HIGH ALTITUDE AND OTHER RISK FACTORS FOR CORONARY ARTERY DISEASE IN YEMEN; PREVALENCE, CLINICAL PRESENTATION, COMPLICATIONS AND PROGNOSIS

By

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TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATION

ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndromes
AMI	Acute myocardial infarction
AST	Aspartate transaminase
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CCU	Coronary care unit
CHD	Coronary heart disease
CHF	Congestive heart failure
CK	Creatine kinase
CK-MB	Creatine kinase iso-enzyme MB
CVA	Cerebro-vascular accident
CVD	Cardiovascular disease
CX	Circumflex coronary artery
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiography
EDCF	Endothelial-derived constricting factor
EDHF	Endothelium-derived hyperpolarizing factor
EDRF	Endothelial-derived relaxing factor
EF	Ejection fraction
ET-1	Endothelin-1
FBG	Fasting blood glucose
GMP	Guanosine monophosphate
HA	High altitude
Hb	Hemoglobin
HDL	High density lipoprotein

HF	Heart failure
HR	Heart rate
HTN	Hypertension
IHD	Ischemic heart disease
LAD	Left anterior descending coronary artery
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LVEF	Left ventricle ejection fraction
MI	Myocardial infarction
MLR	Multiple logistic Regression
MOV2	Myocardial oxygen demand
Non QMI	Non Q wave myocardial infarction
NO	Nitric oxide
NSTE	Non ST segment elevation
PCI	Percutaneous coronary intervention
PO_2	Partial pressure of oxygen
RBG	Random blood glucose
RCA	Right coronary artery
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical package for social science
STE	ST segment elevation
TG	Triglycerides
QMI	Q wave myocardial infarction
WBC	White blood cells
WHO	World Health Organization

LIST OF PUBLICATIONS

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ABSTRAK

Tujuan utama tesis ini adalah untuk mengkaji prevalen faktor risiko, presentasi klinikal, komplikasi, prognosis penemuan ekokardiografi dan angiografi koronari di kalangan pesakit sindrom koronari akut (ACS) pada altitud tinggi dan rendah.

Kajian pertama merupakan analisis penyemakan rekod retrospektif (Retrospective Review of Record) yang bertujuan untuk menganggarkan prevalens faktor-faktor risiko pada pesakit ACS di kedua-dua altitud. Ia juga menyiasat presentasi klinikal dan komplikasi pesakit ACS tersebut. Tujuh ratus enam puluh lapan (768) pesakit ACS dari altitud tinggi dan rendah telah dikaji. Umur, jantina, altitud tempat tinggal, kadar denyutan jantung (HR), tekanan darah sistolik (SBP) dan tekanan darah diastolik (DBP) telah direkodkan. Faktor riwayat penyakit arteri koronari (CAD) telah disiasat. Komplikasi ACS sewaktu kemasukkan di dalam hospital juga telah direkodkan. Keputusan yang diperolehi kajian 1 menunjukkan bahawa umur purata pesakit ACS adalah lebih muda pada altitud tinggi apabila dibandingkan dengan penduduk di altitud rendah. Kadar jantung (HR), SBP dan DBP adalah lebih tinggi pada altitud tinggi. Pesakit altitud tinggi menunjukkan kelebihan hemoglobin (Hb), hematokrit, darah sel putih (WBC), kreatinin kinase (CK), kreatin kinase-isoenzim (CK-MB), paras kolesterol, lipoprotein densiti rendah kolesterol (LDL-C) dan triglesirid (TG). Prevalen riwayat hiperlipidemia dan CAD adalah lebih tinggi di kalangan pesakit altitud tinggi. Prevalen riwayat DM dan merokok

adalah tinggi dengan "border line significance" di kalangan pesakit altitud tinggi. Kerosakkan dinding kardiak yang dikesan oleh ekokardiografi adalah lebih tinggi untuk pesakit altitud tinggi. Fraksi ejeksi ventrikel kiri (LVEF) adalah lebih rendah di kalangan pesakit di altitud tinggi. Bilangan pesakit strok dikalangan pesakit altitud tinggi adalah lebih tinggi. Aritmia, kegagalan jantung dan kematian tidak menunjukkan perbezaan.

Kajian 2 dalam tesis ini merupakan kajian kohot, mengkaji prognosis ACS di kalangan pesakit Yemeni pada altitud tinggi dan rendah. Satu ratus lima puluh tujuh pesakit ACS (157) dari altitud tinggi dan rendah telah dikaji mulai dari waktu kemasukkan ke wad CCU sehingga 12 bulan kemudian. Keputusan yang diperolehi kajian 2 menunjukkan bahawa umur purata pesakit ACS adalah rendah pada altitud tinggi apabila dibandingkan dengan penduduk altitud rendah, Kadar jantung (HR), SBP dan DBP adalah lebih tinggi pada altitud tinggi. Pesakit altitud tinggi menunjukkan paras, kreatinin kinase (CK), kreatin kinase-isoenzim (CK-MB), darah sel putih (WBC), jumlah kolesterol, LDL-C, TG dan paras glukosa rawak (RBG) yang lebih tinggi. Prevalen sejarah hyperlipidemia adalah lebih tinggi di antara pesakit altitud tinggi. Fraksi ejeksi ventrikel kiri ketika di dalam wad adalah lebih rendah di kalangan pesakit altitud tinggi. Penggunaan beta blocker ketika di dalam wad adalah lebih tinggi di kalangan pesakit altitud rendah. Penggunaan agen trombolitik, heparin, aspirin, peracat enzim penukar angiotensin (ACE-I), nitrat, agen mengurangkan kadar lipid, diuretik dan penghalang saluran kalsium adalah sama. Lawatan susulan bulan ke-enam menunjukkan nilai tinggi untuk HR, SBP, DBP dan HF untuk pesakit altitud tinggi. Lawatan susulan di akhir satu tahun menunjukkan nilai tinggi untuk HR, SBP, DBP dan keperluan angiografi diagonostik untuk arteri

