"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"

By

Dr. NUKAVARAPU VASU BABU

Dissertation Submitted to the

Sri Devaraj Urs Academy of Higher Education

And Research, Tamaka, Kolar, Karnataka.

in partial fulfilment of the requirements for degree of

DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

Under the guidance of

Dr. V. LAKSHMAIAH, ***M.B.B.S., D.ch., M.D***

Professor of General medicine and medical superintendent

DEPARTMENT OF GENERAL MEDICINE

SRI DEVARAJ URS MEDICAL COLLEGE,TAMAKA, KOLAR

MAY 2012

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA.

DECLARATION BY THE CANDIDATE

I, hereby declare that this dissertation entitled **"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"** is a bonafide and genuine research work carried out by me under the guidance of ***Dr. V. LAKSHMAIAH,*** **M.B.B.S., D.ch., M.D.,** Professor of General Medicine and Medical Superintendent, R.L.J.H., Kolar.

Date**:** Signature of the candidate

Place: Kolar ***Dr. Nukavarapu Vasu Babu***

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation **"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"** is a bonafide and genuine research work carried out by ***Dr. Nukavarapu Vasu Babu*** in partial fulfilment of the requirement for the degree of **M.D.** in **General Medicine**.

Date:

Place: Kolar

Signature of the Guide

DR. V. LAKSHMAIAH, ***M.B.B.S.,D.*****ch.,M.D.,**

PROFESSOR OF GENERALMEDICINE
DEPARTMENT OF GENERAL MEDICINE
SRI DEVARAJ URS MEDICAL COLLEGE
TAMAKA, KOLAR
AND
MEDICAL SUPERINTENDENT
R.L.J.H.,KOLAR

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR

ENDORSEMENT BY THE HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled **"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"** is a bonafide research work done by ***Dr. Nukavarapu Vasu Babu*** under the guidance of ***Dr. V. LAKSHMAIAH,*** ***M.B.B.S., D.ch,M.D.,*** Professor of General Medicine and Medical Superintendent, R.L.J.H., Kolar in partial fulfilment of the requirement for the degree of **M.D.** in General Medicine.

Date: Signature of the HOD

Place: Kolar

Dr.B.N.RAGHAVENDRA PRASAD, ***M.B.B.S.,M.D.,***

PROFESSOR AND HOD
DEPARTMENT OF GENERALMEDICINE
SRI DEVARAJ URS MEDICAL COLLEGE,
TAMAKA

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR KARNATAKA, BANGALORE.

ENDORSEMENT BY THE PRINCIPAL/ HEAD OF INSTITUTION/ HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled **"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"** is a bonafide research work done by ***Dr. Nukavarapu Vasu Babu*** under the guidance of ***Dr. V. LAKSHMAIAH,*** ***M.B.B.S.,D.ch.,M.D.,*** Professor of General Medicine and Medical Superintendent, R.L.J.H., Kolar in partial fulfilment of the requirement for the degree of **M.D.** in General Medicine.

Dr. B.N. RAGHAVENDRA PRASAD,
Professor and HOD

Dr. M.B. SANIKOP,
Principal

Date:

Place: S D U M C, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH,TAMAKA, KOLAR

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved**,** ***Dr. Nukavarapu Vasu Babu*** student in the Department of General Medicine at Sri Devaraj Urs Medical College, Tamaka, Kolar to take up the dissertation work titled **"HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND THE FIRST DEGREE RELATIVE"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research Centre, Tamaka, Kolar.

DATE:

Member Secretary
Sri Devaraj Urs Medical College,
Kolar–563101

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

COPY RIGHT

Declaration by the candidate

I hereby declare that the Sri Devaraj Urs academy of higher education, Karnataka shall have the rights to preserve, use and disseminate this dissertation/ thesis in print or electronic format for academic / research purpose.

Date: Signature of the Candidate

Place: Kolar *Dr. Nukavarapu Vasu Babu*

A WORD OF GRATITUDE

To my respected teacher and guide:
Dr. V. LAKSHMAIAH, ***M.B.B.S.,D.ch.,M.D***
Professor
Department of General Medicine,
Sri Devaraj Urs Medical College, Kolar
Medical Superintendent,
R.L.J.H, Kolar

Though words falter to acknowledge all my debt, it is with a deep sense of gratitude that I express my thanks to my renowned Teacher, Guide and Professor ***Dr.V.LAKSHMAIAH,*** ***M.B.B.S.,D.ch.,M.D,*** *Department of General medicine whose dynamic personality, mature and friendly attitude, relentless help, proficient ideas, constant supervision, direction, discussion and inspiration has guided me throughout my post-graduate career. I am thankful for his act of kindness in taking immense interest in my dissertation work.*

I once again offer my profound sincere thanks to my guide.

Dr. Nukavarapu Vasu Babu.

ACKNOWLEDGEMENT

First and foremost, I express my sincere and heartfelt gratitude to my respected Professor ***Dr. V.LAKSHMAIAH*** ***M.B.B.S.,D.ch.,M.D,*** Department of General Medicine, Sri Devaraj Urs Medical College, Kolar and Medical Superintendent R.L.J.H., Kolar for his constant encouragement and valuable guidance throughout the course and the present study.

I express my sincere and heartfelt gratitude to ***Dr.B.N.RAGHAVENDRA PRASAD*** M.B.B.S.,M.D., Professor and Head of the department of General Medicine, SDUMC, Kolar, for his constant encouragement and valuable guidance throughout the course and the present study.

With a deep sense of gratitude, I thank **Prof. PRABHAKAR, Prof. P.N. VENKATARATHNAMMA, Prof. SRINIVASA RAO, Prof. RAVEESHA** for their constant encouragement and help throughout my course.

I express my sincere thanks to **Dr. S. KUMAR, Dr. NAGARAJ NAIK,Dr.MUKESHBANGERA,Dr.JAYARAMA,Dr.REVANASIDDAPPA, Dr. SAGAR, Dr. HARISH, Dr. REETHESH, Dr. SRINIVAS.S.V, Dr.SRINIVAS C.** for their invaluable timely suggestions and support.

I acknowledge my thanks to all my teachers of the Department of Medicine for their heartfelt support at all the times.

I also thank my batch mates, **Dr. CHRIS PHILIP MATHEW, Dr. MOOSA.P, Dr. KARTHIK NAIDU, Dr. PRATYUSH MIGLANI, Dr. SAJU HANEEF.** for helping me in many aspects.

The support I got from **Dr. Bino Benjiman, Dr.Anand Kumar, Dr. Sudheer, Dr. Thomas Alex Kodiatte, Dr.Manjunath, Dr.Anjaneya Reddy, Dr. Anil, Mr. Ramswroop, Mr. Joseph** cannot be expressed in words.

I would like to thank **Dr. DEEPTHI KIRAN**, Assistant Professor, Department of community medicine for her constant support while doing my statistics, without which it was not possible to complete statistics.

I am infinitely obliged to my beloved Parents **JANARDHANA RAO** and **KRISHNA KUMARI** and brother **SANDEEP** who are always my pillars of strength. I am truly indebted to them for unwavering support, understanding and untiring patience.

I am also thankful to all nursing staff, attenders for their invaluable help.

Last but not the least, I would also like to thank all the **patients** without whom, this study would not have been possible.

I would like to thank everyone who helped me in my study for all their help throughout the preparation of this dissertation.

Date: *Signature of the Candidate*

Place: Kolar. *Dr. Nukavarapu Vasu Babu*

LIST OF ABBREVIATIONS USED

CAD	—	Coronary artery disease
CVD	—	Cerebro vascular disease
IHD	—	Ischemic heart disease
CVS	—	Cardio vascular system
LDL	—	Low density lipoprotein
tHcy	-	Total homocysteine
CHD	—	Coronary heart disease
WHO	—	World health organization
CK-MB	—	Creatine kinase(muscle and brain type)
CO-Q	—	Coenzyme Q
NADPH	—	Nicotinamide adenine dinucleotide phosphate
DNA	—	Deoxyribo nucleic acid
LFT	—	Liver function test
ATP	—	Adenosine tri phosphate
PVD	—	Peripheral vascular disease
BUPA	—	British united provident Association
TM	---	Thrombomodulin
CRF	—	Chronic renal failure
DM	—	Diabetes Mellitus
IGT	—	Impaired glucose tolerance
NHANES	—	National health and examination survey
SHARE	—	Study of health assessment and risk in ethnic groups
HDL	—	High density lipoprotein
TG	—	Triglyceride
RLJH	---	RL Jalappa hospital
CBS	---	Cystathione beta synthase
MTHFR	---	Methylene tetrahydrofolate reductase
NO	---	Nitric oxide
MI	---	Myocardial infarction

ABSTRACT

BACKGROUND-

Homocysteine is a risk factor for atherosclerotic vascular disease, with adverse influence on endothelial cells, vascular smooth muscle cells, connective tissue, interactions with plasma lipoproteins and platelets. This study was conducted to know the association between homocysteine levels and acute myocardial infarction patients and to compare with the first degree relative of the patients and controls.

OBJECTIVES-

To study the levels of plasma homocysteine in 50 patients of acute myocardial infarction, 50 first degree relative of these patients and 50 healthy controls attending R. L. JALAPPA HOSPITAL, affiliated to SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

METHODOLOGY-

The study included 50 acute myocardial infarction patients, 50 first degree relative of the patients and 50 healthy controls. Serum homocysteine levels were measured in all the groups and the levels were studied and compared among the groups. Serum homocysteine was assayed by chemiluminescent microparticle immunoassay.

RESULTS-

The mean Homocysteine levels in the patient group were 25.2±14.7µmol/l and in the first degree relative of the patient, it was 14.1±3.4 µmol/l and in controls was 11.7±2.9µ mol/l .The levels were higher in patients when compared to the other two groups. Homocysteine levels were elevated in 64% of the patients, and 32% of the first degree relative and 18% of controls. Hyperhomocysteinemia without any risk factors was present in 18% of the patients.

CONCLUSION-

Homocysteine emerged as an independent risk factor in acute myocardial infarction. Therefore it should be evaluated in all patients with acute myocardial Infarction.

Key Words: Homocysteine, Acute myocardial infarction

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Cardiovascular disease is a major global health problem reaching epidemic proportions. Myocardial infarction is one of the most common causes of death in the developing and developed world. Low and middle income countries, including South Asian countries like India, contribute significantly to the global burden of cardiovascular disease, accounting for 78% of all deaths and 86.3% of all loss of disability adjusted life years attributable to this cause.[1]

Coronary artery disease (CAD) has become a major health problem and is the most common cause of mortality and morbidity in the entire world.[2]

WHO and World Bank data indicate that in India, deaths attributed to Coronary Artery disease (CAD) have increased markedly with the expanding population and will continue to increase.[3]

Increasing recognition that as many as 30-50% of patients with established CAD lack the traditional risk factors has led to search for additional new risk factors that may predispose individuals to coronary artery disease over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular disease, the growing list of new and emerging risk factors include elevated blood levels of homocysteine.[4]

Homocysteine recently has been recognised as a risk factor for the presence of atherosclerotic vascular disease and hypercoagulability states.[5]

Evidence from retrospective and prospective clinical studies indicates that elevated levels of homocysteine are associated with increased risk of CAD, ischemic stroke and peripheral vascular disease.[6]

Hyperhomocysteinemia is an easily modifiable risk factor for CAD.[7]

In approximately 10% of the patients with cardiovascular disease, elevated homocysteine level appears to be the major risk factor.[8]

The higher total homocysteine in young offspring of parents with coronary heart disease suggests that elevated total homocysteine precedes manifestation of coronary heart disease.[9]

In humans, hereditary elevations of homocysteine can occur because of less severe genetic mutations associated with enzyme abnormalities in the metabolic pathways involving folate and homocysteine.[10]

Elevated homocysteine levels play a potential role in the pathogenesis of atherosclerosis, thrombo-embolism and vascular endothelial damage.[11]

Patients with angiographically determined coronary artery disease have been reported to experience a concentration dependent increase in risk of death with increased homocysteine concentration.[12]

Prospective studies found an increased risk of myocardial infarction among patients with moderate hyperhomocysteinemia.[13]

Hyperhomocysteinemia is risk factor of cardiovascular events in patients with coronary artery disease and the risk of sudden acute myocardial infarction is increased in hyperhomocysteinic patients.[14]

AIMS AND OBJECTIVES

The study was undertaken to study the levels of homocysteine in acute myocardial infarction patients, the first degree relative of the patients and healthy controls.

REVIEW OF LITERATURE

The words homocysteine and homocystine coined by Du Vigneaud and co-workers who discovered these compounds 60 years ago, to designate respectively, the reduced (sulfhydryl) and the oxidized (disulfide) forms of these homologues of cysteine and cystine.[15]

In 1959 a girl in Ireland was evaluated for seizures, mental retardation and lens dislocation. She had a younger sister of similar appearance. Most initial investigations were unremarkable, analysis of patients urine showed presence of homocysteine. Around same time, a group of investigators in Wisconsin described an infant with congenital anomalies; mental retardation and failure to thrive who also had increased excretion of homocysteine in the urine. These were the first reported cases of homocysteinemia.[16]

In 1969, Kilmer Mc. Cully a young Harvard pathologist first made clinical observation that thromboembolic disease was a characteristic feature of homocysteinemia independent of metabolic defect, thus linking elevated plasma homocysteine level to vascular disease. He reported autopsy evidence of extensive arterial thrombosis and atherosclerosis in 2 children with elevated plasma homocysteine.[17]

In 1976, Wilcken and Wilcken published the first report that patients with IHD frequently have abnormal homocysteine metabolism for the following 15 years. These were scattered reports on the relationship between plasma homocysteine levels and ischemic disease.[15,16]

Since 1990, there has been an exponential increase in number of publications on homocysteine and CVS disease suggesting elevated plasma homocysteine as an independent risk factor.

The first area positive prospective study on plasma homocysteine and IHD was reported in 1992 by Stampfer et al.[18]

Selhub et al[8] in 1995 also reported an association between plasma homocysteine and IHD in the elderly.[16]

Bonshey et al (1995) reviewed most studies on homocysteine and CVS disease and meta analysis of 27 studies including approximately 4000 patients showed that elevated homocysteine was an independent graded risk factor for atherosclerotic disease in the coronary, cerebral and peripheral arteries.[19]

Homocysteine concentration above the 80th percentile of normal has been reported in almost 40% of patients with vascular disease including Ischemic Heart Disease (IHD).

Recent epidemiological data have shown that hyperhomocysteinemia can be detected in 20 and 40% of patients with coronary artery disease and cerebrovascular disease, respectively.[20]

Arnseen et al reported that patients with disorders of homocysteine metabolism carrying high level of homocysteine in plasma and urine are at increased risk of heart disease, regardless of site of enzymatic defect.[2]

High levels of homocysteine are injurious to endothelium promote LDL oxidation and thrombosis formation.

A meta analysis based on 27 studies, involving 4,000 patients have shown that homocysteine is an independent graded risk factor for atherosclerotic vascular diseases.[21]

Smokers with hyperhomocysteinemia are at greatly increased risk of cardiovascular disease and atherosclerosis.[22]

Alfthan et al demonstrated geographical difference in plasma homocysteine concentrations.[21]

They further described that plasma homocysteine may play an important role in variation in CVS disease among different population.

Fasting Total Homocysteine (tHcy) levels are partly genetically determined.[23,24,25]

Several studies have indicated that offspring of patients seem to have higher Serum Total Homocysteine (tHcy) levels. [26,27,28,29]

Vascular endothelial dysfunction shows a familial association, being impaired in offspring of patients with early onset Coronary Heart Disease (CHD) and that endothelial function improved in response to folic acid and vitamin B12 supplementation, which lead to a reduction in tHcy levels.[30,31]

There is limited literature on familial prediction of cardiovascular disease by tHcy in clinically healthy first-degree relatives.

