Prognostic value of Asymmetric dimethylarginine in patients with acute coronary syndrome

Thesis

Submitted for Partial Fulfillment of the Master Degree in
Cardiology

By

Reem Ali Ibrahim
M.B., B.Ch, Ain Shams University

Under Supervision of

Prof. Dr. Mohsen Mahmoud Mahdy

Professor of Cardiology
Faculty of Medicine - Ain Shams University

Ass. Prof. Dr. Ahmed Mohamed Onsy

Assistant professor of Cardiology
Faculty of Medicine - Ain Shams University

Dr. Sameh Attia Amin

Lecturer of Cardiology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

*Thanks first and last to **ALLAH** for his guidance, support and care in every step in our lives.*

I would first like to thank my thesis advisor **Prof. Dr. Mohsen Mahdy,** professor of cardiology at faculty of medicine Ain Shams University, whom I was honored to be under his supervision with his special comments & experience steering me in the right direction whenever he thought I needed it.

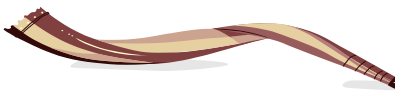
I would also like to thank **Prof, Dr. Ahmed Onsy,** assistant professor of cardiology at faculty of medicine Ain Shams University, for helping and supporting me in every way with patience and care to accomplish this thesis.

I would also like to acknowledge **Dr. Sameh Attia,** lecturer of cardiology at faculty of medicine Ain Shams University, for guiding me to the right path and offering me every help & support I needed in my work.

Finally, I must express my deep gratitude to my precious parents for offering me nonstop love, support and encouragement in every step I always take and to whom I dedicate every success I make in my whole life.

This accomplishment would not have been possible without all of you.

Reem Ali Ibrahim



Contents

List of Abbreviations

Abbrev.	Meaning
ACC	: American college of cardiology.
ACEI	: Angiotensin converting enzyme inhibitor.
AHA	: American heart association.
AVP	: Vasopressin.
B.B.	: Beta receptor blocker.
CBC	: Complete blood picture.
CK	: Creatine kinase.
CKMB	: Creatine kinase muscle and brain subunits.
CMR	: Cardiac magnetic resonance.
CT	: Computed tomography.
ECG	: Electrocardiogram.
eNOS	: Endothelial nitric oxide synthase.
GFR	: Glomerular filtration rate.
LBBB	: Left bundle branch block.
LV	: Left ventricle.
MI	: Myocardial infarction.
NSTEMI	: Non ST segment elevation myocardial infarction.
PCI	: Percutaneous coronary intervention.
RBBB	: Right bundle branch block.
ROS	: Reactive oxygen species.
STEMI	: ST segment elevation myocardial infarction.
SWMA	: Segmental wall motion abnormalities.
UA	: Unstable angina.

List of Figures

List of Tables

Introduction

Acute coronary syndrome (ACS) is a syndrome (set of signs and symptoms) due to decreased blood flow in the coronary arteries such that part of the heart muscle is unable to function properly or dies. The most common symptom is chest pain, often radiating to the left arm or angle of the jaw, pressure-like in character, and associated with nausea and sweating. It is usually caused by one of three problems: ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI), or unstable angina **(Amsterdam et al., 2014).**

Nine factors independently predicted death and the combined end point in the period from admission to six months after discharge: age, congestive heart failure, peripheral vascular disease, systolic blood pressure, Killip class, initial serum creatinine concentration, positive initial cardiac markers, cardiac arrest on admission, and number of leads with ST deviation. The highest hazard ratio for adverse outcome was for cardiac arrest **(Fox et al., 2006).**

Evidence has accumulated that asymmetric dimethylarginine (ADMA), a methyl derivate of the amino acid arginine and produced by the physiological degradation of methylated proteins, is an endogenous

competitive inhibitor of nitric oxide (NO) synthase. ADMA inhibits vascular NO production at concentrations found in pathophysiological conditions; it also causes local vasoconstriction when infused intra-arterially **(Böger, 2005).**