koronori di kalangan penduduk altitud tinggi. Kegagalan jantung adalah lebih kerap dan LVEF mempunyai nilai rendah untuk pesakit altitud tinggi. Penggunaan beta blocker adalah lebih tinggi di kalangan pesakit altitud rendah. Kegunaan ubat yang lain adalah sama.

Kajian 3 dalam tesis ini meliputi penyemakan rekod retrospektif untuk menyiasat sifat ekokardiografi dan untuk menentukan keterukan oklusi arteri koronari ke atas pesakit dari kedua-dua altitud. Sebanyak enam ratus dua rekod (602) pesakit ACS yang telah melalui angiografi diagnostik telah disiasat. Penemuan kajian 3 menunjukkan bahawa umur purata untuk mengambil ujian angiografi koronori adalah lebih muda untuk pesakit altitud tinggi. Pesakit dari altitud tinggi mempunyai nilai yang lebih tinggi untuk HR, SBP dan DBP. Prevalen riwayat hiperlipidemia dan CAD adalah lebih tinggi di kalangan pesakit altitud tinggi. Bilangan riwayat DM dan merokok adalah tinggi dengan "border line significance" di antara pesakit altitud tinggi. Fraksi ejeksi ventrikel kiri mempunyai nilai Satu yang rendah untuk pesakit altitud tinggi. Oklusi tiga saluran adalah lebih kerap untuk pesakit altitud tinggi. Oklusi satu saluran pula adalah lebih kerap untuk pesakit altitud rendah. Pesakit altitud tinggi mempunyai frekuensi yang lebih tinggi untuk menghidapi oklusi arteri circumflex, "left anterior descending artery" dan arteri koronari kanan.

Sebagai kesimpulan, di Yemen, ACS berlaku pada peringkat umur yang muda pada altitud tinggi. Pesakit ACS altitud tinggi menunjukkan prevalen risiko kardiovaskular yang lebih tinggi. Oklusi koronari dan kesudahan klinikal adalah lebih teruk untuk pesakit altitud tinggi. Penemuan ini menunjukan altitud tinggi boleh dianggap salah satu risiko tersendiri ACS.

HIGH ALTITUDE AND OTHER RISK FACTORS FOR CORONARY ARTERY DISEASE IN YEMEN; PREVALENCE, CLINICAL PRESENTATION, COMPLICATIONS AND PROGNOSIS

ABSTRACT

The main objectives of this thesis are to estimate the prevalence of risk factors, to investigate the clinical presentation, complications, prognosis, echocardiographic characteristics and coronary angiography findings among ACS patients at high and low altitudes.

Study 1 was a retrospective review of records aimed at estimating the prevalence of risk factors in the ACS patients living at high and low altitudes. It was also aimed to investigate the clinical presentation and complications of these patients. Seven hundred and sixty eight (768) ACS patients from high and low altitudes were studied. Results of study 1 showed that the mean age of ACS patients at high altitude was significantly younger. Heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher at high altitude. High altitude patients were also seen to have significantly higher hemoglobin (Hb), hematocrit, white blood cells (WBC), creatine kinase (CK), creatine kinase-isoenzyme (CK-MB), total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglycerides (TG). The prevalence of past history of hyperlipidemia and history of coronary artery disease (CAD) were significantly higher for high altitude patients. The prevalence of past history of diabetes mellitus (DM) and smoking were higher with border line significance for high altitude. Cardiac wall motion abnormalities detected by echocardiography was higher for high altitude patients. Left ventricular ejection

fraction (LVEF) was significantly lower at high altitude. High altitude patients were seen to have significantly higher rate of stroke. Arrhythmias, heart failure and death did not show any difference.

Study 2 was a cohort study, aimed at evaluating the prognosis of ACS among patients at high and low altitudes. One hundred and fifty seven (157) ACS patients from high and low altitudes were evaluated from admission to CCU for up to 12 months. Results of study 2 showed that the mean age of ACS patients at high altitude was younger. Heart rate, SBP and DBP were higher for patients at high altitude. High altitude patients had higher CK-MB, WBC, total cholesterol, LDL-C and random blood glucose. The prevalence of past history of hyperlipidemia among ACS patients was higher for patients at high altitude. Left ventricular ejection fraction during hospitalization was lower for high altitude patients. Beta-blocker use was significantly higher at low altitude. Usage of thrombolytic agent, heparin, aspirin, angiotensin converting enzyme inhibitor (ACE-I), nitrates, lipid lowering agent, diuretics, and calcium channel blocker (CCB) were comparable. After six months of follow up, HR, SBP, DBP and incidence of heart failure were higher for high altitude patients. At the end of 1 year follow up, high altitude patients were seen to have higher HR, SBP, DBP and have more diagnostic coronary angiography done. Heart failure was more frequent among high altitude patients and LVEF was lower for high altitude patients. Beta-blocker use was significantly higher at low altitude, the rest of medication usage were comparable.