Homocysteine in 8 to 12-year-old Norwegian children was associated with reported premature CHD death in male relatives (age 55 years) but not with all events (fatal and nonfatal) in relatives.[26]

In Belgian 5 to 19-year olds, tHcy above the 95th percentile was associated with cardiovascular disease in relatives.[27]

In the Bogalusa study, tHcy was associated with reported parental history of CHD in both black and white children.[28]

Among adolescent boys in the United States, serum tHcy was independently associated with documented parental CHD at ages 55 years.[29]

Genest et al, who studied spouses and offspring of probands with CHD, concluded that elevated tHcy associated with CHD is in part genetically determined.[25]

DEFINITION

MYOCARDIAL INFARCTION

The World Health Organization definition, which has been widely used, requires the presence of two of the following three features: symptoms of myocardial ischemia, elevation of cardiac marker (enzyme) concentrations in the blood, and a typical electrocardiographic pattern. Recently American College of Cardiology and European Society of Cardiology published a new definition that for the first time includes elevated troponin levels. The new criteria are elevated troponin or CK-MB levels and either ischemic symptoms or electrocardiographic changes.[32,33]

HYPERHOMOCYSTEINEMIA

According to Kang et al. an abnormal homocysteine level is defined by an arbitrary cut off (95th percentile) of the concentration found in normal population. The normal fasting plasma homocysteine levels in adults usually range between 5 – 15 μ mol/L with mean level of about 10 μmol/L.[33,34]

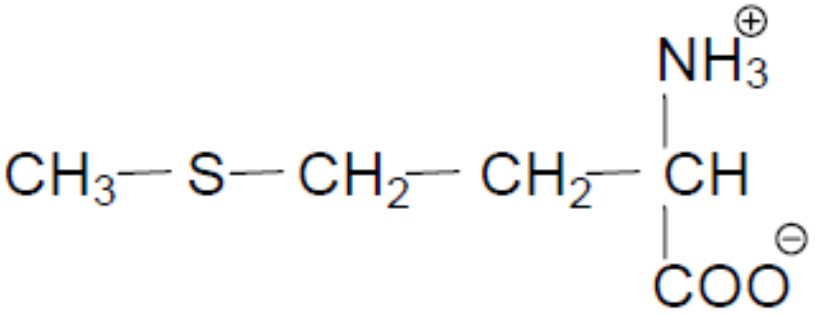
Kang and co-workers have classified hyperhomocystenemia as follows:

Moderate: 15 - 30 μmol/L

Intermediate: 30 - 100μmol/L

Severe: more than 100μmol/L

HOMOCYSTEINE [35,36,37,38]

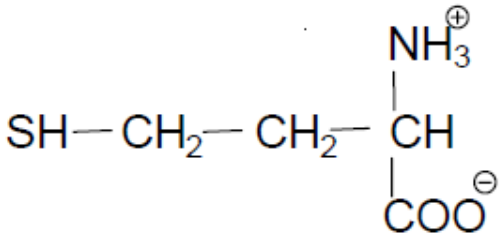


Homocysteine is a Sulphur containing amino acid, which is an intermediary product in methionine metabolism, found in abundance in animal protein. Homocysteine is of no biological role.

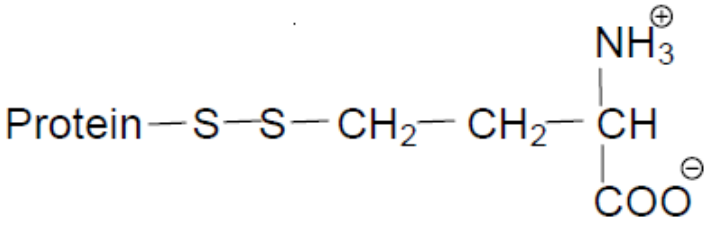
It can be remethylated to methionine or sulfoconjugated with serine to form cysteine in a series of enzymatic reactions.

Less than 1% circulates as free thiols; 70-80% is bound to plasma protein chiefly albumin and remaining 20-30% combines with itself or with other thiols to from dimmers.

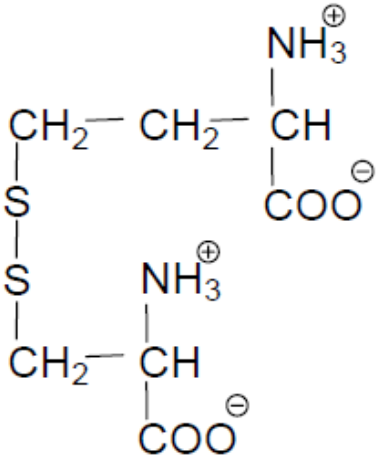
Homocysteine (reduced) – 1%



Protein bond homocysteine mixed disulfide (oxidized) – 70-80%



Homocysteine-cysteine mixed disulfide (oxidized) – 5-10%



SYNTHESIS AND METABOLISM [35,36,39]

Synthesis and metabolism of homocysteine involves three processes,

- Demythylation
- Transmethyation and
- Trans sulphuration

Demethylation

This process converts methionine to homocysteine through intermediate metabolites, S-adenosine methionine and S- adenosine homocysteine.

Transmethylation

In this pathway homocysteine is remethylated to methionine. In the liver, homocysteine is remthylated by betaine-homocysteine methyl transferase, which uses betaine as methyl donor.

Homocysteine is catalyzed by the methionine synthase, which uses vitamin B12 as a co-factor and methyl tetrahydrofolate as a substrate.

Methylene tetra hydrofolate reductase catalyses the formation of methyl tetrahydrofolate.

In normal metabolism the majority (>50%) of homocysteine is remthylated to methionine requiring folate and vitamin B12.

Transsulphuration

In this process homocysteine is irreversibly converted to cysteine.

The first reaction is catalyzed by vitamin B6 dependent cystathione β synthase to form cystathionine.

Cystathionine is hydrolysed to form cysteine, which is in turn, is incorporated into glutathione or is further metabolised to sulphate and is excreted in the urine.

This process occurs when excess of methionine is present or cysteine synthesis is required.

Remethylation of homocysteine and the subsequent formation of S-adenosyl is critical for biosynthesis of L-carnitine, CoQ10, and creatinine.

Similarly, the transulfuration pathway must be functioning properly for optimal biosynthesis of cysteine, pantethine and taurine.

All of these nutrients are used clinically to reduce oxidative stress, improve risk factors markers, or treat heart disease.

Measurement and Classification of Homocysteine Levels-

The normal plasma homocysteine is 5-15 μmoles/L.

Plasma homocysteine level greater than 15 μmoles/L is considered as hyperhomocysteinemia.

The American Heart Association have defined hyperhomocysteinemia as being divided into[40]

Moderate: 15-30 μmol/L

Intermediate: 30 - 100 μmol/L

Severe: >100 μmol/L

Estimation of plasma homocysteine

A single blood sample, which need not be from a fasting patient, is the most widely used investigation to assess homocysteine status.

Meticulous attention in sample handling is important for accurate determination.

Plasma concentrations of homocysteine rise rapidly unless plasma is separated from red cells immediately or kept chilled.

An alternative to prompt separation is the stabilization of blood homocysteine by 3-deaza-adenosine or fluoride.

Methods of estimation of plasma homocysteine [41]

1. High liquid chromatography
2. ELISA
3. Mass spectrometry
4. Fluorescence polaraization immunoassay
5. Chemiluminescent microparticle immunoassay (CMIA)

Aetiology and types of hyperhomocysteinemia-

There are two types of hyperhomocysteinemia.[36]

1. Primary
2. Secondary

1. Primary hyperhomocysteinemia

Due to inherited enzyme deficiency in homocysteine pathways like:

a) Cystathionine beta synthase (CBS) deficiency

It is the most common genetic cause with an estimated frequency of 1 per 300,000 live births, inherited as autosomal recessive trait.

It is characterised by dislocation of lens, skeletal deformities, mental retardation and premature atherosclerosis.

Approximately 1% of the general population is heterozygous for cystathionine beta synthase deficiency and these subjects have raised homocysteine levels in the range of 20-40 μmol/l

b) 5,10 methylene tetrahydrofolate reductase (MTHFR) deficiency

A mutation in the enzyme MTHFR is associated with hyperhomocysteinemia especially in presence of low folic acid.

c) Methylene tetrahydrofolate homocysteine methyl transferase deficiency

2. Secondary hyperhomocysteinemia

a) Physiological

- Increasing age

- Male sex

- Menopause

b) Lifestyle factors

- Tobacco use

- Coffee consumption

c) Vitamin deficiency - Folate , Vit B6 (pyridoxine), Vit B12 (cobalamine)

d) Systemic disorders

(i) Pernicious anaemia

(ii) Severe hepatic impairment

(iii) Renal impairment

(iv) Psoriasis

(v) Hypothyroidism

(vi) Systemic lupus erythematoses

(vii) Anorexia nervosa

(viii) Organ transplantation

(ix) Malignancies of breast and ovary

e) Drugs (toxins)

1) cholestyramine, colestipol, metformin (affect folate and cobalamin absorption)

2) Folate antagonists -- phenytoin

- carbamazapine

3) Vit B6 antagonists (theophylline, oestrogen containing OCP, niacin)

4) L-dopa (increases transmethylation)

5) Androgens

6) cyclosporins, fibric acid derivatives (reduces renal function)

7) Nitrous oxide (inactvates methionine synthesis)

Determinants of plasma total homocysteine[42,43]

Variable		Fasting plasma t-homocysteine (μ moles/L)
Sex		
	Male	10.3
	Female	8.8
Age (years)		
	< 45	8.8
	45-54	9.2
	54-64	9.8
	> 65	10.4
Serum creatinine (mol/L)		
	< 79	8.7
	79-87	9.3
	87-96	9.3
	96-106	9.7
	> 106	10.5
Alcohol intake (g/d)		
	0.1-4.9	9.3
	5-14.9	9.4
	> 15	10.0
Caffeine intake (mg/d)		
	< 88	8.9
	> 420	9.9
Current cigarette smoking (cig/d)		
	0	9.3
	1-15	9.9
	16-25	10.1
	≥ 26	11.0
Body mass index (kg/m^2)		
	< 23.2	9.4
	≥ 30.6	9.9

Dietary intake of folate, vitamin B12 and vitamin B6 are the chief nutritional determinants.

Analysis of the trials of individual vitamins on blood homocysteine levels suggests that folic acid in a dose of 0.5 to 5 mg daily is associated with reductions in homocysteine levels of about 25%.

Addition of vitamin B12 to folic acid is associated with further reduction of about 7%.

Renal function is a strong determinant of plasma homocysteine probably due to homocysteine clearance by renal metabolism.

Coffee intake and smoking showed positive association with homocysteine. Moderate alcohol intake lowers and chronic alcohol intake increases plasma homocysteine.

Pathophysiologic Mechanisms of Hyperhomocysteinemia

Experimental evidence suggests that the atherogenic propensity associated with hyperhomocysteinemia results from endothelial dysfunction and injury followed by platelet activation and thrombus formation.[44]

Studies in humans and animals demonstrate that homocysteine-induced atherosclerosis is characterized by substantial platelet accumulation and platelet-rich thrombus formation in areas of endothelial injury.[45]

Harker and colleagues have proposed that homocysteine-induced endothelial injury exposes the sub endothelial matrix, which in turn leads to platelet activation.[46]

Lentz and colleagues have demonstrated that diet-induced hyperhomocysteinemia in primates leads to impaired vasomotor regulation in vivo and endothelial antithrombotic function ex vivo. These findings are supported by the

work of Celermajer and colleagues, who demonstrated impaired endothelium-dependent vasodilation, and also by van den Berg and colleagues who demonstrated impaired endothelial anticoagulant function in young patients with hyperhomocysteinemia and peripheral vascular disease.[47]

Although the exact mechanism of endothelial dysfunction is unknown, there is growing evidence that homocysteine exerts its effects by promoting oxidative damage.

A key mechanism that predisposes to vascular disease in hyperhomocysteinemia is endothelial dysfunction.[48]

Homocysteine induces endothelial dysfunction in part by promoting oxidant stress, as illustrated in cellular studies and in genetic animal models.[48,49,50,51,52]

The mechanisms for homocysteine-induced oxidant stress are complex and include inhibiting the translation of glutathione peroxidase-191, a major antioxidant enzyme in vascular cells that regulates mitochondrial reactive oxygen species flux and whose over expression rescues the normal vascular phenotype of hyperhomocysteinemic mice;upregulation of NADPH oxidase expression; enhanced expression of inducible nitric oxide synthase and uncoupling of nitric oxide synthases; and decreased glutathione levels owing to decreased cysteine synthesis, thereby shifting the redox balance of endothelial cells toward oxidant stress.[53,54,55,56,57,58]

Effects of homocysteine[35]

Homocysteine produces thromboembolism, atherosclerosis and vascular endothelial damage. It affects endothelial surface, vascular smooth muscle cells, plasma lipoproteins, connective tissues, platelets, coagulation factors and nitric oxide. Homocysteine stimulates vascular smooth muscle proliferation, increases DNA synthesis, growth, cyclin A gene expression and cyclin dependent kinase expression in the aorta.

It promotes platelet aggregation.

It may enhance binding of lipoprotein (a) to fibrin.

In high concentration it activates factor V, reduces protein C activation, inactivates the cofactor activation of thrombomodulin, suppresses thrombomodulin and anticoagulant heparin sulphate expression and blocks tissue plasminogen activator binding to human endothelial cells.

It also, induces endothelial barrier dysfunction and inhibits Von Willebrands factor processing and secretion.

Several studies have demonstrated the direct cytotoxic effects of homocysteine on endothelial cells grown in tissue culture.

It increases platelet adhesion and aggregation and inhibition of sodium potassium ATPase activity and homelessness of erythrocytes.

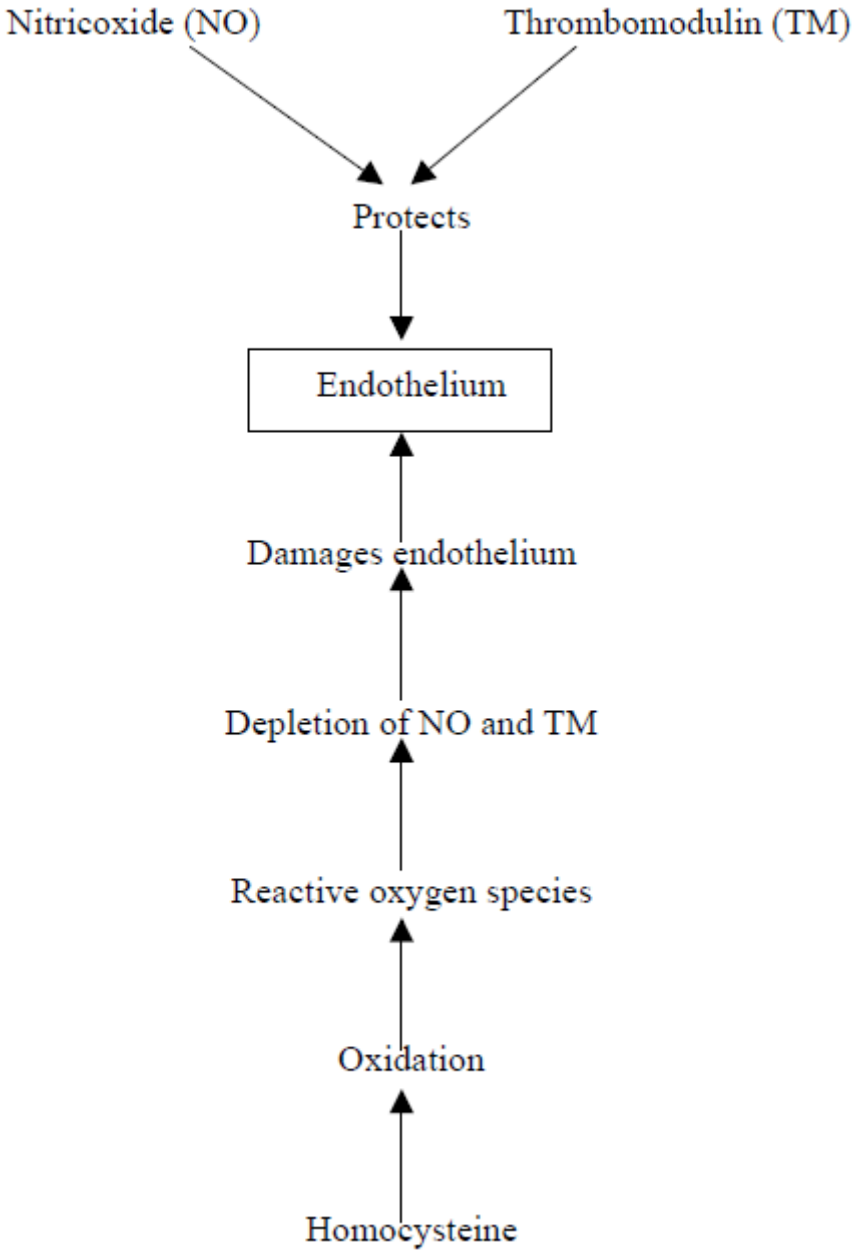
Endothelial cells lack the capacity for Homocysteine(Hcy) transulpuration and depend on the folate cycle for remethylation of Hcy. Thus superimposed folate deficiency may theoretically predispose endothelial cells to damage in the presence of elevated Hcy levels

High levels of Hcy may also alter the redox potential of amino thiols which reflects the dynamic interaction of Hcy, cysteine and glutathione.

Reduced glutathione and glutathioneperoxidase are major intracellular buffers. They maintain intracellular sulfhydryl groups in the reduced form, detoxify hydrogen peroxide, and may have a role in inhibiting platelet aggregation.

In hyperhomocysteinemia a significant reduction in the activity of these intracellular buffers is seen.

Mechanism of homocysteine induced vascular damage[38]



Homocysteine and coronary artery disease[2,9,35,36,59,60,61,62,63,64,65]

Several studies have shown high plasma Homocysteine (Hcy) levels to be an independent risk factor for cardiovascular disease.

The first report, that patients with coronary artery disease frequently experienced abnormal Hcy metabolism was published in 1976.

Boushey et al., carried out quantitative meta-analysis using mostly retrospective case control studies. These were focused on coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral vascular disease (PVD).

As regards CAD, seventeen studies were examined, out of which in 14 studies, homocysteine was found to be a significant risk factor.

It was calculated that 10% of all CAD risk in population was due to elevated homocysteine.

They also observed that the vascular response to homocysteine was graded throughout the range of homocysteine values showing no threshold association.

This is similar to the association between hypercholesterolemia and vascular disease.

It was observed that a prolonged lowering of homocysteine by 3-4 μmol/L was associated with a 30-40% reduction in the risk of CAD.

