients who have ischemic discomfort without an ST-segment elevation are having either unstable angina, or a non-ST-segment elevation myocardial infarction that usually leads to a non-Q-wave myocardial infarction.

Acute coronary syndrome thus covers the spectrum of clinical conditions ranging from unstable angina to non-Q-wave myocardial infarction and Q-wave myocardial infarction. These life-threatening disorders are a major cause of emergency medical care and hospitalization in the United States. Coronary

heart disease is the leading cause of death in the United States. Unstable angina and non-ST-segment elevation myocardial infarction are very common manifestations of the disease.

Classification of Acute Coronary Syndrome

ACS encompasses patients who present to the ED with unstable ischemic heart diseases. They are subdivided into two major groups based on their electrocardiogram (ECG) findings (*Morrow et al., 2007*):

١- Patients with new ST-segment elevation on ECG which is diagnostic of ST elevation myocardial infarction (ACS-STE or STEMI), usually but not always these individuals will develop Q waves on their ECGs, hence the term "Q-wave myocardial infarction".

٢- Patients who present with ST segment depression, T wave inversion, or no ECG abnormalities (non ST elevation ACS, ACS-NSTE). The latter term NSTEACS encompasses both UA and non ST elevation myocardial infarction (NSTEMI); often referred to as "non-Q-wave myocardial infarction".

Unstable angina comprises a heterogeneous group of patients, and is classified into three groups according to the clinical circumstances of the acute ischemic episode: primary unstable angina, secondary angina (e.g., with angina related to obvious precipitating factors such as anemia) and post-MI unstable angina *(Braunwald and Cannon, 2007).*

Both NSTEMI and UA are considered to be closely related conditions sharing common pathogenesis and clinical presentation, however, NSTEMI is distinguished from UA by ischemia which is sufficiently severe in intensity and duration and leads to irreversible myocardial damage and is recognized

clinically by detection of biomarkers of myocardial infarction in serum (*Morrow et al., 2007*). Figure ١ shows a schematic classification of patients with ACS.

It is well established that ACS in their different clinical presentations share a widely common pathophysiological substrate. Pathological, angioscopic, and biological observations have demonstrated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolization, resulting in myocardial underperfusion, represent the basic pathophysiological mechanisms in most ACS.

As this is a life-threatening state of atherothrombotic disease, criteria for risk stratification have been developed to allow the clinician to make timely decisions on pharmacological management as well as on coronary revascularization strategies, tailored to the individual patient. The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain.

At presentation, the working diagnosis of non-STE-ACS (NSTE-ACS), based on the measurement of troponins, will be further qualified into non-ST elevation MI (NSTEMI) or unstable angina. In a certain number of patients, CAD will subsequently be excluded as the cause of symptoms. The therapeutic management is guided by the final diagnosis.