Study 3 was a retrospective review of records aimed at investigating echocardiographic characteristics and severity of coronary artery occlusions among high and low altitudes ACS patients. Records of six hundred and two

(602) ACS patients from high and low altitudes who underwent diagnostic coronary angiography were reviewed. Results of study 3 showed that the mean age of high altitude patients who underwent coronary angiography was younger. High altitude patients were seen to have higher HR, SBP and DBP. The prevalence of past history of hyperlipidemia and history of CAD were significantly higher for high altitude patients. Reported family history of CAD was significantly higher among low altitude patients. The prevalence of history of DM and smoking for patients at high altitude were higher with border line significance. Left ventricular ejection fraction was lower for high altitude patients. Three vessel occlusions were significantly more common for patients at high altitude while single vessel occlusion was significantly more common for low altitude patients. High altitude patients were seen to have more occlusions in circumflex coronary artery (CX), left anterior descending artery (LAD) and right coronary artery (RCA).

In conclusion, in Yemen, ACS occurs at younger age in high altitude residence. High altitude ACS patients also have more prevalent cardiovascular risk factors. They also demonstrated more severe coronary lesion and more adverse clinical outcome. These findings suggest that high altitude itself should be considered as an independent risk factor for ACS.

CHAPTER 1

INTRODUCTION

1.1 Background

Coronary artery disease is defined as a wide spectrum of conditions ranging from silent ischemia and exertion-induced angina, through unstable angina, to acute myocardial infarction (AMI). Unstable angina occupies the centre of this spectrum, causing disability and risk greater than that of chronic stable angina but less than that of acute myocardial infarction (AMI) (Braunwald *et al* 1994., Suraj *at al* 2005). Coronary Artery Disease (CAD) is a well-established major cause of death and disability in developed countries as well as in developing countries (Lopez and Murray., 1998).

Coronary Artery Disease continues to be a leading cause of morbidity and mortality among adults in Europe and North America (McGovern *et al*., 1996). British Heart Foundation estimated that 2.6 million in the UK have had coronary artery disease (British Heart Foundation., 2006). Coronary artery disease alone is the most common cause of death in Europe, accounting for nearly 2 million deaths each year (British Heart Foundation., 2000). According to the WHO, in 2001 there were 7.2 million deaths from coronary artery disease globally, and this is expected to increase to 11.1 million deaths in 2020 (WHO., 2002).

Although cardiovascular mortality has been diminishing for the past decades in all of Western Europe and North America, it is still one of the major contributors to mortality, especially premature death (Tunstall *et al*., 1999). Despite declines in developed countries, both CAD mortality and the prevalence of CAD risk factors continue to rise rapidly in developing countries (Okrainec., 2004). Traditional risk factors for CAD are age, male sex, family history, diabetes mellitus, dyslipidemia, hypertension, obesity, and tobacco

smoking. These risk factors are useful for assessment of each individual's cardiovascular risk (Spence *et al.,* 1999). Many other risk factors however, are still under scientific scrutiny (WHO., 1988), Several studies suggested that classical risk factors partially explain the prevalence of CAD (Menotti *et al* 1993., Al-Nuaim 1993., WHO 1994).

Geographical variations in CAD prevalence and mortality have been reported both between and within countries (Zareba *et al*., 1994). Geographical variations in CAD have been explained by variations in major risk factors and/or socioeconomic factors in a number of studies but, some variations tend to remain even after controlling for these factors. Disparities in cardiovascular outcomes across geographical regions are common, and yet not well understood (Moise and Jacobzone., 2003). Despite reported sizable geographical variations in CAD occurrence and outcome, only a few environmental contributors have been identified. Differences in environmental and genetic factors lead to differences in the incidence of CAD worldwide (Dawber *et al* 1996., Kerhuis *et al* 2000).

One environmental risk factor which may contribute to CAD is high altitude. Evidence for this is so far conflicting. Many studies have examined some risk factor profile for CAD in high altitude and low altitude population with conflicting findings, (MiraKhimov and Rafibekae 1985., Wolf *et al* 1994., Sharma 1990., Temte 1996., Pasini *et al* 1999., Fujimoto *et al* 1989 Fiori *et al* 2000., Dominguez *et al* 2000., Jefferson *et al* 2002., Nikos *et al* 2005).

There are a few studies investigating a possible association between altitude residence and mortality from CAD. Those that have been undertaken did not fully adjust for potential confounders and were conducted in

heterogeneous populations consisting of different ethnic subgroups (Mortimer *et al* 1977., Buechley *et al* 1979, Roberts *et al* 1979., Wei-Ching *et al* 2005). It has been postulated that the residual variation may be due to differences in environmental factors.

Hypoxia at high altitude is associated with increase in myocardial work which leads to increase the oxygen demand for cardiac muscle which may precipitate the presence of angina and development of myocardial infarction. Cardiovascular effects of high altitude residence on coronary artery disease patients raise a question concerning the tolerability of exposure to high altitude. Firstly, the observed increase in the numbers of patients admitted with ACS, all over the world, as well as in the Middle-East has raised many questions about the precipitating factors and etiological background. Epidemiological data have shown the importance of traditional and other risk factors in the pathogenesis of atherosclerosis. Recent studies, however suggest that the pattern of risk factor profile may differ according to age, gender, racial, geographical and environmental factors. However, only a few studies have investigated the effect of altitude on the prevalence of risk factors for CAD. The populations which were investigated were of heterogeneous ethnicity. This provides us with the incentive to further investigate the association of CAD risk factors and altitudes in a country like Yemen where the population is predominantly of the same ethnicity. Such study will enable us to establish the independent role of altitude on the prevalence of risk factors for CAD. One way of doing this is to study patients with documented cardiovascular events. This will not only allow us to investigate altitude as an independent risk factor for CAD but will also enable us to study whether differences exist in clinical characteristics of patients with