Wald et al., (1998) carried out a case control study from London and Dublin involving 21,520 men (35-64 years old) who were members of the British United Provident Association (BUPA) and who had no evidence of IHD to start with.

Subsequently 229 men died of IHD during one mean follow up of 8.7 years. They also selected total of 1,126 age matched controls with no evidence of IHD for comparison.

Homocysteine was higher in cases than controls.

Stampfer et al in their United States physicians health study reported on the development IHD events, both fatal and non-fatal in their cohort of 14,916 US male physicians. These were matched by 271 controls, average age at the time of IHD events was sixty two. Initially there was an association between IHD and homocysteine in the upper 5% of the homocysteine distribution compared with lower 90%. Men with plasma homocysteine concentrations 12% above the upper limit of normal had approximately a three-fold increase in risk of myocardial infarction. The prospective Tromso study and other prospective studies reported similar results.

Arnesen et al demonstrated a significantly positive association between CAD and homocysteine. In their case control study of 21,656 subjects, 123 developed IHD within a mean follow up period of 4 years.

Nygard et al reported secondary prospective study in which 587 angiographically documented cases were followed up for a median period of 4.6 years. During that period sixty four patients died, they found a strong graded correlation between raised homocysteine and mortality.

Chacko studied patients with CAD in Asian Indians, and 53 control subjects. They studied various risk factors including plasma homocysteine levels. They concluded that homocysteine is not a major risk factor for coronary heart disease in Asian Indians.

Chambers et al studied UK Indian Asians with coronary artery disease and compared them with European having coronary artery disease. They studied 764 male patients (257 Indian Asian, 507 European). Fasting and post-methionine load homocysteine, vitamin B12 and folate concentrations, and conventional coronary heart disease risk factors were measured. Their results revealed that plasma homocysteine concentrations were higher in Indian Asians, compared with Europeans.

In a large multicenter European investigation of several hundred patients and controls the Concerted action committee (COMAC study), high homocysteine concentrations were independently associated with a risk of premature atherosclerotic disease, including coronary artery disease.

Graham et al in the large European collaborated study showed mean homocysteine to be 11.25 μmol/l. In cases it was significantly higher than in controls and they concluded that homocysteine was an independent risk factor for atherosclerotic disease.

Giles et al also concluded that two fold increase in myocardial infarction occurred in patients with a mean level of plasma homocysteine more than 25 μmol/l.

In a prospective study involving 587 patients, initial homocysteine(Hcy) measurements were made and the patients followed for a median of 4.6 years. They found a strong graded association between plasma Hcy levels >15μmol/l and overall mortality.

The risk of any coronary heart disease event increased approximately 20% for each increase of 5 μmol/L of homocysteine.

A 5 μmol/L homocysteine increment elevates coronary artery disease risk by as much as 0.5 μmol/L (20 mg/dl) increase of cholesterol.

Homocysteinemia, cerebrovascular disease and peripheral vascular disease [16,35,66,67,68,69]

As regards cerebrovascular disease (CVD), eleven clinical studies looked at relationship between homocysteine levels and CVD.

In nine studies, there was significant relationship while two prospective studies lacked evidence for an association between hyperhomocysteinemia and CVD.

The significant correlation was seen even after taking into account the temporary lowering of homocysteine levels during the acute phase following a stroke.

More recent studies have revealed an association between hyperhomocysteinemia and microvasculopathy, particularly cerebral small vessel disease as regards peripheral vascular disease (PVD), two population-based case-control studies and nine other case-control studies presented evidence in favour of the hypothesis of PVD.

It has been concluded that as a risk factor, hyper-homocysteinemia independently increased risk of vascular disease to the same extent as smoking and hyperlipidemia. The risk increases significantly if associated with smoking and hypertension.

In a cross-sectional study of 1041 elderly subjects, Selhub et al reported a strong association between elevated levels of Hcy and occlusive vascular disease even after adjustment for other conventional risk factors.

Raised Hcy levels was associated with increased risk of stroke.

A prospective study reported a graded risk for stroke in middle aged British men. A meta-analysis based on 26 studies involving 4000 patients showed that Homocysteine was an independent risk factor for atherosclerosis in cerebral and peripheral vessels.

A population based cross sectional study involving 2484 patients showed that the magnitude of association between hyperhomocysteinemia and cardiovascular disease is similar for peripheral arterial, coronary artery and cerebrovascular disease in a 50 – 75 year old population.

Boers et al measured plasma Hcy after methionine loading in 75 patients with premature atherosclerosis. They observed that nearly 33% of all patients with cerebrovascular disease and peripheral vascular disease had hyperhomocysteinemia.

Clarke et al. reported that measurement of Hcy after methionine loading in cohort of men with premature vascular disease and normal controls showed that 42% patients with cerebrovascular disease, 28% of patients with peripheral vascular disease and 30% of patients with CAD had hyper homocysteinemia.

Homocysteine and venous thrombosis [35,70,71]

Hyperhomocysteinemia is an independent risk factor for venous thromboembolism.

A plasma homocysteine concentration of more than 22μmol/L increased the matched odds ratio for deep venous thrombosis to 4.

DenHeijer et al reported that plasma Hcy concentrations of patients with recurrent venous thrombosis were high.

The combination of hyperhomocysteinemia and factor V leiden further increases the relative risk of venous thromboembolism up to 3.6 fold.

Martin Den Heijer et al estimated plasma total homocysteine concentration in patients younger than 70 years of age who had a first episode of deep-vein thrombosis, objectively confirmed (by impedance plethysmography, Doppler ultrasonography), between 1988 and 1993 and who had no known cancer.

They concluded that mild hyperhomocysteinemia is a risk factor for deep-vein thrombosis in the general population.

Homocysteine and renal disease[35]

Kidneys play an important role in Hcy metabolism.

Patients with renal failure, end stage renal disease and chronic uraemia have hyperhomocysteinemia and are at risk for atherosclerosis.

Chauveau et al studied 79 patients with CRF who were not on dialysis and found significantly higher homocysteine value in patients who had prior histories of occlusive arterial disease.

Data from other studies shows that plasma homocysteine values represent an independent risk factor for vascular events in patients on peritoneal dialysis and haemodialysis.

Homocysteine and neoplasia[72]

Modestly elevated serum homocysteine levels were detected in patients with various carcinomas.

James Wu has shown that it is most evident in patients with cancers of the breast, ovary, colon and possibly the prostate.

The homocysteine concentrations correlate with levels of serum tumor markers in their serial specimens and reliably decline when the tumor regresses during treatment.

Homocysteine and diabetes mellitus [35,73]

Type 2 DM patients who had macro vascular disease had elevated Hcy levels.

Hoogeveen et al have shown that hyperhomocysteinemia appears to a stronger risk factor for CAD in these subjects than with normal or IGT subjects.

Homocysteine and hypertension [1,38,74,75,76,77,78,80,81,82,83,84]

Mendis S et al in their study conducted in Sri Lanka demonstrated the association between hypertension and homocysteine levels. They found that patients with hypertension had significantly higher mean serum concentration of homocysteine.

Bortolotto LA et al demonstrated that hypertensive patients with high levels of homocysteine are associated with increased arterial stiffness.

Homocysteine is an independent determinant of large artery stiffness.

Among the possible mechanisms that these effects are exerted on are increased smooth muscle cell proliferation, endothelial dysfunction, increased collagen synthesis and deterioration of elastic material of the arterial wall.

With regard to the relationship between homocysteine levels and hypertension, a synergistic effect of these two parameters on cardiovascular risk and an independent relationship between high homocysteine levels and isolated systolic hypertension are reported which was attributed to arterial stiffening.

Associations of homocysteine with cardiovascular risk and with alterations in vascular properties have led to studies of its association with arterial stiffness.

Hyperhomocysteinemia is associated with increased carotid intima-media thickness extracranial carotid artery stenosis and more advanced atherosclerotic changes in coronary arteries.

Shen WH et al in their study showed that the fasting plasma homocysteine concentrations were significantly higher in hypertensive patients than in normotensive control subjects.

Organ transplant and Homocysteine [35]

Hcy concentration is elevated in patients with cardiac, kidney, lung and liver transplants. The vascular complications in these patients may be due to hyperhomocysteinemia

Homocysteine and women

Homocysteine level in excess of 14.2 μmol/L in middle-aged women is an independent risk factor for future myocardial infarction.[85]

Ridker et al in a nested case-control study in the United States, demonstrated that tHcy was a risk factor for cardiovascular disease among postmenopausal women after 3 years of follow-up.[86]

Morris et al found a significant relation between tHcy and heart attack or stroke, especially in postmenopausal women, in their The united states third national health and examination survey(NHANES III) study[87].

Knekt et al with the longest reported follow-up of 13 years, found a significant relation between tHcy and coronary artery disease in women with prevalent heart disease at baseline but not among women free of heart disease at baseline.[88]

HOMOCYSTEINE AND CARDIOVASCULAR RISK IN INDIANS

India contributes a much larger share to the global CAD and excess absolute CVD mortality because of the larger population involved.[89]

Coronary artery disease in India will rise by 1 or 3% in males and 90% in women during the period from 1985 to 2015.[89]

The prevalence of CAD is four-fold higher in urban India and two-fold higher in rural India than in the United States.[90]

Coronary artery disease was considered to be a result of an urban lifestyle, however recently published studies have indicated that CAD is also on the rise in rural areas.[91,92]

The incidence of CAD in the young has been reported to be 12%–16% in Indians.[93,94]

This predilection of CAD is attributable to clustering of various traditional and non-traditional risk factors like insulin resistance with or without glucose intolerance or DM, central obesity, hypertension and dyslipidemia characterized by elevated triglycerides, relative increase in small dense LDL-C and low HDL-C.[89]

Elevated Hcy levels might be an important determinant of risk for CAD in Indians.[89]

Chambers et al. conducted two parallel case control studies, one in Europeans and other in Indians to evaluate fasting and post methionine load Hcy as risk factors CAD.[89]

They found that elevated plasma Hcy levels were independently associated with CAD in both UK Indians and Europeans.

However, Indians in this study were not evaluated for the other known associations of CAD risk factors characteristic of Indian ethnicity, namely abnormal waist hip ratio, raised lipoprotein (a) and hyperinsulinemia.

The strength of this association after correction for these potentially confounding risk variables, would have provided better insight into the place of Hcy in the risk factor spectrum.

Elevated plasma Hcy levels seems to be a feature of south Asian populations. In both the study of health assessment and risk in ethnic groups (SHARE) and the UK study the levels of Hcy in the south Asians / Indians were higher than those found in the other ethnic groups. Several explanations have been put forward to account for this observation. The most popular ones relate to the reduced intake of vitamin B12 and the prolonged cooking of vegetables, which may destroy up to 90% of folate content. Diabetes mellitus and the resultant renal impairment are known to be much more common in Indians [89].

Two other comparative studies from southern India failed to show any difference in plasma Hcy levels between patients with CAD and those without CAD. One provocative view holds that hyperhomocystenemia, instead of being an antecedent of cardiovascular events, may be a marker of tissue damage or repair following them[89].

TREATMENT [37,38,90,95,96]

Elevated plasma homocysteine level is a risk factor for atherosclerotic disease. Plasma homocysteine levels are influenced by genetic, physiological and lifestyle factors.

Prevalence of subclinical deficiencies of vitamins B2, B6, B12 is high in Indian populations. Folate status is a major determinant of plasma homocysteine level and there is a strong inverse co-relationship between plasma homocysteine and serum folate levels.

To maintain low plasma homocysteine concentration people should be advised to increase their consumption of pulses, eggs, green leafy vegetables and fruits which are rich in vitamins.

Dietary intake of vitamins B2, B6, B12 and folate is inversely related to plasma homocysteine level.

A strong negative co-relationship between folate status and plasma homocysteine levels has been reported.

The recommended folate intake needs a revision in the Indian context.

Since the level of folate intake recommended for the prevention of hyperhomocysteinemia in women and men is about 300µg and 350µg per day respectively. It is difficult to obtain this amount from food.

Strict vegetarians may develop vitamin B12 deficiency and have been reported to have higher plasma homocysteine concentration than the non vegetarians.

The results have showed that folic acid supplementation reduced plasma homocysteine by 41%, whereas vitamin B12 supplement lowered homocysteine level by 14.8% and both were significant.

The daily vitamin B6 did not significantly reduce plasma homocysteine level.

The combination of three vitamins reduced plasma homocysteine level by 49.8% was not significantly different from reduction achieved by folate supplementation alone.

A higher concentration may be necessary in patients with reduced renal function and folate deficient subjects.

Treatment of hyperhomocysteinemia

Regimen (I)

650 mcg folic acid 6 weeks

400 mcg vitamin B12

100 mg vitamin B6

Regimen (II)

5 mg folic acid 12 weeks

250 mg pyridoxine

Supplements

Folinic acid : 800 mcg tid

Methylcobalamin : 800 mcg tid

Pyridoxal S phosphate : 20 mg tid

Betaine (Participates in another remethylation pathway): 1.200 mg tid

N-acetylcysteine-500 mg tid (offers sulfahydryl group to detoxify homocysteine

MATERIALS AND METHODS

Source of Data

50 patients of acute myocardial infarction , 50 first degree relative of these patients and 50 healthy controls of more than 18 years of age and any sex were included in the study who attended R.L.JALAPPA HOSPITAL, affiliated to SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR from March 2010 to August 2011.

Method of Collection of Data

The present study was done on patients admitted to the R.L.JALAPPA HOSPITAL, with the diagnosis of acute myocardial infarction as per W.H.O. criteria. Cases were selected on the basis of simple random sampling method. A detailed history and thorough clinical examination was done as per the proforma and were investigated further

The levels of homocysteine were measured by Chemiluminescent microparticle immunoassay (CMIA) in acute myocardial infarction patient and any of his first degree relative and selected healthy controls more than 18 years of age and any sex. The levels were analysed and compared between different groups.

Inclusion Criteria :

1. Patients aged more than 18 years.
2. Patients with clinically, biochemically and electrocardiographically proven MI.

Exclusion Criteria:

1. Patients with MI who are on anti convulsants, bronchodilators, methotrexate and cyclosporine.
2. Patients with MI who are suspected of having hypothyroidism, malignancy, renal disorder and liver disorder.

Investigations:

The following investigations were done on admission of patients

1. Complete haemogram
2. Urine Routine
3. ECG
4. Serum Homocysteine Levels
5. CK-MB or Cardiac troponin
6. Blood urea, serum creatinine
7. Liver function tests
8. Thyroid stimulating hormone

STATISTICAL ANALYSIS

The results were analysed by calculating percentages, the mean values, the standard deviation, standard error, unpaired t test.

The observed values were compared with the table values at 0.05 plevel of significance for the corresponding degrees freedom

$P<0.05$ was significant

$P>0.05$ was not significant.

SPSS version 14 software was used for statistical analysis.

ESTIMATION OF PLASMA HOMOCYSTEINE [100,101,102,103]

Intended use

The ARCHITECT Homocysteine assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of total L-homocysteine in human serum or plasma on the ARCHITECT i System.

Biological principle of the procedure

The ARCHITECT Homocysteine assay is a one step immunoassay for the quantitative determination of total L-homocysteine in human serum or plasma using CMIA technology, with flexible assay protocols, referred to as Chemiflex.

Bound or dimerised homocysteine (oxidized form) is reduced by dithiothreitol (DTT) to free homocysteine, which is then converted to S-adenosyl homocysteine (SAH) by the action of the recombinant enzyme S-adenosyl homocysteine hydrolase (rSAHHase) in the presence of excess adenosine.

The SAH then competes with acridinium-labeled S-adenosyl cysteine for particle-bound monoclonal antibody.

Following a wash stage and magnetic separation, pre-trigger and trigger solutions are added to the reaction mixture and the resulting chemiluminescence is measured as relative light units (RLUs).

An indirect relationship exists between the amount of homocysteine in the sample and the RLUs detected by the ARCHITECT i System optics.

Specimen collection and preparation for analysis

Human serum and Serum Separator tubes

Human plasma collected in:

- lithium heparin
- potassium EDTA
- separate serum or plasma immediately & refregerate

As synthesis of homocysteine continues in red blood cells after drawing, it is very important to centrifuge and separate plasma and serum from the blood cells.

Samples may be kept in ice for up to 6 hours prior to separation by centrifugation. Centrifuge samples at 1000g for 10 minutes.

Do not store plasma samples at room temperature prior to centrifugation.

If the assay will be performed within 2 weeks after collection, the sample should be stored at 2-8°c.

If testing will be delayed more than 2 weeks, the specimen should be stored frozen at –20°C. Samples have been shown to be stable at -20^{o}C for 8 months.

Mix thoroughly after thawing to ensure consistency in the results. Avoid repeated freezing and thawing.

Specimens showing particulate matter, erythrocytes, or turbidity should be centinfuged before testing.

Sample volume—

100 µL of specimen is the minimum volume required to perform the assay**.**

Dilution information—

Specimens with a homocysteine value exceeding 50 µmol/L are flagged ">50". To quantitate the concentration result the Automated Dilution Protocol or the Manual Dilution Procedure is performed.

Limitation of the procedure—

If the ARCHITECT Homocysteine assay results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.