Nitric oxide reduction is considered the hallmark of endothelial dysfunction **(Eren et al., 2013).**

Endothelial dysfunction is associated with reduced anticoagulant properties as well as increased adhesion molecule expression, chemokine and other cytokine release, as well as reactive oxygen species production from the endothelium. This leads to inflammation and myofibroblast migration and proliferation inside the vessel all of which play important roles in the development of atherosclerosis **(Gokce, 2011).**

ADMA levels are associated with reduced NO synthesis as assessed by impaired endothelium-dependent vasodilation or reduced NO metabolite levels. In several prospective and cross-sectional studies, ADMA has evolved as a marker of cardio-vascular risk. An increasing number of prospective clinical trials have shown that the association between elevated ADMA levels and major cardiovascular events and total mortality is robust and extends to diverse patient populations **(Böger, 2005).**

Aim of the Work

The aim of the study is to determine the value of the asymmetric dimethylarginine in patients with acute coronary syndrome as a predictor of MACE and mortality during hospitalization and up to 6 months.

Chapter (1)

Acute Coronary Syndrome

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non– ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina **(Coven et al., 2016).**

Atherosclerosis is the primary cause of ACS, mostly occurring from the disruption of atherosclerotic plaque in a coronary artery stimulating platelet aggregation and thrombus formation **(Coven et al., 2016).**

The process of atherogenesis, lipid accumulation, cell proliferation, and extracellular matrix synthesis is neither linear nor predictable **(Shah et al., 1995)**. Pathological studies have revealed that such atherosclerotic plaques prone to rupture are commonly composed of a crescentic mass of lipids separated from the vessel lumen by a fibrous cap **(Fuster et al., 1992).** Plaques that undergo disruption tend to be relatively soft and have a high concentration of cholesterol esters rather than of free cholesterol monohydrate crystals. In addition, plaques rich

in extracellular matrix and smooth muscle cells, not necessarily considered vulnerable or lipid rich, may have a superficial erosion with complicated thrombosis also leading to unstable angina and other acute coronary syndromes **(Burke et al., 1997).** In addition to this rather "passive" phenomenon of plaque disruption, a better understanding of an "active" phenomenon related to macrophage activity is evolving **(Shah et al., 1995).**

Passive plaque disruption occurs most frequently where the fibrous cap is the thinnest, most heavily infiltrated by foam cells, and therefore the weakest. For eccentric plaques, this is often the shoulder between the plaque and the adjacent vessel wall. Pathoanatomic examination of intact and disrupted plaques and in vitro mechanical testing of isolated fibrous caps from aorta indicate that vulnerability to rupture depends on three factors: circumferential wall stress or cap "fatigue"; location, size, and consistency of the atheromatous core; and blood flow characteristics, particularly the impact of flow on the proximal aspect of the plaque (i.e., configuration and angulation of the plaque) **(Fuster et al., 1994).**

An active phenomenon of plaque disruption is probably important. Thus, atherectomy specimens from

patients with acute coronary syndromes revealed macrophage-rich areas. Macrophages can degrade extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and a family of matrix metalloproteinases (collagenases, gelatinases, and stromelysins) that may weaken the fibrous cap, predisposing it to rupture **(Moreno et al., 1996)**.