established CAD at different altitudes. Secondly, the effect of altitude on the prognosis of acute coronary syndrome has been never studied. There was only one study which studied the effect of altitude in on CAD mortality among general population. However it was done among a heterogeneous population and the altitude studied was not high altitude enough (980 meters above sea level), (Nikos *et al*., 2005). Thirdly, the relation between altitude residence and the severity of coronary arteries occlusion has not been studied before. The effect of altitude on the prognosis of ACS poses some interesting questions. Does high altitude increase the risk factors for coronary artery disease? Does hypoxia at high altitude increases ischemia, or provokes the transition to unstable syndromes such as unstable angina or acute myocardial infarction? Finally, does living at a high altitude increase the severity and risk of mortality among ACS patients and should altitude be taken into account when comparing cardiovascular risk for ACS?

A lack of data provides incentives to further investigate the association of risk factors profile for CAD, mortality, prognosis and different altitudes residence in a country such as Yemen where the population are predominantly of the same ethnicity (Arab), and its capital is located at high altitude of 2400 meters above sea level as well as the second capital located at low altitude region (sea level).

1.2 Aim of studies in this thesis

1. To investigate the effect of altitude on the prevalence of risk factors, clinical presentation, complications and prognosis of acute coronary syndrome patients at high and low altitude regions in Yemen.

2. To investigate the effect of altitude on the severity of coronary arteries occlusions at different altitudes.

1.3 Objectives

1. To estimate the prevalence of risk factors of ACS Yemeni patients at high versus low altitude regions.
2. To investigate the clinical presentation and complications of ACS during hospitalization among high versus low altitude patients.
3. To evaluate the effect of altitude on prognosis of ACS followed up for one year.
4. To investigate the effect of the altitude on echocardiographic characters and severity of coronary arteries occlusions among high and low altitude ACS patients.

CHPTER 2

LITERATURE REVIEW

2.1 Definition of acute coronary syndrome

Acute coronary syndrome is defined as a spectrum of clinical manifestations include unstable angina, acute myocardial infarction and to some extent, sudden cardiac death (Kristain *et al* 2001).

2.2 Diagnosis of acute coronary syndrome

2.2.1 Diagnostic guidelines

The World Health Organization criteria for the diagnosis of acute coronary syndrome required at least two of the following three elements to be present; AMI with ST elevation (typical symptoms or ECG with ST elevation and raised CK-MB or troponin), AMI without ST elevation (typical symptoms or ECG without ST elevation and raised CK-MB or troponin) and unstable angina (symptoms or ECG indicative of ischemia, with normal enzymes) (WHO database, 2003., Gomes *et al* 2005).

There is considerable variability in the pattern of presentation of ACS with respect to these three elements. ST-segment elevation and Q waves on the ECG, two features that are highly indicative of AMI, are seen in only about half of AMI cases on presentation (Goldberg *et al*., 1988). Approximately one-fourth of patients with AMI do not present with classic chest pain, and the event would go unrecognized unless an ECG were recorded fortuitously in temporal proximity to the infarction or permanent pathological Q waves are seen on later tracings (Kannel.,1987). Non-diagnostic ECG's are recorded in approximately half of patients presenting to emergency departments with chest pain suspicious for AMI who ultimately are shown to have an AMI (Gibler *et al*., 1990). Among patients admitted to the hospital with a chest pain syndrome,

fewer than 20 per cent are subsequently diagnosed as having had an AMI (Gilber *et al*., 1992). Therefore, in the majority of patients, clinicians must obtain serum cardiac marker measurements at periodic intervals to either establish or exclude the diagnosis of AMI (Sacks., 1994). Such measurements may also be useful for a rough quantitation of the size of infarction (Murray and Alpert., 1994).

2.2.2 Clinical presentation

2.2.2.1 Prodromal symptoms

Despite recent advances in the laboratory detection of AMI, history remains of substantial value in establishing a diagnosis (Huggins *et al*., 1996). The prodrome is usually characterized by chest discomfort, resembling classic angina pectoris, but it occurs at rest or with less activity than usual and can therefore be classified as unstable angina. However, the latter is often not disturbing enough to induce patients to seek medical attention. Among patients who are hospitalized for unstable angina, fewer than 10 per cent develop AMI. Of the patients with AMI presenting with prodromal symptoms of unstable angina, approximately one-third have had symptoms from 1 to 4 weeks before hospitalization. In the remaining two-thirds, symptoms predated admission by 1 week or less, with one-third of these patients having had symptoms for 24 hours or less (Harper *et al*., 1979). A feeling of general malaise or frank exhaustion often accompanies other symptoms preceding AMI.

2.2.2.2 Nature of the pain

The pain of AMI is variable in intensity; in most patients it is severe and in some instances intolerable. The pain is prolonged, usually lasting for more than 30 minutes and frequently for a number of hours. The discomfort is described as constricting, crushing, or compressing. The pain is usually retrosternal in location, spreading frequently to both sides of the anterior chest, with predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm, producing a tingling sensation in the left wrist, hand, and fingers. Some patients note only a dull ache or numbness of the wrists in association with severe substernal or precordial discomfort. However, it is generally much more severe, lasts longer, and is not relieved by rest and nitroglycerin.