The following drugs may elevate levels of homocysteine: methotrexate, carbamazepine, phenytoin, nitrous oxide, anticonvulsants and 6-azauridine triacetate. The mechanism of action of these drugs affects different parts of the metabolic pathway of homocysteine

S-adenosyl-methionine is an antidepressant whose molecular form is similar to S-adenosyl-homocysteine. This drug may interfere with the ARCHITECT Homocysteine assay**.**

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA).

Specimens containing HAMA may produce anomalous values when tested with assay kits such as ARCHITECT Homocysteine that employ mouse monoclonal antibodies.

Heterophilic antibodies in human specimens can react with reagent immunoglobulins, interfering with in vitro immunoassays.

Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed.

Sensitivity

The sensitivity of the IMX Homocysteine assay was calculated to be ≤ 1.0 μmol/L which corresponds to the upper limit of the 95% confidence interval.

Specificity

Cross - reactivity was found for compounds whose chemical structure or concurrent usage may potentially interfere with the Homocysteine assay.

OBSERVATION AND RESULTS

In this study, 50 patients with evidence of acute myocardial infarction, the first degree relatives of the patients and 50 controls were recruited. Homocysteine levels were studied in all the groups.

AGE DISTRIBUTION-

Table 1: Age wise distribution of cases

Age (years)	No of cases	Percentage (%)
<30	2	4
31-40	5	10
41-50	17	34
51-60	12	24
61-70	9	18
>70	5	10
Total	50	100

Mean=53.86 years, S.D=13.7

Table 2: Age wise distribution of the first degree relatives

Age(years)	No of first degree relatives	Percentage (%)
<30	29	58
31-40	14	28
41-50	6	12
51-60	1	2
61-70	0	0
>70	0	0
Total	50	100

Mean=30 years, S.D=9.10

Table 3: Age wise distribution of controls

Age (years)	No of controls	Percentage (%)
<30	2	4
31-40	5	10
41-50	18	36
51-60	11	22
61-70	9	18
>70	5	10
Total	50	100

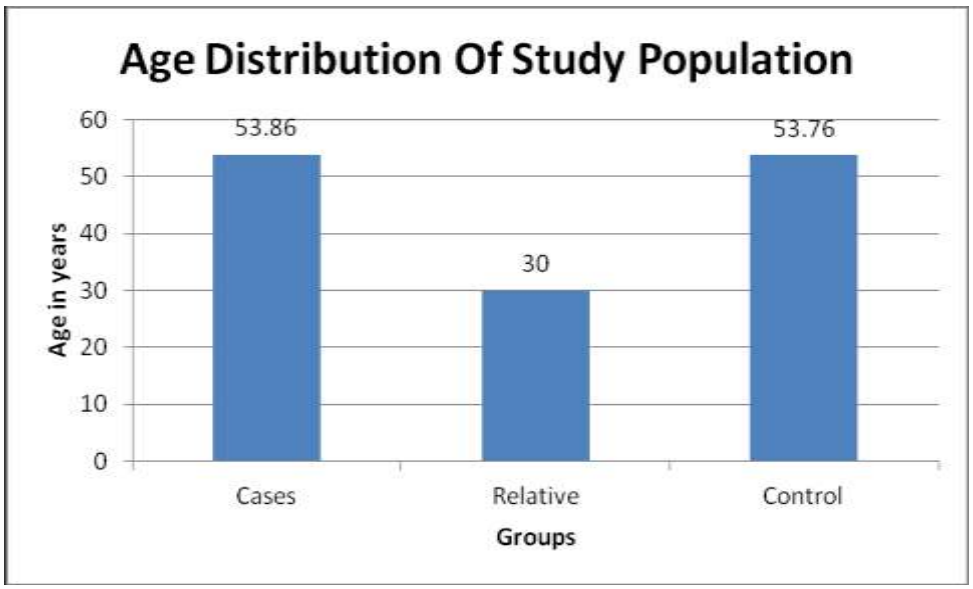
Mean=53.76 years, S.D=13.5

Table 4: Mean age of cases, first degree relatives and controls

	Mean age	S.D
Cases	53.86	13.78
First degree relatives	30	9.10
Controls	53.76	13.52

In this study, most of the cases were between 41-50 yrs, controls were between 41-50 yrs and the first degree relatives of the patients were less than 30 yrs.

Graph 1: Age wise distribution of cases, first degree relatives and controls



SEX DISTRIBUTION-

Table 5: Sex wise distribution of cases

Sex	Cases	Percentage (%)
Male	42	84
Female	8	16
Total	50	100

The sex ratio between male and female is 6:1.

Table 6: Sex wise distribution of controls

Sex	Controls	Percentage (%)
Male	40	80
Female	10	20
Total	50	100

The sex ratio between male to female is 4:1.

Table 7: Sex wise distribution of the first degree relative of the cases

Sex	First degree relative	Percentage (%)
Male	36	72
Female	14	28
Total	50	100

The sex ratio between male to female is 5:2.

Graph 2: Gender Distribution of Study Population

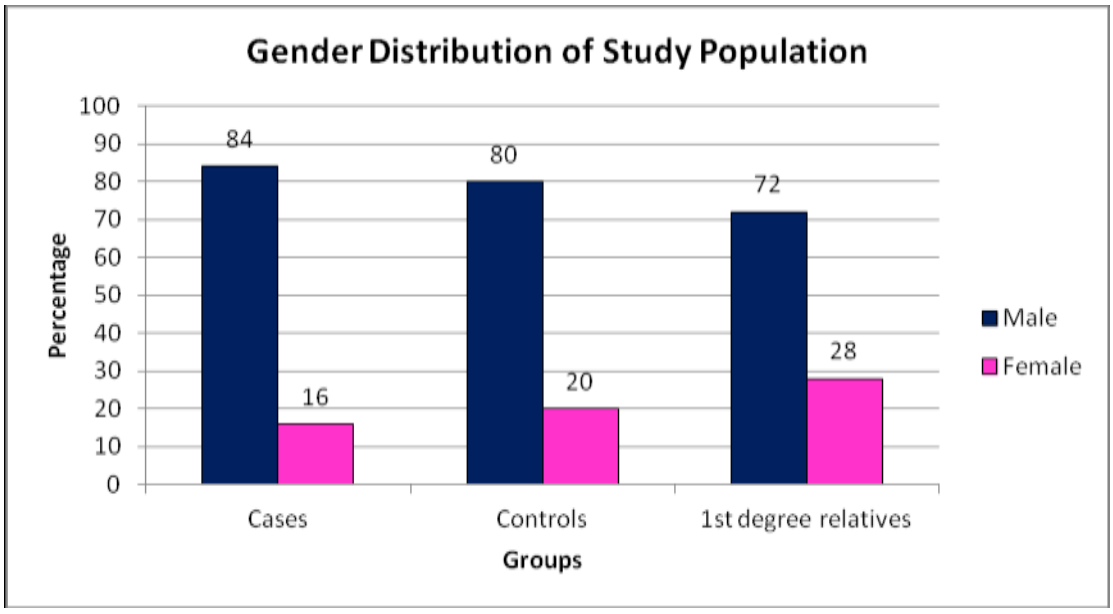


Table 8: Symptoms at the time of presentation in cases

Symptoms	Cases	Percentage (%)
Chest pain	50	100
Dyspnoea	17	34
Palpitation	2	4
Sweating	29	58
Syncope	0	0
Vomiting	5	10

Chest pain was the most common symptom present in all patients (100%), followed by sweating (58%), and dyspnoea (34%). vomiting was present in 10% and palpitation in 5%.

Graph 3: Distribution of symptoms in cases

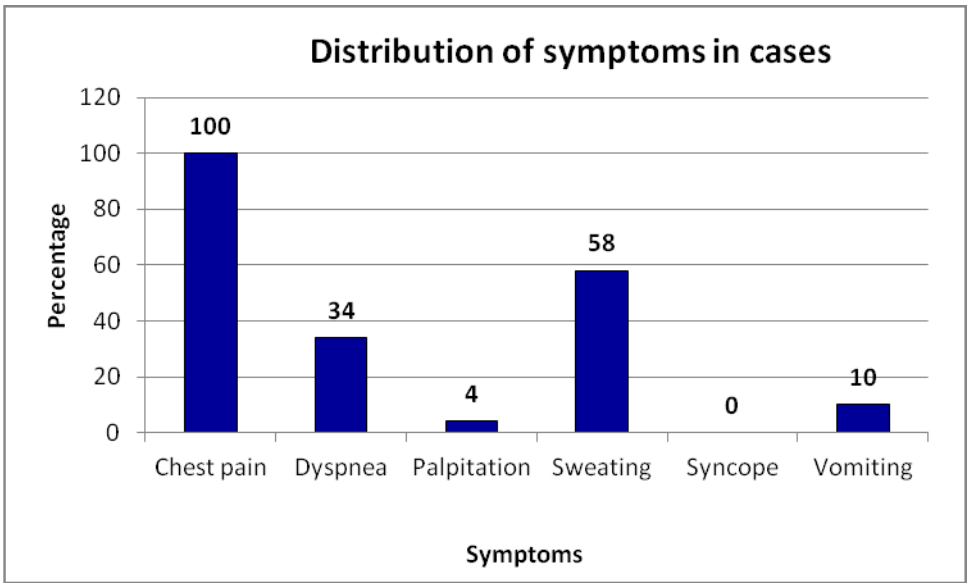


Table 9: Risk factors in cases

Risk factors	No of cases	Percentage (%)
Smoking	26	52
Hypertension	23	46
Diabetes	15	30
Dyslipidemia	20	40

In this study, smoking (52%) was the most common risk factor followed by Hypertension (46%). Dyslipidemia was present in 40% of the patients and diabetes in 30 % .

Graph 4: Risk factors in cases

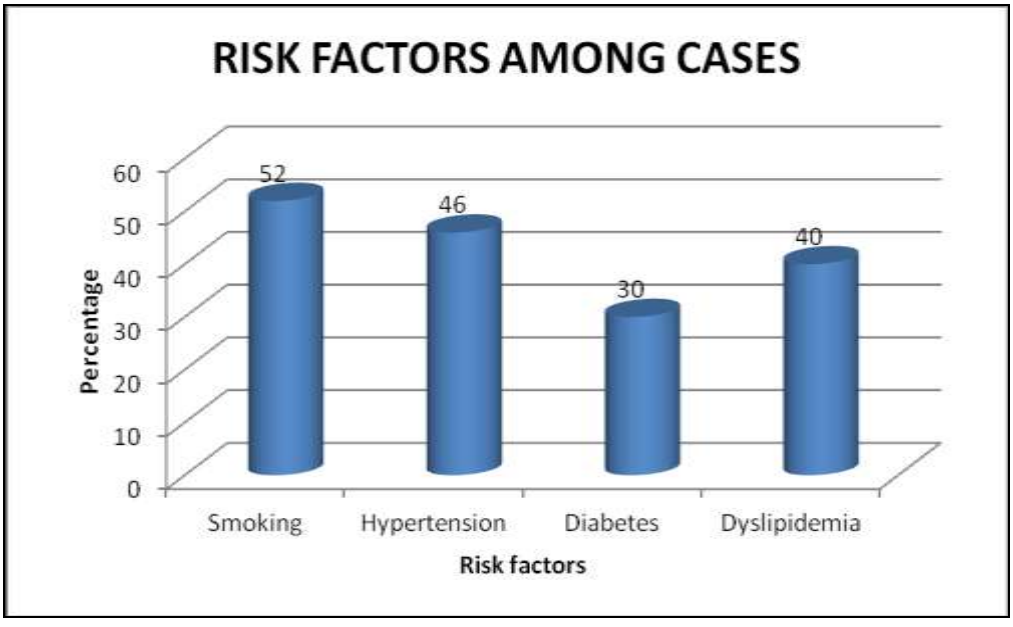


Table 10: Mean serum homocysteine levels in cases, first degree relatives and controls

Serum homocysteine	Mean	S.D
Cases	25.2	14.74
Controls	11.7	2.93
First degree relative	14.1	3.39

In this study, the mean homocysteine level in the cases was 25.2±14.74 µmol/l and in controls it was 11.7 ±2.93 µmol/l and in the first degree relatives of the patient it was 14.1±3.39 µmol/l .

Graph 5: Mean serum homocysteine levels in study population

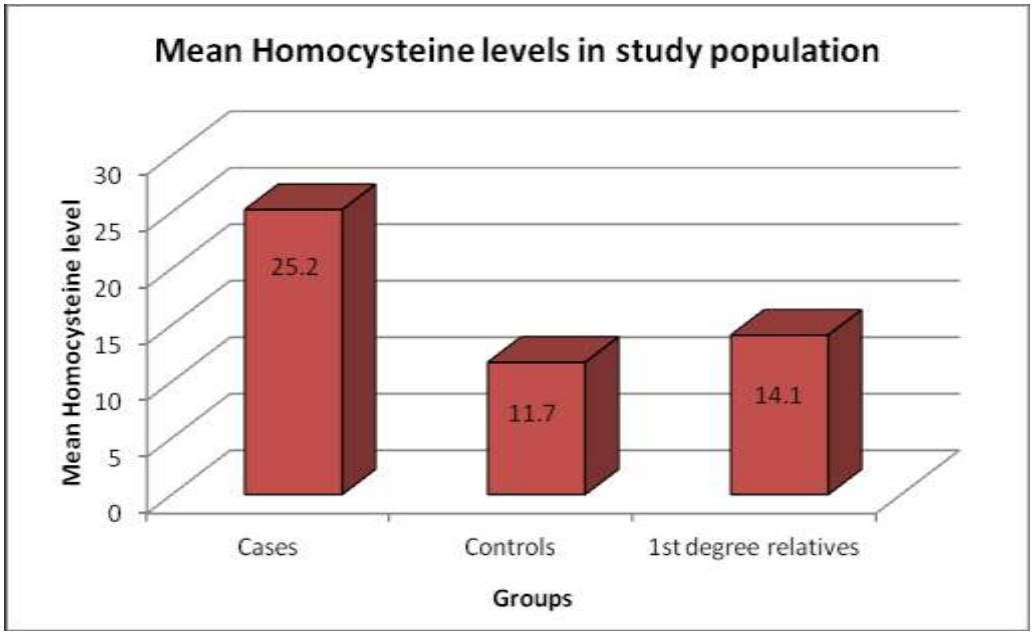


Table11: Comparison of mean homocysteine levels between vegetarians and non vegetarians in cases

	Vegetarian	Non-vegetarian	t value	p value
Homocysteine	32.189±14.56	19.327±12.29	3.42	0.001

The mean homocysteine level in vegetarians was 32.189±14.56 µmol/l and in non vegetarians, it was 19.327±12.29 µmol/l which was statistically significant (p value=0.001).

Graph 6: Comparison of mean homocysteine levels between vegetarians and non vegetarians in cases

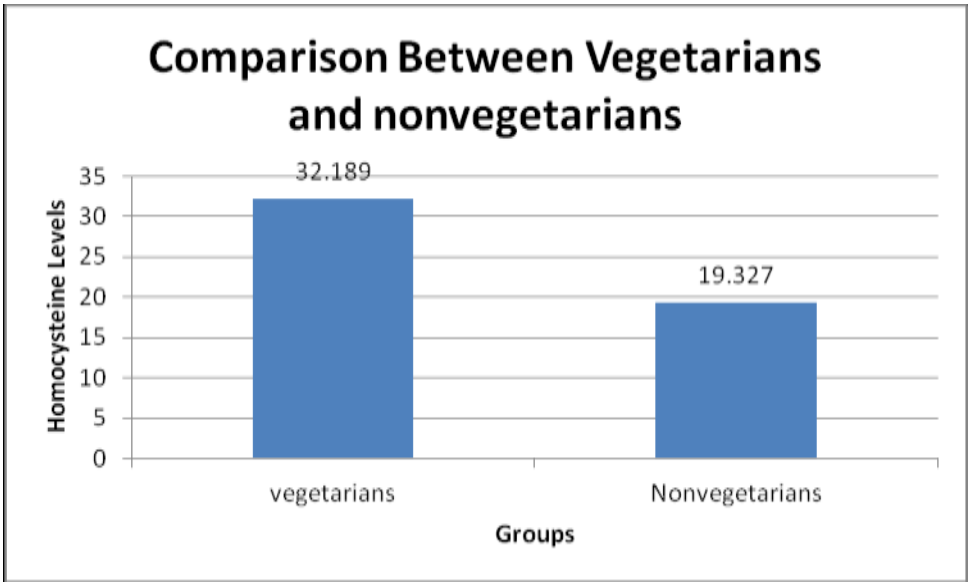


Table 12: Comparison of mean homocysteine levels between smokers and non smokers in cases

	Smoker	Non smoker	t value	p value
Homocysteine	31.1 ± 16.2	18.9 ± 2.0	3.15	0.003

The mean serum homocysteine level (31.1±16.2) µmol/l was higher among smokers when compared to non smokers (18.9±2.0) µmol/l which was statistically significant (p value=0.003).