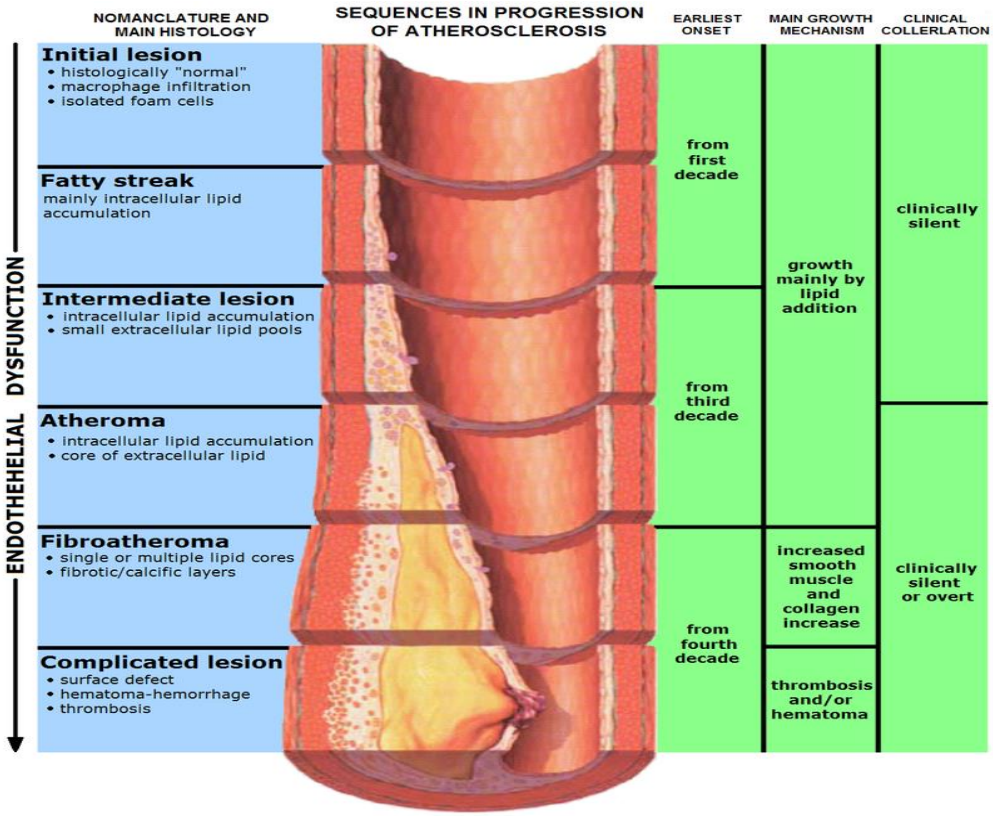


Fig. (1): Sequence in progression of atherosclerosis **(https://en.wikipedia.org/wiki/Atherosclerosis).**

Symptoms of ACS:

Complaints reported by patients with ACS include palpitations, chest Pain (which is usually described as pressure), squeezing or a burning sensation across the precordium and may radiate to the neck, shoulder, jaw, back, upper abdomen, or either arm,Eexertional dyspnea that resolves with rest, Diaphoresis from sympathetic discharge, Nausea from vagal stimulation & Decreased exercise tolerance **(Coven et al., 2016).**

Diagnosis:

The main methods used to confirm a diagnosis of ACS and to distinguish between the three types of ACS are as follows: **(Hamm et al., 2011)**

- **ECG:** UA and NSTEMI are associated with ST depression, transient elevation and/or T-wave changes, persistent ST elevation is characteristic of STEMI.

- **Cardiac troponins,** Troponin levels are sensitive markers of myocardial injury, elevated troponin levels as a result of myocardial damage can be used to distinguish UA from NSTEMI.

- **Imaging:**

A- Non-invasive imaging techniques:

Among non-invasive imaging techniques, echocardiography is the most important modality in the acute setting because it is rapidly and widely available. LV systolic function is an important prognostic variable in patients with CAD and can be easily and accurately assessed by echocardiography **(Heitlin et al., 2003).**

In patients with non-diagnostic 12-lead ECGs and negative cardiac biomarkers but suspected ACS, stress imaging may be performed, provided that the patient is free of chest pain **(Nucifora et al., 2007).**

Cardiac magnetic resonance (CMR) imaging can integrate assessment of function and perfusion, and detection of scar tissue in one session **(kwong et al., 2003).** Similarly, nuclear myocardial perfusion imaging has been shown to be useful **(Udelson et al., 2002)** also, Multidetector computed tomography (CT) offers direct visualization of the coronary arteries **(Hoffmann et al., 2009).**