In some patients, particularly the elderly, AMI is manifested clinically not by chest pain but rather by symptoms of acute left ventricular failure and chest tightness or by marked weakness or frank syncope. These symptoms may be accompanied by diaphoresis, nausea, and vomiting (Muller *et al*., 1990).

The pain of AMI may have disappeared by the time the physician first encounters the patient (or the patient reaches the hospital), or it may persist for many hours. Opiates, in particular, morphine, usually relieve the pain. Both angina pectoris and the pain of AMI are thought to arise from nerve endings in ischemic or injured, but not necrotic, myocardium (Malliani and Lombardi., 1982). Thus, in AMI, stimulation of nerve fibers in an ischemic zone of myocardium surrounding the necrotic central area of infarction probably gives rise to the pain. Pain often disappears suddenly and completely when blood flow to the infarct territory is restored. In patients in whom re-occlusion occurs after thrombolysis, pain recurs if the initial reperfusion has left viable

myocardium. Thus, what has previously been thought of as the “pain of infarction,” sometimes lasting for many hours, probably represents pain caused by ongoing ischemia. The recognition that pain implies ischemia and not infarction heightens the importance of seeking ways to relieve the ischemia, for which the pain is a marker.

2.2.2.3 Other symptoms

Nausea and vomiting occur in more than 50 per cent of patients with transmural MI and severe chest pain (Ingram *et al*., 1980). It is due to activation of the vagal reflex or to stimulation of left ventricular receptors as part of the Bezold-Jarisch reflex. These symptoms occur more commonly in patients with inferior MI than in those with anterior MI. Occasionally a patient complains of diarrhea or a violent urge to evacuate the bowels during the acute phase of MI. Other symptoms include feelings of profound weakness, dizziness, palpitations, cold perspiration, and a sense of impending doom. On occasion, symptoms arising from an episode of cerebral embolism or other systemic arterial embolism are the first signs of AMI. The aforementioned symptoms may or may not be accompanied by chest pain.

Sigurdsson *et al*., (1995) reported that more than 20 percent of non fatal myocardial infarction are unrecognized by the patient and are discovered only on subsequent routine electrocardiographic tests. It also reported that unrecognized or silent myocardial infarction occurs more commonly in diabetic and hypertensive patients.

2.3 Investigations and procedures

2.3.1 Electrocardiogram (ECG)

A serial standard 12-lead ECG remain a clinically useful method for the detection and localization of acute myocardial infarction (Murray and Alpert.,1994).

Parameters of ECG with suspected ACS are ST-elevation with or without Q wave in two leads at least, pathological Q-wave, ST depression, peaked or hyper acute T waves, T wave flattening or inversion with or without ST segment depression, R wave changes, left bundle branch block and arrhythmias.

2.3.2 Laboratory finding in ACS

2.3.2.1 Serum cardiac markers

Serum cardiac marker determinations play a vital role in the diagnosis of ACS. Serum markers such as aspartate transaminase (AST), lactate dehydrogenase, (LDH) and lactate dehydrogenase subforms no longer are used because they lack cardiac specificity and their delayed elevation precludes early diagnosis (Braunwald *et al*., 2001).

2.3.2.1.1 Creatine kinase (CK)

It is an enzyme that is found in striated muscle and tissues of the brain, kidney, lung, and gastrointestinal tract. This widely available marker has low sensitivity and specificity for cardiac damage. Furthermore, CK levels may be elevated in a number of noncardiac conditions, including trauma, seizures, renal insufficiency, hyperthermia, and hyperthyroidism. The serum CK level rises within three to eight hours after myocardial injury, peaks by 12 to 24 hours, and returns to baseline within three to four days (Karras *et al*., 2001). A serum CK

level may be used as a screening test to determine the need for more specific testing. Although CK commonly was measured serially (along with CK-MB) at the time of hospital admission and six to 12 hours after admission, this marker largely has been replaced by cardiac troponins and CK-MB (Braunwald *at al*., 2001).

2.3.2.1.2 CK-MB isoenzyme

CK-MB is one of the most important myocardial markers (in spite of not being altogether cardiac-specific), with well-established roles in AMI and in monitoring reperfusion during thrombolytic therapy following AMI (Apple *et al*., 1994). In AMI, plasma CK-MB typically rises some 4-6 hours after the onset of chest pains, peaks within 12-24 hours, and returns to baseline levels within 24-48 hours. The pattern of serial CK-MB determinations is more informative than a single determination: one CK-MB measurement, even when taken at an appropriate time, cannot definitively confirm or rule out the occurrence of AMI. Accordingly, it has been recommended that CK-MB be measured on admission to the emergency room and at intervals thereafter (eg, at 3-hour intervals over a 6- to 9-hour period in patients with nonspecific electrocardiogram changes; 1, 2 or at 6- to 8-hour intervals over a 24-hour period (Apple *et al*., 1994).