Graph 7: Comparison of mean homocysteine levels between smokers and non smokers in cases

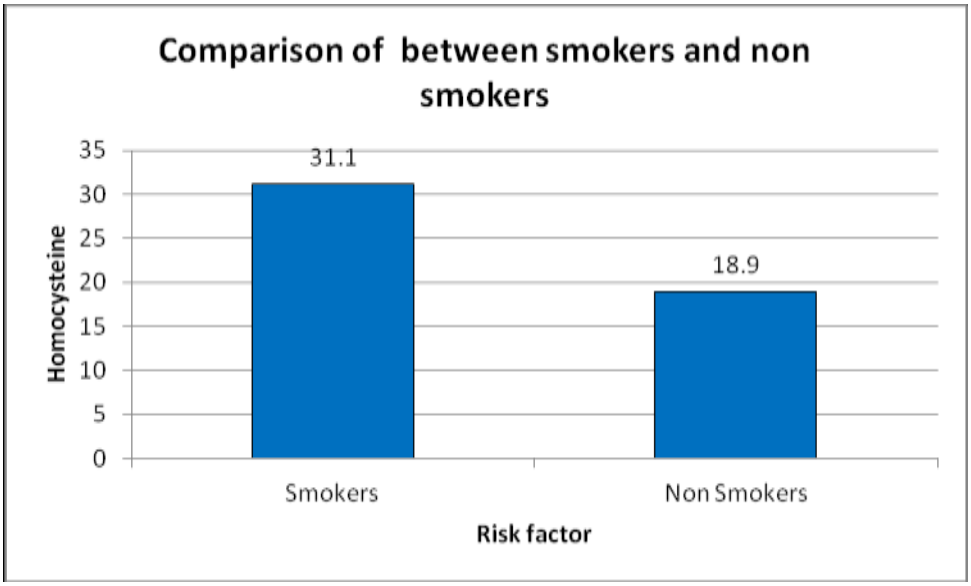


Table 13: Comparison of mean homocysteine levels between hypertensives and normotensives in cases

	Hypertensive	Normotensives	t value	p value
Homocysteine	32.9 ±16.7	18.7 ± 8.9	3.83	<0.001

The mean serum homocysteine levels (32.9±16.7) µmol/l was high among hypertensives when compared to normotensives (18.7±8.9) µmol/l which was statistically significant(p value-<0.001).

Graph 8: Comparison of mean homocysteine between hypertensives and normotensives in cases

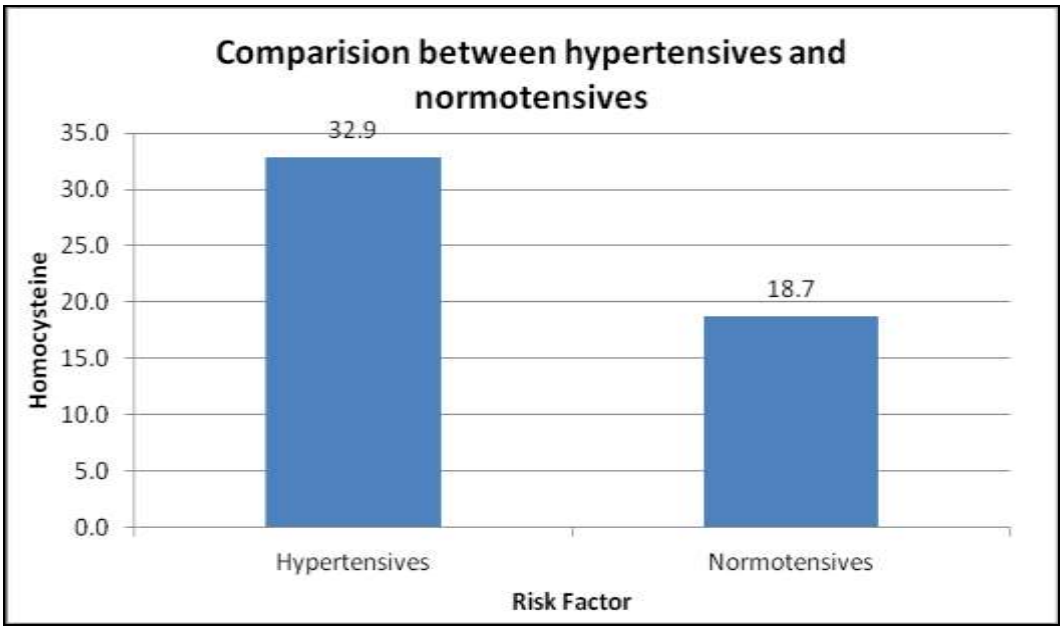


Table 14: Comparison of mean homocysteine levels between diabetics and non diabetics in cases

	Diabetics	Non diabetics	t value	p value
Homocysteine	35.0 ± 18.8	21.1 ± 10.4	3.38	0.001

The mean serum homocysteine levels was higher in diabetics (35.0±18.8 µmol/l) when compared to non diabetics (21.1±10.4 µmol/l) which was statistically significant(p value=0.001).

Graph 9: Comparison of mean homocysteine levels between diabetics and non diabetics in cases

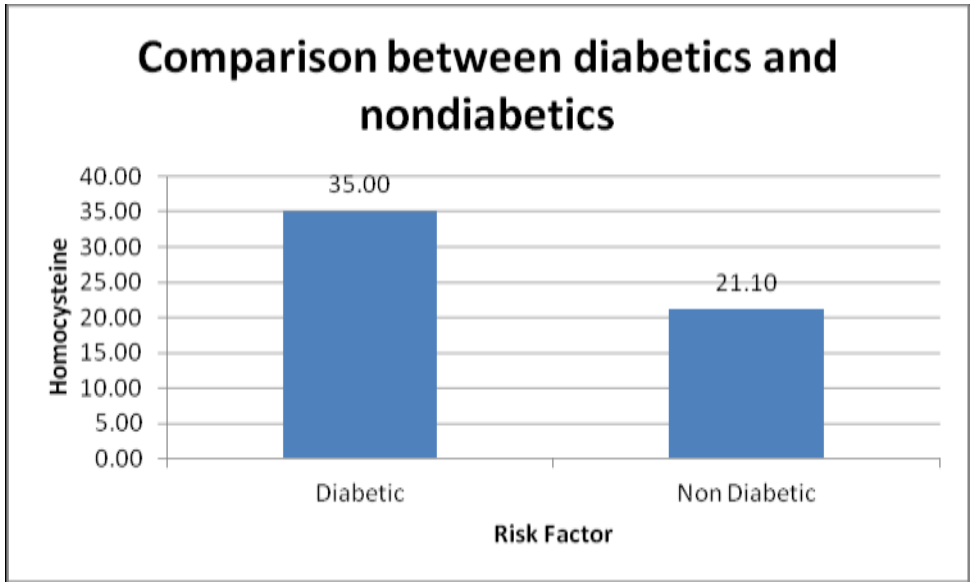
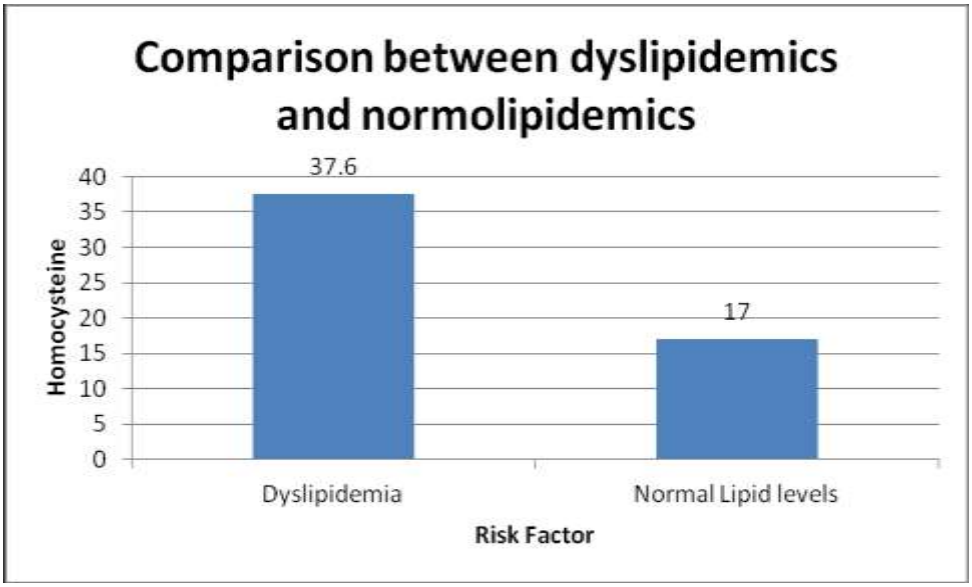


Table 15:Comparison of mean homocysteine levels between dyslipidemics and normolipidemics in cases

	Dyslipidemics	Normolipidemics	t value	p value
Homocysteine	37.6 ± 14.1	17.0 ± 7.8	6.66	<0.001

The mean serum homocysteine levels among dyslipidemics (37.6±14.1 µmol/l) was higher compared to normolipidemics(17.0±7.8 µmol/l) which was statistically significant(p value-<0.001).

Graph 10: Comparison of mean homocysteine levels between dyslipidemics and normolipidemics in cases



COMPARISON OF SERUM HOMOCYSTEINE LEVELS IN BETWEEN DIFFERENT GROUPS

Table 16: Comparison of mean homocysteine levels between cases and the first degree relative of the patient

	Mean	S.D	t value	p value
Cases	25.2	14.7	5.20	<0.001
First degree relative	14.1	3.39		

The mean serum homocysteine levels in cases (25.2 µmol/l) was greater compared to the first degree relative (14.1 µmol/l) which was statistically significant (p value-<0.001).

Graph 11: Comparison of mean homocysteine levels between cases and the first degree relative of the case.

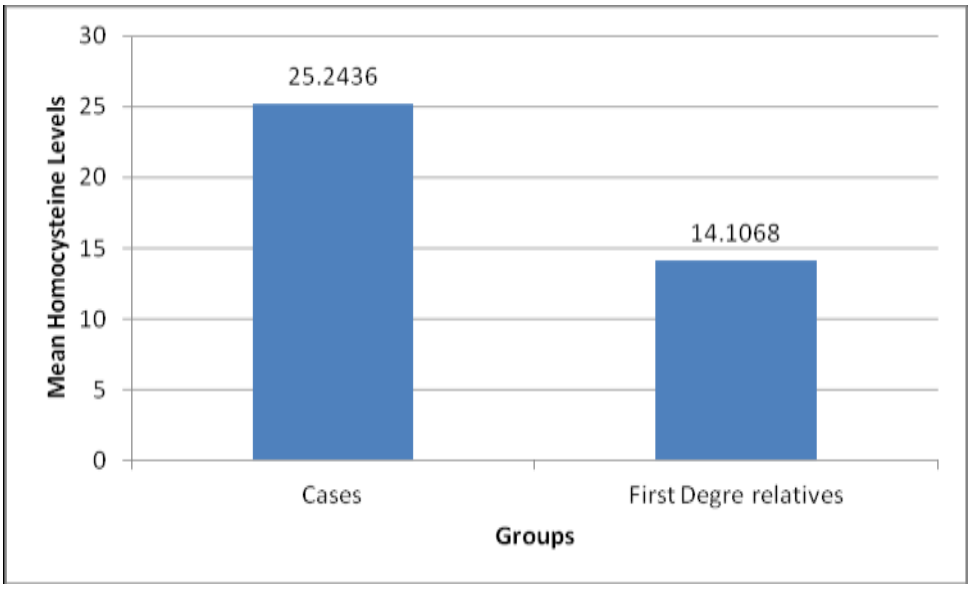


Table 17: Comparison of mean homocysteine levels between cases and controls

	Mean	S.D	t value	p value
Cases	25.2	14.74	6.35	<0.001
Controls	11.7	2.93		

The mean homocysteine levels in cases (25.2 µmol/l) was more than controls (11.7 µmol/l) which was statistically significant (p value-<0.001)

Graph 12: Comparison of mean homocysteine levels between cases and controls

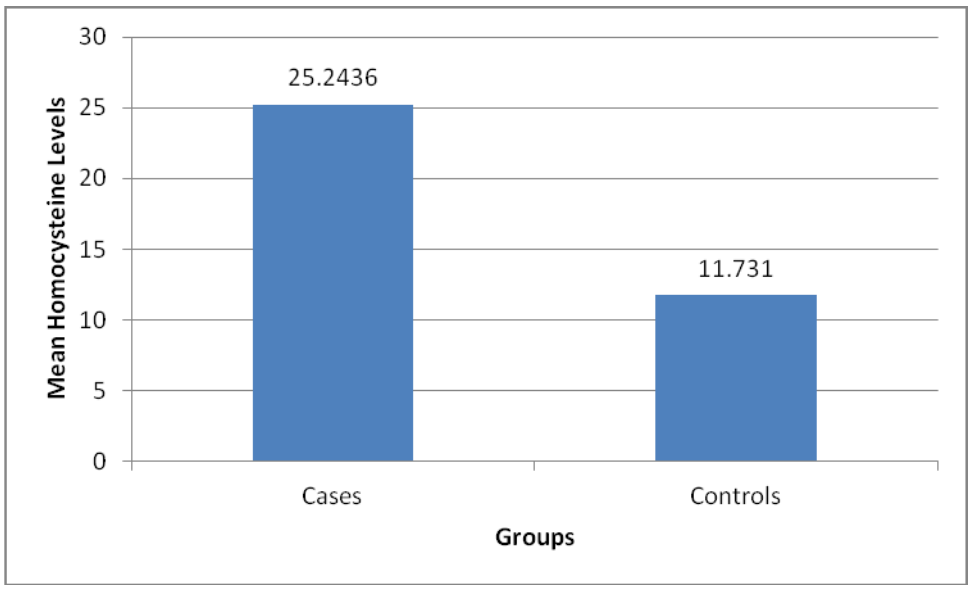


Table 18: Comparison of mean homocysteine levels between the first degree relative of the case and the controls

	Mean	S.D	t value	p value
First degree relative	14.1	3.39	3.74	<0.001
Control	11.7	2.93		

The mean homocysteine levels in the first degree relative of the patient (14.1 µmol/l) was greater than that of controls (11.7 µmol/l) which was statistically significant (p value-<0.001).

Graph 13: Comparison of mean homocysteine levels between the first degree relative and controls

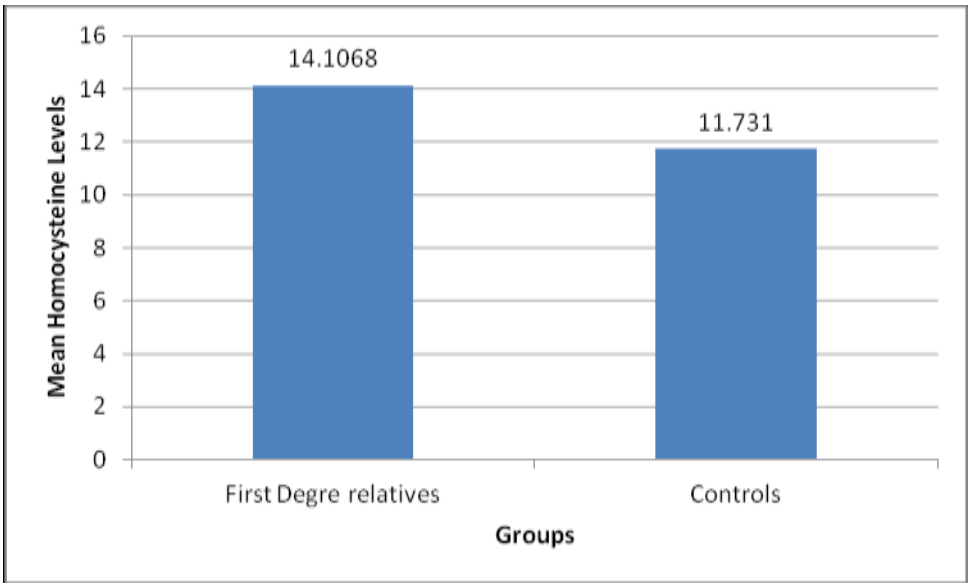


Table 19: Comparison of mean homocysteine levels between all the groups in the study

	Mean	S.D	S.E	f value	p value
Cases	25.2436	14.74479	2.085228	32.86246	<0.001
First degree relative	14.1068	3.392296	0.479743		
Control	11.731	2.938785	0.415607		

Significance : p value <0.001

The mean homocysteine levels were compared between the three groups and there was significant comparison with a p value of <0.001.

DISCUSSION

Fifty cases of acute myocardial infarction, fifty cases of their first degree relatives and fifty controls were taken for the study and compared.

Table 20: Comparison of age wise distribution of cases and controls with other studies

Study	Cases	Controls
Angeline et al[11]	46.5±10.5 years	44.4±12.6 years
Joshaghani et al[8]	52.5 years	48.6 years
Saleh et al[39]	55.3±6.7 years	53.0±7.5 years
Present study	53.86 years	53.76 years

Table 21: Comparison of age wise distribution of first degree relative with other study

Study	Age (years)
Kark et al[9]	29.9
Present study	30

The mean ages of cases (53.86 years), relatives (30 years), controls (53.76 years) were comparable to other studies.

Most of the cases were between 41-50 years (34%) and the first degree relative of the patient was less than 30 years (58%) and controls were between 41-50 years (36%).

The minimum age at which acute myocardial infarction that had occurred in this study was 25 years.