Like the CK level, the peak CK-MB level does not predict infarct size; however, it can be used to detect early re-infarction (Karras., 2001). Three isoenzymes of CK (MM, BB, and MB) have been identified by electrophoresis. Extracts of brain and kidney contain predominantly the BB isoenzyme, skeletal muscle contains principally MM but does contain some MB (1 to 3 per cent), and both MM and MB isoenzymes are present in cardiac muscle (Tsung *et al*.,

1986). Serial CK-MB levels commonly are obtained at admission to the emergency department and are repeated in six to 12 hours, depending on the assay that is used (American College of Emergency Physicians 2000). CK-MB isoform may be further characterized into isoforms. CK-MB2 is found in myocardial tissue, and CK-MB1 is found in plasma. The CK-MB isoform assay takes about 25 minutes to perform (Puleo *et al*., 1989). A CK-MB2 level greater than 1 U per L in combination with a sub-form ratio greater than 1.5 suggests myocardial injury (Bock *et al*., 1999).

2.3.2.1.3 Cardiac troponins

The troponin complex consists of three subunits that regulate the calcium-mediated contractile process of striated muscle (Katus *et al*., 1992). These are troponin C which binds Ca++, troponin I which binds to actin and inhibits actin-myosin interactions and troponin T which binds to tropomyosin, thereby attaching the troponin complex to the thin filament (Katus *et al*., 1991). Troponin T and I generally have similar sensitivity and specificity for the detection of myocardial injury. Unlike troponin I levels, troponin T levels may be elevated in patients with renal disease, polymyositis, or dermatomyositis. The cardiac troponins typically are measured at emergency department admission and repeated in six to 12 hours (American College of Emergency Physicians. 2000). Patients with a normal CK-MB level but elevated troponin levels are considered to have sustained minor myocardial damage or micro-infarction, whereas patients with elevations of both CK-MB and troponins are considered to have had acute myocardial infarction. The cardiac troponins may remain elevated up to two weeks after symptom onset, which makes them useful as late markers of recent acute myocardial infarction (Braunwald *et al*., 2001). An elevated

troponin T or I level is helpful in identifying patients at increased risk for death or the development of acute myocardial infarction (Karras *et al*., 2001). Increased risk is related quantitatively to the serum troponin level. The troponins also can help identify low-risk patients who may be sent home with close follow-up. In a study of 773 patients presenting to an emergency department with acute chest pain, those with a normal or nearly normal ECG and a normal troponin I test six hours after admission had a very low risk of major cardiac events (0.3 percent) during the next 30 days. Bedside troponin assays have been developed.

2.3.2.1.4 Myoglobin

Myoglobin is a low-molecular-weight protein that is present in both cardiac and skeletal muscle. It can be detected in the serum as early as two hours after myocardial necrosis begins. Myoglobin has low cardiac specificity but high sensitivity, which makes it most useful for ruling out myocardial infarction if the level is normal in the first four to eight hours after the onset of symptoms (Braunwald *et al*., 2001). Time changes in the myoglobin value also can be extremely helpful. Combining a doubling of the baseline myoglobin level at two hours after symptom onset with an abnormal myoglobin test at six hours v symptom onset increases the sensitivity to 95 percent at six hours (Decker *et al.*, 2006). Myoglobin should be used in conjunction with other serum markers, because its level peaks and falls rapidly in patients with ischemia.

2.3.3 Hematological functions

2.3.3.1 Leukocytes

Acute coronary syndrome is usually accompanied by leukocytosis, which is related to the necrotic process and its magnitude and to elevated glucocorticoid

levels. Activation of neutrophils may produce important intermediates, such as leukotriene B4 and oxygen free radicals that have important microcirculatory effects (Engler *et al*,. 1983).

2.3.3.2 Hemoglobin and hematocrit

Clinical and epidemiological studies suggest that several hemostatic and hemorheological factors (e.g., fibrinogen, Factor VII, plasma viscosity, hematocrit, red blood cell aggregation, total white cell count) are involved in the pathophysiology of atherosclerosis and also play an integral role in acute thrombotic events (Koenig and Erns., 1992). An increase in blood viscosity also occurs in patients with AMI. During the first few days after infarction, this is mainly attributable to hemoconcentration, but later the increases in plasma viscosity and red cell aggregation correlate with elevated serum concentrations of alpha2 globulin and fibrinogen, which are nonspecific reactions to tissue necrosis and are also responsible for the elevated sedimentation rate characteristic of AMI (Hershberg *et al*., 1972). The high values of blood viscosity indices are observed most frequently in patients with complications such as left ventricular failure, cardiogenic shock, and thromboembolism.

2.3.4 Lipid profile

These are often determined in patients with AMI. However, the results may be misleading because numerous factors that can alter the values are operating at the time of the patient's admission to the hospital. Serum triglycerides are affected by caloric intake, intravenous glucose, and recumbency. During the first 24 to 48 hours after admission, total cholesterol and HDL cholesterol

remain at or near baseline values but generally fall precipitously after that. The fall in HDL cholesterol after AMI is greater than the fall in total cholesterol; thus, the ratio of total cholesterol to HDL cholesterol is no longer useful for risk assessment early after MI (Ronnemaa *et al*., 1980). In review of the revised, more aggressive guidelines for management of hyperlipidemia in patients with clinical manifestations of coronary artery disease (The Third Report of the National Cholesterol Education Program., 2001), a lipid profile should be obtained on all AMI patients who are admitted within 24 to 48 hours of symptoms.

2.3.5. Echocardiography

2.3. 5.1 Two dimensional echocardiography

The relative portability of echocardiographic equipment makes this technique ideal for the assessment of patients with AMI hospitalized in the coronary care unit or even in the emergency department before admission (Nishimura., 1996). In patients with chest pain compatible with AMI but with a non-diagnostic ECG, the finding on echocardiography of a distinct region of disordered contraction can be helpful diagnostically because it supports the diagnosis of myocardial ischemia (Hepner and Armstrong., 1995). Echocardiography is also useful in evaluating patients with chest pain and a non-diagnostic ECG who are suspected of having an aortic dissection. The identification of an intimal flap consistent with an aortic dissection is a crucial observation because it represents a major contraindication to thrombolytic therapy. Areas of abnormal regional wall motion are observed almost universally in patients with AMI, and

the degree of wall motion abnormality can be categorized with a semiquantitative wall motion score index (Segar *et al*., 1992).

2.3.5.2 Doppler echocardiography

This technique allows for assessment of blood flow in the cardiac chambers and across cardiac valves. Used in conjunction with two-dimensional echocardiography, it is helpful in detecting and assessing the severity of mitral or tricuspid regurgitation following AMI (Harrison and Bashore., 1995). Identification of the site of acute ventricular septal rupture, as well as quantification of shunt flow across the resulting defect, is also possible (Smyllie *et al*., 1990).

2.3.6 Stress testing

Stress testing is a mean of further assessing for the presence of flow-limiting, functionally significant coronary artery disease. The preferred method of cardiovascular stress testing is exercise, utilizing a treadmill or bicycle. Through aerobic exercise, one achieves a greater rate pressure product and therefore greater cardiovascular stress. This permits an assessment of an individual's functional capacity, providing prognostic data utilizing the sole parameter of attained metabolic equivalents or oxygen utilization. Heart rate recovery, the rapidity of the heart rate to decline after exercise cessation, is also an important prognostic parameter. Exercise-induced arrhythmias are also commonly observed and provide information concerning efficacy of heart arrhythmias and also may represent the initial manifestation of CAD.

The most common agent used for pharmaclogic stress testing is dobutamine. Dobutamine acts as beta-receptor 1 and 2 agonist, increasing myocardial contractility, heart rate, and inducing peripheral vasodilation; in sum raising myocardial oxygen demand. It is usually combined with echocardiography. Dobutamine echocardiography is useful in assessing for the presence of functionally significant obstructive coronary artery disease and also in assessing a post-myocardial infarction patient. Utilizing echocardiography, be it combined with exercise or dobutamine, the physician interpreter is focusing upon the global and regional myocardial response to cardiovascular stress. Under normal circumstances, the end systolic left ventricular volume at peak stress diminishes and myocardial thickening is symmetrically enhanced. When abnormal, a regional decrement of myocardial thickening is observed, supporting inducible myocardial ischemia. In the presence of advance multivessel coronary artery disease, the left ventricle actually dilates and a marked reduction in global myocardial thickening is observed. Dobutamine echocardiography is additionally useful for the assessment of myocardial viability in patients with known ischemic left ventricular systolic dysfunction. In this circumstance, when contemplating myocardial revascularization, it is important to determine, pre-procedure, what areas are dysfunctional yet alive versus dysfunctional with irreversible scarring.

2.3.7 Coronary arteriography

Cardiac catheterization is currently the "gold standard" for determining the presence of obstructive coronary artery disease. A cardiac catheterization yields a two-dimensional rendering of the coronary artery circulation. To assist in

circumventing the limitations of a two-dimensional depiction of three-dimensional anatomy, multiple views from varying angles are obtained as a standard. It is exceedingly important to visualize each coronary artery segment from at least two orthogonal views. Coronary artery plaque formation is usually eccentric in location, not a smooth cylindrical encroachment upon the coronary artery lumen, and variable in appearance from different vantage points. This eccentricity can lead to both under- and overestimation of coronary artery disease severity, necessitating a methodical approach to view acquisition.

A more accurate assessment of coronary arterial lumen is by assessing the cross-sectional area of the coronary artery, expressed as a percentage obstruction. This requires the direct visualization of the coronary artery from within the lumen. This limitation has proved the catalyst for the development of intravascular ultrasound. During this procedure, a small flexible ultrasound probe is threaded down the coronary artery. The images are obtained in real time, with a percentage lumen diameter readily calculated. For coronary artery lesions not well seen on routine coronary artery arteriography, this has been an extremely helpful technique providing clarification as to disease severity. Additionally, intravascular ultrasound can help guide the interventional cardiologist as to device selection prior to performing percutaneous coronary artery revascularization. A subset of patients where intravascular ultrasound has proven extremely helpful is the cardiac transplantation population. These patients develop a coronary arteriopathy where compromise of the coronary arterial lumen is smooth, cylindrical, and diffuse throughout the coronary arterial tree. A routine cardiac catheterization may demonstrate the somewhat smaller coronary arteries with a distal, tapered appearance. Without a normal reference

segment, it is not possible to accurately ascribe a percentage of lumen compromise. The indications for cardiac catheterization in patients with CAD were presented by the ACC/AHA guidelines (Stary *et al*., 1994).

2.4 Pathophysiology of ACS

Acute coronary syndrome is a spectrum of clinical manifestations ranging from unstable angina, acute myocardial infarction to some extent, sudden cardiac death (Kristian *et al*., 2001). This spectrum shares common underlying pathophysiological mechanisms. The central features consist of fissuring or erosion of atheromatous plaque with superimposed platelet aggregation and thrombosis. This is complicated by microfragmentation and distal embolisation with alterations in vascular tone in affected myocardium. As a consequence, clinical manifestations are dependent upon the severity of obstruction in the affected coronary artery, the presence or absence of collateral perfusion, and the volume and myocardial oxygen demand within the affected territory. Thus, the spectrum extends from abrupt occlusion with acute ischemia leading to infarction, through partial coronary obstruction and distal ischemia with minor enzyme release (minimal myocardial injury), to non-occlusive thrombosis with normal cardiac enzymes (unstable angina), (Fox., 2000).