Table 22: Comparison of sex wise distribution of cases with other studies

	Male	Female
Angeline et al[11]	49	11
Joshanghani et al[8]	36	12
Saleh et al[39]	72	18
Present Study	42	8

Table 23: Comparison of sex wise distribution of controls with other studies

	Male	Female
Angeline et al[11]	28	7
Joshanghani et al[8]	29	19
Saleh et al[39]	72	18
Present Study	40	10

Table 24: Comparison of sex wise distribution of first degree relative with other study

	Male	Female
Kark et al[9]	133	62
Present study	36	14

The study was predominantly male, and was comparable with other studies. This may be attributed to the protective effects of oestrogen in premenopausal age.

Table 25: Comparison of symptoms in patients with other study

	Patil CN et al[99]	Present study
Chest pain	93.3%	100%
Dyspnoea	16.7%	34%
Palpitation	3.3%	4%
Sweating	50%	58%
Syncope	-	O%
Vomiting	16.7%	10%

In this study chest pain was the most common symptom and was present in all patients (100%). Sweating was also present in most of the patients (58%). Dyspnoea was also present in significant number of patients (34%). Vomiting was present in 10% of the patients and palpitation was present in 4% of the patients.

Table 26: Comparison of mean homocysteine levels of cases and controls with other studies

	Cases (µmol/l)	Controls(µmol/l)
Angeline et al[11]	30.5±5.3	11.1±3.1
Joshanghani et al[8]	24.59±6.14	13.73±3.54
Saleh et al[39]	18.5±7.8	12.0±8.4
Present Study	25.2±14.17	11.7±2.9

The mean homocysteine levels of cases were 25.2±14.17 µmol/l and in controls it was 11.7±2.9 µmol/l.

There was moderate hyperhomocysteinemia (15-30µ mol/L) in cases.

In controls, the mean homocysteine levels were within normal range (<15µ mol/L).

The levels of homocysteine in cases were twice that of controls. This was correlating with Angeline et al study where levels in cases were also twice that of controls.

In Joshanghani et al and Saleh et al study, the mean homocysteine levels were more in cases than controls. In this study, the levels were also high in cases when compared to controls.

Hyperhomocysteinemia(>15µ mol/L) was present in 64% of the cases in this study and it was present in 18% of the patients without any risk factor.

Hyperhomocysteinemia(>15 µmol/l) was also present in 32% of the first degree relative and 18% of controls.

Table 27: Comparison of mean homocysteine levels in first degree relative with other study

	Male	Female
KARK et al[9]	13.2	8.1
PRESENT STUDY	14.4	13.3

The mean homocysteine levels in male first degree relative were 14.4 µmol/l and in female first degree relative were 13.3 µmol/l and when compared with Kark et al study, similar results were found.

Table 28: Comparison of mean homocysteine levels between vegetarians and non vegetarians with other study

	Vegetarians(µmol/l)	Non-vegetarians(µmol/l)
Jayantee et al[97]	20.42±12.98	16.43±10.66
Present Study	32.189±14.56	19.327±12.29

The mean homocysteine level in vegetarian patients (32.189±14.56 µmol/l) was higher as compared to non-vegetarian patients (19.327±12.29µmol/l) and it correlated with the results of Jayantee et al study.

Vegetarian patients showed higher homocysteine levels compared to non vegetarians in this study.

Table 29: Comparison of incidence of smoking, diabetes and hypertension in cases with other study

	Smokers (%)	Diabetics (%)	Hypertension (%)
Saleh et al[39]	54	44	30
Present study	52	30	46

In this study smoking was the most common risk factor and was present in 52% of the patients, diabetes mellitus was present in 30% of the patients and hypertension was present in 46% of patients.

The study by Saleh et al showed that smoking was present in 54% of patients and diabetes mellitus in 44% of patients and hypertension in 30% of patients.

Table 30: Comparison of mean homocysteine levels between smokers and non smokers with other study

	Non smokers(µmol/l)	Smokers(µmol/l)
Shahid et al[22]	6.88±1.15	28.6±7.95
Present study	18.9±2.0	31.1±16.2

Among cases, the levels of homocysteine in smokers in our study were elevated and it was around 31.1±16.2 µmol/l when compared to 18.9±2.0 µmol/l in non-smokers. This was comparable with the study done by Shahid et al.

Table 31: Comparison of mean homocysteine levels between diabetics and non diabetics with other study

	Non Diabetic(µmol/l)	Diabetic(µmol/l)
Arshad et al[98]	13.1±1.8	23.14±2.4
Present Study	21.1±10.4	35.0±18.8

Among the cases the levels of homocysteine in diabetics were elevated and it was around 35.0±18.8 µmol/l when compared to 21.1±10.4 µmol/l in non diabetics .This elevation of levels were also seen in the other study by Arshad et al.

Table 32: Comparison of mean homocysteine levels between hypertensives and normotensives with other study

	Normotensive(µmol/l)	Hypertensive(µmol/l)
Vyssoulis et al[76]	9.3±0.2	11.7±0.1
Present Study	18.7±8.9	32.9±16.7

Among cases, the levels of homocysteine in hypertensives were elevated and it was around 32.9±16.7 µmol/l compared to 18.7±8.9 µmol/l in non hypertensives. This elevation was also seen in other study by Vyssoulis et al.

Table 33: Comparison of lipid profile in cases with other study

	Saleh et al[39]	Present Study
T.cholesterol(mg/dl)	225.4±50.7	181.16
LDL(mg/dl)	161.4±28.5	97.68
Triglycerides(mg/dl)	200.2±65.4	147.96
HDL(mg/dl)	40.5±18.6	39.86

The mean levels of Total Cholesterol (181.16 mg/dl), LDL (97.68 mg/dl), Triglyceride(147.96 mg/dl),HDL(39.86 mg/dl) were less in this study when compared to other study by Saleh et al.

Table34: Comparison of mean homocysteine levels in dyslipidimics and normolipidemics

	Normolipidemics	Dyslipidemics
Present Study	17.0±7.8 µmol/l	37.6±14 µmol/l

The mean homocysteine Levels in dyslipidemics (37.6±14 µmol/l) were more compared to normolipidemics(17.0±7.8 µmol/l) .

Comparison of homocysteine levels among different groups

Table 16: Comparison of mean homocysteine levels between cases and the first degree relative of the patient

	Mean	S.D	t value	p value
Cases	25.24	14.7	5.204	<0.001
Relative	14.10	3.39		

The mean levels of homocysteine in cases were 25.24µmol/l and in the first degree relative of the patient, mean homocysteine levels were 14.10µmol/l. When their mean levels were compared by independent student t-test, there was statistical significance with a p value of <0.001.

Table 17: Comparison of mean homocysteine levels between cases and controls

	Mean	S.D	t value	p value
Cases	25.24	14.74	6.35	<0.001
Control	11.73	2.93		

The mean levels of homocysteine in cases were 25.24µmol/l and in controls, it was 11.73 µmol/l. When their mean levels were compared by independent student t-test, there was statistical significance with a p value of <0.001.

Table 18: Comparison of serum homocysteine levels between the first degree relative of the case and the controls

	Mean	S.D	t value	p value
Control	11.7	1.93	3.74	<0.001
First degree relative	14.1	3.39		

The mean levels of homocysteine in controls were 11.7 µmol/l and in the first degree relative of the patient, it was 14.1 µmol/l. When their mean levels were compared by independent student t-test, there was statistical significance with a p value of <0.001.

Table 19: Comparison between all the groups in the study

	Mean	S.D	S.E	f value	p value
Cases	25.2436	14.74479	2.085228	32.86246	<0.001
First degree relative	14.1068	3.392296	0.479743		
Control	11.731	2.938785	0.415607		

Significance : p value <0.001

The mean homocysteine levels were compared between the three groups and there was significant difference with a p value of <0.001

CONCLUSION

- Homocysteine levels were elevated in patients with acute myocardial infarction.
- Hyperhomocysteinemia (>15 μmol) was present in 64% (n=32) of the patients, 32% (n=16) of the first degree relative and 18% of controls (n=9) in this study.
- Hyperhomocysteinemia without any risk factor was present in 18 % (n=9) of the patients in this study.
- The first degree relative of the patients has a higher mean homocysteine levels when compared to the controls.
- Significantly higher levels of homocysteine were present in smokers, hypertensive patients, diabetic patients and dyslipidemic patients when compared to non smokers, normotensives , non Diabetics and normo lipidemics respectively.
- Hyperhomocysteinemia has emerged as a strong and independent risk factor for acute myocardial infarction.

SUMMARY

In this study, homocysteine levels of 50 acute myocardial Infarction, 50 first degree relative of these patients and 50 healthy controls were studied.

- The mean age of cases was 53.86 years, the first degree relative was 30 years and control was 53.76 years.
- The male to female ratio in cases, first degree relative of the patient and in controls was 6:1, 5:2, 4:1 respectively.
- Most of the patients presented with chest pain (100%).
- Smoking (52%) was the most common risk factor seen in patients followed by hypertension(46%), dyslipidemia (40%), diabetes mellitus(30%).
- The mean homocysteine levels in cases, in the first degree relative of the patient and in the controls were 25.2±14.7 µmol/l, 14.1±3.4 µmol/l,11.7±2.9 µmol/l respectively.
- Hyperhomocysteinemia(>15µmol) was present in 64% of the patients,32% of the first degree relative and 18% of the controls.
- The mean levels of homocysteine in cases were almost twice that of the controls. The levels in the first degree relative were more when compared to controls.
- Significantly higher levels of homocysteine were present in smokers, hypertensive patients, diabetic patients and dyslipidemic patients when compared to non smokers, normotensives, non Diabetics and normo lipidemics respectively.

BIBILOGRAPHY

1. Bortolotto LA, Safar ME, Billaud E, Lacroix C, Asmar R, London GM, et al. Plasma homocysteine, aortic stiffness and renal function in hypertensive patients. Hypertension 1999;34:837-42.
2. Arnesen E, Refsums H, Bonaa KH, Ueland PM, Forde OH, Nordrehaug JE. Serum total homocysteine and coronary heart disease. Int J Epidemiol 1995;24:704-709.
3. Boers GH, Smals AG, Trijibels FJ, Fowler B, Bakkeren JA, Schoonderwalt HC, et al. Heterozygocity for homocysteinuria is premature peripheral and cerebral occlusive arterial disease. N Eng J Med 1985;313(12):709-715.
4. Murray CL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020:Global burden of disease Study. Lancet 1997;349(9064):1498-1504.
5. Abraham R, John MJ, Calton R, Dhanoa J. Raised serum homocysteine levels in patients of coronary artery disease and the effect of vitamin b12 and folate on its concentration. *Indian Journal Of Clinical Biochemistry* 2006;21(1):95-100.
6. Enas EA, Dhawan J, Petkar S. Coronary Artery Disease in Asian Indians:lessons learnt and the role of Lipoprotein(a). Indian Heart J 1997;49:25-34.
7. Refsum H, Ueland PM, Nygard O, Vollset SE. *Homocysteine and cardiovascular disease. Annu Rev Med 1998;49:31-62.*
8. Hamid RJ, Ahmad AS, Abdoljalal M. Serum homocysteine levels in patients with myocardial infarction in gorgan(in northern iran). *Asian Journal Of Biochemistry* 2007;2(2):157-160.
9. Kark JD, Sinnreich, Rosenberg, Jacqes, Selhub. Plasma homocysteine and parental myocardial infarction in young adults in jerusalem. *Circulation* 2002;105:2725-2729.

10. Linda LH, Rongwei F, Kevin R, Michele F, Mark H. Homocysteine level and coronary heart disease incidence:a systemic review and meta analysis. *Mayo Clin Proc* 2008;83(11):1203-1212.
11. Angeline T, Aruna RT, Ramadevi K, Mohan K, Nirmala J. Homocysteine status and acute myocardial infaction among tamilians. *Indian Journal Of Biochemistry* 2005;20(1):18-20.
12. Mohamad K, AlObaidi, Stubbs PJ, paul C, Ronan C, Ian G, et al. Elevated homocysteine levels are associated with increased ischemic myocadial injury in acute coronary syndromes. *J Am Coll Cardiol* 2000;36:1217-1222.
13. Mohammad M, Abbas B, Masoud M, Alireza N. Plasma homocysteine concentrations in young patients with acute myocardial infarction. *Arya Atherosclerosis Journal* 2007;2(4):193-196.
14. Arif S, Ghosia L, Bushra I, Jamir UR, Muhammad RW, Sunia AK. Homocysteine and acute myocardial infarction. J Med Sci 2010;18(1):54-58.
15. Wilcken DE, Wilcken B. The pathogenesis of coronary artery disease:A possible role for methionine metabolism. J Clin Invest 1976;57:1079-1082.
16. Selhub J, Jacques PF, Bostom AG, Dagostino RB, Wilson PW, Belenger AJ, et al. Association between plasma homocysteine concentration and extracranial carotid artery stenosis. N Eng J Med 1995;332(5):286-291.
17. McCully KS. Vascular pathology of homocysteinemia:Implication for the pathogenesis of arteriosclerosis. Am J Patho 1969;56(1):111-128.
18. Stampfer MJ, Mainlow MR. Can lowering homocysteine levels reduce cardiovascular risk. N Engl J Med 1995;332(5):328-9.
19. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease:

Probable benefits of increasing folic acid intakes. JAMA 1995;274:1049-1057.

20. Ansari MN, Nigam GK, Uma B. Effect of folic acid on haematological changes in methionine-induced hyperhomocysteinemia in rats. Indian Journal of Pharmaceutical Sciences 2009;71:270-275.
21. Alfthan G, Aro A, Gey KF. Plasma homocysteine and cardiovascular mortality. LANCET 1997;349:395-397.
22. Shahid A, Muja W, Vinayak WP. Folic acid and vitamin B12 levels and their correlation in cigarette smoker and Hyperhomocysteinemia. Al Amen J Med Sci 2011;4(2):169-174.
23. Reed T, Malinow MR, Christian JC, Upson B. Estimates of heritability of plasma homocyst(e)ine levels in aging adult male twins. *Clin Genet* 1991;39(6):425–428.
24. Berg K, Malinow MR, Kierulf P, Upson B. Population variation and genetics of plasma homocyst(e)ine level. *Clin Genet* 1992;41:315–321.
25. Genest JJ, McNamara JR, Upson B, Salem DN, Ordovas JM, Schaefer EJ, et al. Prevalence of familial hyperhomocyst(e)inemia in men with premature coronary artery disease. *Arterioscler Thromb* 1991;11(5):1129–1136.
26. Tonstad S, Refsum H, Sivertsen M, Christophersen B, Ose L, Ueland PM. Relation of total homocysteine and lipid levels in children to premature cardiovascular death in male relatives. *Pediatr Res* 1996;40:47–52.
27. De LC, Wautrecht JC, Brasseur D, Dramix M, Boeynaems JM, Decuyper J, et al. Plasma homocysteine concentration in a Belgian school-age population. *Am J Clin Nutr* 1999;69:968–972.
28. Greenlund KJ, Srinivasan SR, Xu JH, Dalferes EJ, Myers L, Pickoff A, Berenson GS. Plasma homocysteine distribution and its association with

parental history of coronary heart disease in Black and White children:the Bogalusa Heart study. *Circulation* 1999;99(16):2144–2149.

29. Morrison JA, Jacobsen DW, Sprecher DL, Robinson K, Khoury P, Daniels R. Serum glutathione in adolescent males predicts parental coronary heart disease. *Circulation* 1999;100:2244–2247.
30. Gaeta G, Michele MD, Cuomo S, Guarini P, Foglia MC, Bond MG. Arterial abnormalities in the offspring of patients with premature myocardial infarction. *N Engl J Med* 2000;343:840–846.
31. Chambers JC, Ueland PM, Obeid OA, Wringley J, Refsum H, Kooner JS, et al. Improved vascular endothelial function after oral B vitamins:an effect mediated through reduced concentrations of free plasma homocysteine. *Circulation* 2000;102:2479–2483.
32. Mark AM, Wisam HA, Jeanna VC, Eva MKR, Dean ES, Kim AE, et al. The new definition of myocardial infarctions–Diagnostic and prognostic implications in patients with acute coronary syndromes. Arch Intern Med 2002;162:1585-1589 .
33. Puri A, Gupta OK, Dwivedi RN, Bharadwaj RPS, Narain VS, Singh S. Homocysteine and lipid levels in young patients with coronary artery disease. JAPI 2003;51:681-685.
34. Kang SS, Wong PWK, Malinow MR. Hyperhomocysteine as a risk factor for occlusive vascular disease. Ann Rev Nut 1992;12:279-298.
35. Kailash P. Homocysteine, a risk factor for cardiovascular disease. International Journal of Angiology 1999;8:76-86.
36. Neki NS. Hyperhomocysteinemia–An independent risk factor for cardiovascular disease. Indian Heart J 2001;53:44-47.

37. Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J. Determinants of plasma total homocysteine concentration in the Framingham offspring cohort. Am J Clin Nutr 2001:73;613-621.
38. Yoelekar MM, Shete MM. Homocysteine and hypertension. J Assoc Physicians India 2002;50(suppl):29-35.
39. Saleh A, Basher N. Serum Homosysteine levels in patients with acute myocardial infarction in Jordan. J Med J 2010;44(2):193-197.
40. Malinow MR, Bostom AG, Krauss RM. Homocysteine, diet, and cardiovascular diseases, a statement for health care professionals from the nutritional committee, American heart association. Circulation 1999;99: 178-82.
41. Ebba N, Frode E. Evaluation of novel assays in clinical chemistry–quantification of plasma total homocysteine. Clinical Chemistry 2000;46(8): 1550-1556.
42. Paul FJ, Bostom AG, Peter WF, Rich S, Irwin HR, Jacob S. Determinants of plasma total homocysteine concentration in the Framingham offspring cohort. Am J Clin Nutr 2001;73:613-21.
43. Homocysteine lowering trialists collaboration, lowering blood homocysteine with folic acid based supplements: meta analysis of randomized trials. BMJ 1998;316:894-98.
44. Angelo DA, Selhub J. Homocysteine and thrombotic disease. Blood 1997;90:1-11.
45. Thomas GD, Adam E, Abbas S, Jeffrey MW, David H, Lloyd MT, et al. Common mutation in methylene tetrahydrofolate reductase: Correlation with homocysteine metabolism and late onset vascular disease. Circulation 1996;94:3074-3078.

46. Jacobsen DW. Homocysteine and vitamins in cardiovascular disease. Clin Chem 1998;44:1833-1843.

47. Ubbink JB, Vermaak WJH, Vander MA, Becker PJ. Vitamin B12, Vitamin B**6**, folate nutritional status in men with hyperhomocysteinemia. Am J Clin Nutr 1993;57:47-53.

48. Eberhardt RT, Forgione MA, Cap A, Leopold JA, Rudd MA, Trolliet M, et al. Endothelial dysfunction in a murine model of mild hyperhomocyst(e)inemia. *J. Clin. Invest 2000;***106(4)**:483–491.

49. Upchurch GR, Welch GN, Fabian AJ, Freedman JE, Johnson JL, Keaney JF, et al. Homocyst(e)ine decreases bioavailable nitric oxide by a mechanism involving glutathione peroxidase. *J. Biol. Chem 1997;***272(27)**:17012–17017.

50. Heydrick SJ, Weiss N, Thomas SR, Cap AP, Pimentel DR, Loscalzo J, et al. L-Homocysteine and L-homocystine stereospecifically induce endothelial nitric oxide synthase-dependent lipid peroxidation in endothelial cells. *Free Radic. Biol. Med 2004;***36(5)**:632–640.

51. Dayal S, Lentz SR. Murine models of hyperhomocysteinemia and their vascular phenotypes. *Arterioscler. Thromb. Vasc. Biol 2008;***28(9)**:1596–1605.

52. Dayal, S, Lentz SR. Role of redox reactions in the vascular phenotype of hyperhomocysteinemic animals. *Antioxid. Redox Signal 2007;***9(11)**:1899–1909.

53. Handy DE, Zhang Y, Loscalzo J. Homocysteine downregulates glutathione peroxidise (GPx1) by decreasing translation. *J. Biol. Chem* 2005;**280**:15518–15525.

54. Handy DE, Lubos E, Yang Y, Galbrith JD, Kelly N, Zhang YY, et al. Glutathione peroxidase-1 regulates mitochondrial function to modulate redox-dependent cellular responses. *J. Biol. Chem 2009;***284(18)**:11913–11921.

55. Weiss N, Zhang YY, Heydrick S, Bierl C, Loscalzo J. Overexpression of cellular glutathione peroxidase rescues homocyst(e)ineinduced endothelial dysfunction. *Proc. Natl. Acad. Sci 2001;***98**:12503–12508.

56. Ungvari Z, Csiszar A, Edwards JG, Kaminski PM, Wolin MS, Kaley G, et al. Increased superoxide production in coronary arteries of hyperhomocysteinemia: role of tumor necrosis factor-alpha, NAD(P)H oxidase, and inducible nitric oxide synthase. *Arterioscler. Thromb. Vasc. Biol 2003;***23(3)**:418–424.

57. Topal G, Brunet A, Millanvoye E, Boucher JL, Rendu F, Devynck MA, et al. Homocysteine induces oxidative stress by uncoupling of NO synthase activity through reduction of tetrahydrobiopterin. *Free Radic. Biol. Med 2004;***36(12)**:1532–1541.

58. Vitvitsky V, Dayal S, Stabler S, Zhou Y, Wanq H, Lentz SR, et al. Perturbations in homocysteine- linked redox homeostasis in a murine model for hyperhomocysteinemia. *Am. J. Physiol 2004;***287(1)**:R39–R46.

59. Stampfer MJ, Malinow MR, Willett WC, Upson B, Newcomer LM, Ullmann D, et al. A prospective study of plasma homocysteine and risk of myocardial infarction in United States Physicians. JAMA 1992;268:877-881.

60. Wald NJ, Watt HC. Homocysteine and ischemic heart disease: Results of a prospective study with implications on prevention. Arch Intern Med 1998;158:862-7

61. Nygard O, Nordrehaug JE, Refsum H, Ureland PM, Farstad M, Vollset SE. Plasma homocysteine level and mortality in patients with coronary artery disease. N Engl J Med 1997;337(4):230-236.

62. Chambers JC, Obeid OA, Refsum H, Ureland P, Hackett D, Hooper J, et al. Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European Men. Lancet 2000;355(9203):523-527.

63. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ureland PM, et al. Plasma homocysteine as a risk factor for vascular disease.The European concerted action project. J Am Med Assoc 1997;277(22):1775-1781.

64. Chacko KA. Plasma homocysteine levels in patients with coronary artery disease. Indian Heart J 1998;50:295-299.

65. Akram S, Basher N. Serum homocysteine levels in patients with acute myocardial infarction in Jordan. *J Med J 2010;44(2):193-196*

66. Sainani GS, Sainani R. Homocysteine and its role in the pathogenesis of atherosclerotic vascular disease. JAPI 2002;50(suppl):16-23.

67. Tambe AB. Homocysteine and atherosclerotic vascular disease. Cardiology Today 2000;4:269-71.

68. Boers GHJ, Smals AGH. Heterozygocity for homocysteinuria is premature peripheral and cerebral occlusive arterial disease. N Engl J Med 1985;313:705-715.

69. Markus HS. Genes, endothelial function and cerebral small vessel disease in man. *Exp. Physiol 2007;***93**:121–127.

70. Martin DH. Hyperhomocysteinemia as a risk factor for deep vein thrombosis. NEJM 2003;334:759-62.

71. Ridker PM, Hennekens CH, Selhub J, Miletich JP, Malinow MR, Stampfer MJ. Interrelation of hypermohocysteinemia, factor V Lieden and risk of future venous thromboembolism. Circulation 1997;95:1777-1782.

72. David A, Cramer. Homocysteine Vs. Cholesterol. Laboratory Medicine 1998;29:406-411.

73. Hogeveen EK, Kostense PJ, Beks PJ, Mackaay AJC, Jakobs C, Bouter LM, et al. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in noninsulin dependent diabetes mellitus-A population based study. Arterioscl Thromb Vasc Biol 1998;18:133-138.

74. Mendis S, Athauda SB. Association between hyperhomocysteinemia and hypertension in Sri Lankans. J Int Med 1999;27:138-44.

75. Peterson JC, Spence JD. Vitamins and progression of atherosclerosis in hyperhomocysteinemia. Lancet 1998;351:263.

76. Vyssoulis G, Karpanou E, Kyvelou SM, Adamopoulos D, Gialernios T, Gymnopoulou E, et al. Associations between plasma homocysteine levels, aortic stiffness and wave reflection in patients with arterial hypertension, isolated office hypertension and normotensive controls. Journal of Human Hypertension 2010;24:183–189.

77. Welch GN, Loscalzo J. Homocysteine and atherotrombosis. N Engl J Med 1998;338:1042–1050.

78. Tawakol A, Omland T, Gerhard M, Wu JT, Greager MA. Hyperhomocysteinemia is associated with impaired endothelium-dependant vasodilatation in humans. Circulation 1997;95:1119–1121.

79. Charpiot P, Bescond A, Augier T, Chareyre C, Fraterno M, Rolland PH, et al. Hyperhomocysteinemia induces elastolysis in minipig arteries: structural consequences,arterial site specificity and effect of captoril–hydroclorothiazide. Matrix Biol 1998;17(8-9):559–574.

80. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstorm LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. JAMA 1997;227:1775–1781.

81. Sutton TK, Bostorm A, Selbhub J, Zeigler JC. High homocysteine levels are independently related to isolated systolic hypertension in older adults. Circulation 1997;96:1745–1749.

82. Malinow MR, Nieto FJ, Szklo M, Chambless LE, Bond G. Carotid artery intimalmedial wall thickening and plasma homocysteine in asymptomatic adults. Circulation 1993;87:1107–1113.

83. Selhub J, Jacques PF, Bostorn AG, Agostino RB, Wilson PWF, Belanger AJ, et al. Association between plasma homocysteine concentrations and extra-cranial carotid artery stenosis. N Engl J Med 1995;32:218–220.

84. Montalescot G, Ankri A, Chadefaux VB, Blacher J, Philippe F, Drobinski G, et al. Plasma homocysteine and the extent of atherosclerosis in patients with coronary artery disease. Int J Cardiol 1997;60:295–300.

85. Dimtri EZ, Calle B, Cecilia B, Sverre L, Valter S, Dag T, et al. Circulation 2004;109:601-606.

86. Ridker PM, Manson JE, Buring JE, Shih J, Matis M, Hennekens. Homocysteine and risk of cardiovascular disease among postmenopausal women. *JAMA* 1999;281(19):1817–1821.

87. Morris MS, Jacques PF, Rosenberg IH, Selhub J, Bowman BA, Gunter EW, et al. Serum total homocysteine concentration is related to self-reported heart attack or stroke history among men and women in the NHANES III. *J Nutr* 2000;130:3073–3076.

88. Knekt P, Alfthan G, Aromaa A, Heliovaara M, Maaniemi J, Rissanen H, et al. Homocysteine and major coronary events:a prospective population study amongst women. *J Intern Med* 2001;249(5):461–465.

89. Karthikeyan G, Prabhakaran D, Reddy KS. Plasma homocysteine levels and cardiovascular risk in Indians. JAPI 2002;50(suppl):24-28.

90. Kumar A, Khan SA, Parvez A, Zaheer MS, Rabbani MU. The prevalence of Hyperhomocysteinemia and its correlation with conventional risk factors in young patients with myocardial infarction in a tertiary care centre in india. Biomedical Research 2011;22(2):225-229.

91. Patil SS, Joshi R, Gupta G, Reddy MV, Pai M, Kalantri SP. Risk factors for acute myocardial infarction in a rural population of central India: a hospital-based case-control study. Natl Med J Ind 2004;17:189-194.

92. Goel PK, Bharti BB, Pandey CM, Singh U, Tewari S, Kapoor A, et al. A tertiary care hospital-based study of conventional risk factors including lipid profile in proven coronary artery disease. Ind Heart J 2003;55:234-240.

93. Mammi MV, Pavithran K, Rahiman PA, Pisharody R, Sugathan K. Acute myocardial infarction in north kerala a 20 year hospital study. Ind Heart J 1991;43:93-96.

94. Negus BH, Willard JE, Glamann DB, Landau C, Synder RW, Hillis LD, et al. Coronary anatomy and prognosis of young asymptomatic survivors of acute myocardial infarction. Am J Med 1994;96:354-358.

95. Kamala K, Lakshmi AV. Role of nutritional supplementation in reducing the levels of homocysteine. JAPI 2002;50:36-42.

96. Eric BR, Walter CW, Hu FB, Sampson L, Colditz GA, Manson JE, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. JAMA 1998;279: 359-364.

97. Jayantee K, Usha KM, Amit KS, Bindu IS. A study of Homocysteine level in North Indian subjects with specisl reference to their dietary habit.The European e-journal of clinical nutrition and metabolism 2007;2(6):116-119.

98. Arshad HL, Allah NM, Afsheen MS, Syed FA, Muhammad SM. Pakistan Journal Of Nutrition 2009;8(11):1753-1755.

99. Patil CN, Christopher CP, Chakrapani M. A study of risk factors of acute myocardial infarction in young adults. KJMS 2005;4(1):44.

100. Ueland PM, Refsum H, Stabler SP, Malinow MR, Andersson A, Allen RH. Total homocysteine in plasma or serum: methods and clinical applications. *Clin Chem* 1993;39(9):1764-79.

101. Primus FJ, Kelley EA, Hansen HJ, Goldenberg DM. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy. Clin Chem 1988;34(2):261-4.

102. Schroff RW, Foon KA, Beatty SM, Oldham RK, Morgan AC. Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. Cancer Res 1985;45:879-85.

103. Boscato LM, Stuart MC. Heterophilic antibodies: A problem for all immunoassays. Clin Chem 1988;34(1):27-33.

PROFORMA

TITLE OF THE STUDY: "HOMOCYSTEINE LEVELS IN ACUTE MYOCARDIAL INFARCTION AND FIRST DEGREE RELATIVE".
CASE NO:
NAME OF THE PATIENT:
I.P.NO:
AGE:
SEX:
OCCUPATION:
ADRESS:

DATE OF ADMISSION:
DATE OF DISCHARGE/DEATH:
NAME OF THE FIRST DEGREE RELATIVE:
AGE OF THE FIRST DEGREE RELATIVE:
SEX OF THE FIRST DEGREE RELATIVE:
RELATION WITH THE PATIENT:
NAME OF THE CONTROL:
AGE OF THE CONTROL:
SEX OF THE CONTROL:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

1. Chest pain

Site	substernal/left side/right side
Onset	sudden/insidious
Nature	heavy/squeezing/gripping/crushing/burning
Duration	_____
Radiation	L-arm/R-arm/back/neck/jaw/shoulder/ear
Severity	mild/moderate/severe
Aggravating factors	exertion/stress/heavy meals/others
Precipitating factors	exertion/stress/heavy meals/others
Relieving factors	rest/posture/drugs

Associated symptoms -sweating/giddiness/nausea/ vomiting/cough/others

2. Dyspnoea

Duration	_____
Onset	sudden/insidious
Onset in relation to pain	_____
Aggravating factors	exertion/stress/heavy meals/others

Precipitating factors	exertion/stress/heavy meals/others
NYHA Class	I / II / III / IV
PND	Yes/No
Orthopnoea	Yes/No

3. Palpitation

Onset	sudden/insidious
Onset in relation to pain	_____
Nature	continuous/intermittent
Duration	_____
Precipitating factors	exertion/excitement/fear/drugs/others
Relieving factors	rest/drugs/other

4.SWEATING YES/NO

Duration

Onset associated with pain

5.SYNCOPE YES/NO

6.PAIN ABDOMEN YES/NO

7.OTHER SYMPTOMS

Past history

Anginal pain	Yes/No	Duration-
Diabetes mellitus	Yes/No	Duration-
Hypertension	Yes/No	Duration-
Dyslipidemia	Yes/No	Duration-
Ischemic heart disease	Yes/No	Duration-
SIMILAR COMPLAINTS	YES/NO	
Cerebrovascular accident	Yes/No	
Thyriod disorder	Yes/No	
Rheumatic fever	Yes/No	
Liver disease	Yes/No	
Renal disease	Yes/No	

Pesronal history

Diet	vegetarian/non-veg/mixed
Appetite	good/poor
Bowel habit	normal/constipation/diarrhea
Bladder	normal/polyuria/oliguria
Physical activity	Sedentary/Moderate/Heavy

Smoking	beedis/cigggarettes	
	duration	_____yrs
	number	_____/day.
Alchol	duration	_____years.
	quantity	_____
Tobbaco chewing	yes/no	
Marital life	single/married.	

Treatment history:Any intake of anti convulsants –yes/no.

Bronchodilators-yes/no.

methotrexate –yes/no

cyclosporine-yes/no.

Family history

Ischemic heart disease	Yes/No
Diabetes	Yes/No
Hypertension	Yes/No
Dyslipidemia	Yes/No
Sudden deaths	Yes/No
Other illnesses	Yes/No

MENSTRUAL HISTORY

1) Age of menarche
2) Married life/no of children
3) Age of menopause

GENERAL PHYSICAL EXAMINATION

1)	Appearance	normal/ill looking
2)	Pallor	present/absent
3)	Icterus	present/absent
4)	Cyanosis	present/absent
5)	Clubbing	present/absent
6)	Signs of hyperlipidemia	xanthoma /xanthalesma/arcus senilis
7)	Pedal edema	present/absent
8)	Significant lymphadenopathy	present/absent
9)	Height	_____cm.
10)	Weight	_____kg.
11)	BMI	
12)	Thyroid	normal/enlarged.

Vitals

Pulse _____/min

Peripheral pulses- Felt/Not felt

Locomotar brachii-seen/Not seen

B.P. _____mm Hg

Respiratory rate _____/min

Temperature _____^{0} Celsius

SYSTEMIC EXAMINATION-

CARDIOVASCULAR SYSTEM

INSPECTION

JVP

1) Shape of chest normal/abnormal
2) Precordial pulsations yes/no
3) Apical impulse _____
4) Pulsations (epigastric,parasternal) yes/no.