Myocardial ischemia occurs when the oxygen supply to the heart is deficient in relation to the oxygen need. Oxygen consumption is closely related to the physiologic effort. Therefore, the heart must rely primarily on an increase in the coronary blood flow for obtaining additional oxygen. A relatively slight alteration in coronary luminal diameter below a critical level can produce a large decrement in coronary flow, provided that other factors remain constant. When

the epicardial coronary arteries are narrowed critically, the intramyocardial coronary arterioles dilate in an effort to maintain total flow at a level that will avert myocardial ischemia at rest. Hence any condition in which increased HR, SBP, DBP occurs in the presence of coronary obstruction tends to precipitate IHD due to oxygen needs. Cardiac ischemia results from an imbalance between myocardial oxygen supply and demand. Cardiac ischemia is taken as myocellular hypoxia or the condition resulting when oxygen supplied to a region of heart muscle is insufficient to meet its needs. The clinical phenotype accompanying cardiac ischemia has traditionally been subdivided into the IHD and ACS. A sudden reduction in coronary flow and hence, myocardial oxygen supply, is usually the mechanism of ACS. Here, recent plaque injury (e.g., rupture, erosion, hemorrhage), often superimposed on thrombosis and/or micro-embolism, endothelial dysfunction and heightened smooth muscle reactivity abruptly reduce coronary blood flow and lead to acute ischemic myocyte injury (Libby and Theroux., 2005). By contrast, an abrupt increase in myocardial oxygen demand, in the setting of limited ability to increase myocardial oxygen supply, is usually the mechanism of ischemia in the IHD. Disorders of coagulation, endothelial and/or smooth muscle cell function, as well as the myocardium also play a role (Naghavi *et al*., 2003).

2.4.1 Pathology of coronary atherosclerosis

Coronary artery disease is a chronic process that begins during adolescence and slowly progresses throughout life. Independent risk factors include a family history of premature coronary artery disease, smoking, DM, HTN, hyperlipidemia, a sedentary lifestyle, and obesity. These risk factors accelerate

or modify a complex and chronic inflammatory process that ultimately manifests as fibrous atherosclerotic plaque.

Atherosclerotic lesions develop in medium-sized and large arteries and may cause circulation disturbances in the heart, brain and extremities. The first step in atherosclerotic process is accumulation of lipoprotein particles which are called lipid-laden foam cells in the arterial intima (Stary *et al* 1994., Kruth 1997). These cells are monocyte-derived macrophages which have ingested oxidized LDL via their scavenger receptors, probably to protect tissues against toxic effects of oxidized LDL. These macrophages are subsequently transformed to lipid-laden foam cells.

These early lesions, fatty streaks, can already be found during childhood (Pesonen *et al*., 1975). During the following decades early lesions advance, and accumulation of lipids, fibrous tissue and inflammatory cells, growth of smooth muscle cells and endothelial dysfunction characterize coronary atherosclerosis (Stary *et al* 1994., Ross 1999). Irregular thickenings of the arterial intima restrict the lumen of coronary artery and reduce the nourishing blood flow to the myocardium. A fibrous cap covers the plaque and separates it from the vascular lumen. This cap varies in thickness and content of collagen, smooth muscle cells and inflammatory cells (Hansson and Libby*.,* 1998). An atherosclerotic plaque, which is prone to rupture, is characterized by a large, lipid-rich atheromatous core and a thin fibrous cap, in which both collagen content and smooth muscle cell density are reduced. Moreover, the amount of inflammatory cells in the plaque is increased (Van der Wal *et al*., 1994, Falk *et al* 1995). In the event of erosion or rupture of atherosclerotic plaque, exposure of its thrombogenic content into the lumen of the coronary artery activates

thrombocytes and the coagulation system. Activated thrombocytes aggregate at the site of rupture and together with the activated coagulation system, form a thrombus, which may partially or even totally occlude the lumen of the coronary artery (Falk *et al*., 1995). With decreasing or complete cessation of blood flow, the myocardium becomes ischemic. As a consequence, the clinical setting of ACS can manifest itself in a variety of conditions; namely unstable angina, acute myocardial infarction or sudden cardiac death. The relation between elevated serum cholesterol and atherosclerosis was first published in the 1930s by Muller (Muller., 1939). Since then the causal role of elevated serum cholesterol in the pathogenesis of atherosclerosis has been well documented (Kannel *et al* 1992., Pekkanen *et al* 1992). Further studies have shown that the principal causal component in the development of atherosclerosis is LDL cholesterol, whereas HDL seems to exert a protective effect (Castelli *et al*., 1992). Smoking, hypertension, diabetes, obesity, physical inactivity and genetic inheritance are important risk factors in the progression of primary atherosclerosis.

The second morphologically event in the initiation of atheroma is leukocyte recruitment and accumulation. The normal endothelial cell generally resists adhesive interactions with leukocytes. However, after initiation of hypercholesterolemia, leukocytes adhere to the endothelium between endothelial cell junctions to enter the intima, where they begin to accumulate lipids and transform into foam cells (Gimbrone *et al*., 1995). In addition to the monocyte, T lymphocytes also tend to accumulate in early human and animal atherosclerotic lesions (Emeson and Robertson 1988., Hansson and Libby 1995).