PALPATION

1) Apical impulse site _____
2) Apical impulse character normal/tapping/hyperdynamic/heaving.
3) Parasternal heave
4) Epigastric pulsations
5) Trill
6) Other palpable sounds

PERCUSION

Cardiac borders

Liver dulness

ASCULTATION

1) Heart sounds normal/faint/accentuated
2) Added sounds S3/S4/S3S4
3) Murmur yes/no
    1. Site
    2. Grade
    3. Position best heard
    4. Radiation

2. Respiratory system examination:

Rate	_____/min
Rhythm	regular/irregular
Depth	normal/deep/shallow
Breath sounds	vescicular/bronchial/others
	Wheeze/crepitations/ronchi/others
Inspection	
Palpation	
Percussion	

3. Abdominal examination

Tenderness	present/absent
Hepatomegaly	present/absent
Splenomegaly	present/absent
Ascites	present/absent
Other findings	Yes/No

4.Central nervous system

Higher mental functions	orientation / memory
Speech	normal/abnormal
Cranial nerves	normal/abnormal
Motor system	normal/abnormal
Sensory system	normal/abnormal
Cerebellar system	normal/abnormal
Autonomic nervous system	normal/abnormal
Optic fundus	normal/abnormal

INVESTIGATIONS

1) Haemogram Hb TC DC-N- L- M-
   Platelets- ESR-
2) Urine Albumin-
   Sugar-
   Microscopy-
3) Blood sugar RBS FBS PPBS
4) Blood urea Sr. creatinine
5) Serum electrolytes Sr. sodium Sr.potassium

6) Lipid profile Sr. cholesterol- Triglycerides-
LDL - HDL-

7)Liver function test- Sr.total bilirubin-
Sr.direct bilirubin-
SGOT- SGPT- ALP-

8)CPK-MB/CARDIACTROPONINS

9)TSH-

10)Serum homocysteine of the patient-

11)Serum homocysteine of the first degree relative-

12)Serum homocysteine of the control-

13) E.C.G

Rate _____/min
Rhythm _____
Voltage _____
Mechanism _____
Axis _____
Position _____
P-wave _____
Q-waves _____
QRS comlpex _____
PR interval _____
Q-T interval _____
ST segment _____
T wave _____
Remarks _____

14)ECHOCARDIOGRAM

15)OTHERS

FINAL DIAGNOSIS

TREATMENT GIVEN

OUTCOME

DISCUSSION

SIGNATURE OF GUIDE **SIGNTURE OF CANDIDATE.**

KEYS TO MASTER CHART

SL NO	-	serial no
IP NO	-	Inpatient number
M	-	Male
F	-	Female
Y	-	Present
N	-	Not present
V	-	Vegetarian
NV	-	Non vegetarian
RBS	-	Random blood sugar
CK-MB	-	Creatine kinase (muscle, brain)
HDL	-	High density lipoprotiene
LDL	-	Low density lipoproteine
SH	-	Serum homocysteine levels
SON	-	Son
DAU	-	Daughter
BRO	-	Brother
SIS	-	Sister
ECG	-	Electrocardiogram
MI	-	Myocardial infarction
RV	-	Right ventricular
Ext.	–	Extension

STATISTICAL FORMULA

If $x_1, x_2 \ldots . x_n$ are 'n' observations then,

(1) The arithmetic mean denoted by $\overline{x}$ or AM is calculated by the formula

$$x = \frac{\text{Sum of observations}}{\text{Total number of observations}}$$

$$\overline{x} = \frac{x_1 + x_2 + \ldots + x_n}{n} = \left[\frac{\Sigma x}{n}\right]$$

For a grouped data the A.M.

$$\overline{x} = \frac{\Sigma xf}{N}$$

where f = frequency

and N = total frequency

(2) The standard deviation denoted by 'σ' is calculated by the formula

$$\sigma = \sqrt{\Sigma \frac{(x - \overline{x})^2}{n}} \text{ if } n > 30$$

and

$$\sigma = \sqrt{\Sigma \frac{(x - \overline{x})^2}{n - 1}} \text{ if } n \leq 30$$

(3) The standard error is given by

$$SE = \left(\frac{\sigma}{\sqrt{n}}\right)$$

(4) Student's t-test is calculated by the relation

$$t = \frac{\left|(\overline{x} - \overline{y})\right|}{\sqrt{\left(\frac{s_1^2}{n} + \frac{s_2^2}{n_2}\right)}}$$

where $\overline{x}$ = mean of the first set of observation n_1
$\overline{y}$ = mean of the second set of observation n_2
s_1 = standard deviation of the first set
s_2 = standard deviation of the second set

(5) The calculated values are compared with the standard value at 0.05 level significance for the corresponding degrees of freedom
If $P<0.05$ the difference is considered as significant and
If $P>0.05$ the difference is considered as non significant

SL.NO	Name	IP.NO	Age	Sex	Chest pain	Dyspnoea	Palpitation	Sweating	Syncope	Vomiting	Diet	Family History	Smoking	Hypertension	Diabetismellitus	RBS(mg/dl)	Blood Urea (mg/dl)	Serum Creatine (mg/dl)	CK-MB(IU/L)	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL(mg/dl)	LDL(mg/dl)	Dyslipedemia	S.Homocysteine (case)(µmol/L)	Age of first degree relative	Sex of first degreerelative	Relation with patient	SH of frst degre relative	Age of control	Sex of control	SH of control	Electro cardiogram
1	Shanthamma	635691	47	F	Y	Y	N	Y	N	N	V	Y	N	N	N	110	26	1.4	106	201	202	42	124	Y	23.8	21	M	SON	26.8	45	F	9.76	Inferior wall MI
2	VenkataRamaiah	636860	75	M	Y	Y	N	Y	N	N	NV	N	Y	N	N	147	42	1.1	458	130	99	38	72	N	13.5	38	F	DAU	10.1	75	M	10.3	Extensive Anterior wall MI
3	Easikal	656065	43	M	Y	N	N	N	N	N	NV	N	N	N	N	154	31	0.9	13	146	148	49	70	N	19.2	19	F	DAU	16.1	45	M	21.6	Anterior wall MI
4	KrishnaReddy	656579	70	M	Y	Y	N	Y	N	N	NV	Y	Y	N	N	96	28	0.9	11	140	126	36	78	N	13.5	48	M	SON	13.3	70	M	7.08	Anterior wall MI
5	Kavitha	584616	27	F	Y	Y	Y	N	N	N	NV	N	N	N	N	112	21	0.9	28	142	145	35	42	N	8.4	31	F	SIS	14.5	29	F	9.74	Anterior wall MI
6	Amjad Khan	645890	33	M	Y	N	N	Y	N	N	NV	N	Y	N	N	146	22	0.9	645	283	185	40	206	Y	28.9	23	M	BRO	17	33	M	12.1	Inferior wall MI
7	Gangappa	583608	35	M	Y	Y	N	N	N	N	V	N	Y	N	N	144	21	1.4	855	230	185	39	154	Y	14.8	33	M	BRO	8.97	35	M	8.19	AnteroLateral wall MI
8	Nagaraj	645406	25	M	Y	N	N	Y	N	Y	V	N	Y	N	N	119	24	0.8	680	234	298	36	138	Y	42.7	24	M	BRO	13.1	25	M	13.08	Anterior wall MI
9	Venkataramanappa	654404	60	M	Y	Y	N	Y	N	N	V	Y	Y	Y	N	102	37	1.6	399	170	143	37	99	N	30.2	36	M	SON	9.2	60	M	10.6	Anterior wall MI
10	Ramachandrappa	653961	50	M	Y	N	N	Y	N	N	V	N	Y	Y	N	124	24	1.2	100	213	152	41	109	Y	34.3	21	M	SON	14.5	50	M	9.9	Anterior wall Mi
11	SalamSab	635421	70	M	Y	N	N	Y	N	N	NV	N	N	N	N	123	26	1.1	42	136	145	45	76	N	17.3	29	M	SON	16.2	70	M	12.08	Anterior wall MI
12	VenkataReddy	658335	53	M	Y	N	N	N	N	N	NV	N	Y	Y	Y	117	15	1	71	215	199	36	102	Y	34.9	22	M	SON	14.9	54	M	16.07	Inferoposterior wall MI
13	Dathatraiah	658027	58	M	Y	N	N	N	N	N	V	Y	N	N	N	119	23	1.1	32	219	165	35	124	Y	32.9	27	F	DAU	10.3	55	M	9.78	Anterior wall MI
14	ChandraGowda	647989	50	M	Y	Y	N	Y	N	Y	NV	N	N	N	N	115	24	1.2	51	194	101	47	89	N	18	24	M	SON	13.5	50	M	9.26	Anterior wall MI
15	Parvathamma	676589	75	F	Y	N	Y	Y	N	N	NV	Y	N	Y	Y	153	19	1.2	242	153	138	48	77	N	12.1	40	M	SON	12.1	75	F	10.98	Extensive Anterior wall MI
16	PooSwamy	620053	61	M	Y	N	N	N	N	N	NV	N	Y	N	Y	174	21	1.1	17	134	86	39	77	N	14.3	37	M	SON	11.7	63	M	11.08	Inferior wall MI
17	Dhamodharan	674627	55	M	Y	N	N	Y	N	N	NV	N	N	N	N	124	40	2	32	130	149	47	53	N	19.1	29	F	DAU	16.5	55	M	10.7	Inferior wall MI with RV Ext.
18	Muniyappa	719251	60	M	Y	Y	N	Y	N	N	V	Y	Y	Y	N	108	34	1.2	56	145	135	49	59	N	22.4	28	M	SON	14.9	60	M	11.21	Infero Posterior wall MI
19	Panjamani	676504	55	F	Y	N	N	Y	N	Y	V	N	N	Y	N	154	22	1	42	172	192	35	97	N	19.6	26	M	SON	14.6	55	F	7.98	Inferior wall MI with RV Ext.
20	NarayanRaju	679484	45	M	Y	N	N	N	N	N	NV	N	N	N	N	137	25	0.9	39	167	131	47	98	N	18.9	23	M	SON	13.5	45	M	10.78	Anteroseptal wall MI
21	Prasad	678412	42	M	Y	N	N	Y	N	N	V	N	Y	N	Y	213	16	1	15	170	122	35	110	N	14	45	M	BRO	15.7	44	M	9.98	Anterior wall MI
22	ChangalaRayappa	720951	70	M	Y	Y	N	Y	N	N	NV	Y	Y	N	N	106	32	1.3	33	121	86	30	73	N	11.6	32	M	SON	19.2	70	M	10.23	Inferior wall MI with RV Ext.
23	Venkatamma	720179	60	F	Y	Y	N	Y	N	N	NV	N	N	Y	Y	180	30	0.9	13	142	112	36	89	N	4.31	26	F	DAU	14.8	60	F	15.78	Anteroseptal wall MI
24	Kumar	726448	50	M	Y	N	N	N	N	N	NV	N	N	N	N	108	18	0.9	21	189	111	62	125	N	11.9	22	M	SON	14.2	50	M	15.23	Anterior wall MI
25	Ramaiah.D	726282	58	M	Y	N	N	N	N	N	V	N	N	N	N	98	36	1	20	121	110	27	72	N	14.4	28	M	SON	14.2	58	M	9.07	Anteroseptal wall MI

SL.NO	Name	IP.NO	Age	Sex	Chest pain	Dyspnoea	Palpitation	Sweating	Syncope	Vomiting	Diet	Family History	Smoking	Hypertension	Diabetismellitus	RBS(mg/dl)	Blood Urea (mg/dl)	Serum Creatine (mg/dl)	CK-MB(IU/L)	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL(mg/dl)	LDL(mg/dl)	Dyslipedemia	S.Homocysteine (case)(µmol/L)	Age of first degree relative	Sex of first degreerelative	Relation with patient	SH of frst degre relative	Age of control	Sex of control	SH of control	Electro cardiogram
26	Narayanappa	734100	75	M	Y	N	N	N	N	N	NV	Y	N	Y	Y	125	35	1.4	25	199	140	36	136	N	13.4	45	M	SON	9.83	75	M	7.87	Anteroseptal wall MI
27	Husmuddin	733767	65	M	Y	N	N	Y	N	N	NV	N	Y	N	N	107	20	1.1	26	151	83	46	88	N	9.23	35	M	SON	10.2	65	M	9.09	Inferior wall MI with RV Ext.
28	RaniRoselin	731700	45	F	Y	Y	N	Y	N	N	NV	N	N	Y	Y	130	18	0.8	23	234	167	36	108	Y	55.7	19	M	SON	14.6	45	F	15.12	Inferior wall MI
29	Muniyamma	731702	65	F	Y	N	N	N	N	N	NV	N	N	Y	N	103	20	1.1	34	143	97	42	56	N	11.1	34	F	DAU	13.5	65	F	16.78	Anteroseptal wall MI
30	Munivenkatappa	733503	85	M	Y	Y	N	Y	N	N	V	N	Y	Y	Y	213	30	1.3	40	187	131	36	125	N	33.5	58	M	SON	16	81	M	12.89	Anteroseptal wall MI
31	Ramana	728294	45	M	Y	Y	N	N	N	Y	V	N	Y	Y	N	129	27	1.5	189	205	156	34	102	Y	53.8	43	M	SON	9.89	45	M	10.98	Anterior wall MI
32	Balaraj	725293	52	M	Y	N	N	Y	N	N	V	N	Y	Y	Y	198	27	1.1	106	213	198	39	109	Y	54.6	24	F	DAU	10.4	41	M	9.08	Inferior wall MI with RV Ext.
33	Gopalappa	636181	67	M	Y	N	N	N	N	N	NV	N	N	N	N	132	33	1.1	116	177	106	49	89	N	21.4	24	M	SON	16.7	67	M	9.98	Anteroseptal wall MI
34	Vasudeva Holle	721540	53	M	Y	Y	N	N	N	N	V	N	Y	Y	Y	145	27	0.9	39	208	160	42	124	Y	42.5	23	F	DAU	19.5	53	M	15.89	Anterior wall MI
35	SyedAbdul Kareem	719911	41	M	Y	N	N	N	N	N	NV	N	Y	N	N	123	28	1	25	254	175	34	108	Y	43.6	19	M	SON	11.2	43	M	11.77	Anterior wall MI
36	Venkateshappa	716601	65	M	Y	N	N	N	N	N	V	N	N	Y	N	107	23	1	18	199	261	49	97	Y	26.1	33	M	SON	15.1	65	M	9.39	Anteroseptal wall MI
37	Narayanamma	736395	42	F	Y	N	N	N	N	N	NV	N	N	N	N	102	24	0.9	112	149	126	39	84	N	19.8	19	M	SON	19.3	43	F	7.8	Inferior wall MI with RV Ext.
38	CliveAnthonyBowers	736314	48	M	Y	Y	N	N	N	N	NV	N	N	N	N	145	37	1.1	105	132	98	59	65	N	13.5	22	F	DAU	10.5	48	M	11.8	Anteroseptal wall MI
39	Rudrappa	736241	70	M	Y	N	M	N	N	N	V	N	N	Y	N	108	22	0.8	640	207	151	36	107	Y	26.3	35	M	SON	17.4	70	M	9.7	Inferior wall MI
40	SriRamappa	722503	56	M	Y	N	N	Y	N	N	V	Y	N	N	N	105	12	0.8	24	187	145	42	89	N	14.2	28	F	DAU	14.7	56	M	15.9	Inferior wall MI with RV Ext.
41	Venkatesh	727867	40	M	Y	N	N	Y	N	Y	V	N	Y	Y	N	105	34	0.9	169	209	188	30	141	Y	23.5	42	F	SIS	10.6	40	M	14.6	Inferior wall MI
42	KodandaRamaReddy	723319	38	M	Y	Y	N	Y	N	N	V	N	Y	Y	Y	118	28	0.9	40	243	165	32	104	Y	48.9	39	M	BRO	19.5	38	M	9.07	Anteroseptal wall MI
43	SyedRajak	738467	42	M	Y	N	N	N	N	N	NV	N	N	N	N	103	18	0.9	165	132	75	54	96	N	16.2	41	F	SIS	13.6	45	M	12.08	Anteroseptal wall MI
44	MuniSwamy	738543	49	M	Y	N	N	Y	N	N	NV	N	Y	Y	N	120	20	0.8	88	210	145	25	98	Y	12.6	19	M	SON	16.6	50	M	10.97	Anteroseptal wall MI
45	Ramachari	738600	85	M	Y	N	N	Y	N	N	V	N	N	N	N	122	39	1	167	193	90	42	89	N	17.3	39	M	SON	13.2	85	M	11.6	Inferoposterior wall MI
46	SureshKumar	698320	47	M	Y	N	N	Y	N	N	V	N	Y	Y	Y	171	22	1	203	112	102	34	50	N	44.2	20	M	SON	12	45	M	14.97	Anterior wall MI
47	Mubarak	698651	37	M	Y	N	N	Y	N	N	NV	N	Y	Y	Y	63	32	1.3	33	231	307	45	123	Y	46.5	36	M	BRO	9.18	38	M	12.6	Inferior wall MI with RV Ext.
48	Raju	699288	50	M	Y	N	N	Y	N	N	V	N	Y	Y	Y	123	23	0.9	10	201	179	32	102	Y	63.1	23	M	SON	16.2	50	F	13.6	Inferior wall MI
49	MuniReddy	704210	50	M	Y	N	N	N	N	N	NV	Y	Y	N	N	124	36	1.3	46	154	137	37	79	N	13.2	22	F	DAU	11.2	50	M	14.21	Anterior wall MI
50	Prakash	699265	54	M	Y	Y	N	Y	N	N	V	N	Y	Y	Y	184	23	1	49	231	151	32	102	Y	43.5	26	M	SON	14.8	54	F	16.25	Anterior wall Mi