"TO STUDY PREVALENCE OF ACUTE MYOCARDIAL INFARCTION WITH ATYPICAL PRESENTATION – A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY"

REG NO. BG0112007

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"TO STUDY PREVALENCE OF ACUTE MYOCARDIAL INFARCTION WITH ATYPICAL PRESENTATION – A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0112007**

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LIST OF ABBREVIATIONS USED

/Min	-	Per minute
ACS	-	Acute coronary syndrome
AMI	-	Acute myocardial infarction
ASMI	-	Anteroseptal myocardial infarction
AV	-	Atrioventricular
AWMI	-	Anterior wall myocardial infarction
BP	-	Blood pressure
CAD	-	Coronary Artery Disease
CHD	-	Coronary heart disease
CK MB	-	Creatine kinase MB
CNS	-	Central nervous system
CVA	-	Cerebro vascular accident
CX	-	Circumflex artery
DM	-	Diabetes mellitus
e.g.	-	For example
ECG	-	Electrocardiogram
GI	-	Gastrointestinal
GRACE	-	Global Registry of Acute Coronary Events
HDL	-	High density lipoprotein
HLMI	-	High lateral wall myocardial infarction
IHD	-	Ischaemic heart disease
IP No.	-	In Patient Number
IWMI	-	Inferior wall myocardial infarction
LAD	-	Left anterior descending
LCA	-	Left coronary artery

LCX	-	Left circumflex
LDL	-	Low density lipoprotein
LMCA	-	Left main coronary artery
mg/dL	-	Milligram per deciliter
MI	-	Myocardial infarction
MIBG	-	Metaiodobenzylguanidine
mm Hg	-	Millimeters of mercury
mm	-	Millimeter
MPS	-	Myocardial perfusion
mV	-	Milli volt
n	-	Total number
NRMI-2	-	National Registry of Myocardial Infarction 2
NSTEMI	-	Non ST elevation myocardial infarction
PDA	-	Posterior descending artery
PET	-	Positron emission tomography
PTCA	-	Percutaneous transluminal coronary angioplasty
RCA	-	Right coronary artery
SMI	-	Silent myocardial infarction
SPECT	-	Single photon emission computed tomography
STEMI	-	ST elevation myocardial infarction
U.S.	-	United States
UK	-	United Kingdom
USA	-	United States of America
vs	-	Versus
WHO	-	World Health Organization
β	-	Beta

ABSTRACT

Background and objectives

Atypical myocardial infarction is characterized by lack of unequivocal objective signs of myocardial infarction and minimal, atypical, or no symptoms at all. This study was aimed to assess the prevalence of atypical MI.

Methodology

This one year hospital based cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients presenting with atypical myocardial infarction. Patients were assessed for clinical signs and symptoms, and underwent ECG for the diagnosis.

Results

During the study period that is, from January 2013 to December 2013 there were 526 admissions with acute myocardial infarction. Of these, 64 patients had atypical acute myocardial infarction and the prevalence was 12.16%. Atypical myocardial infarction was seen more commonly among males (70.31%; male to female ratio was 2.36:1) and in the age group between 51 to 60 years (32.81%) and mean age was 58.28 ± 12.55 years. More than half of the study population that is, 56.25% of the patients presented with history of diabetes mellitus and personal history of smoking was noted in 31.81%. Breathlessness was the commonest clinical presentation noted in 64.06% and commonest clinical sign was heart failure present in 32.81%. The investigations revealed raised random blood sugar levels in 65.60%, raised CK MB in 90.62%, and troponin I

was found to be raised in all the patients (100%). Most of the patients were diagnosed to have anterior wall myocardial infarction (43.75%) followed by anteroseptal MI (21.88%).

Conclusion and interpretation

Overall the present study showed higher prevalence of atypical myocardial infarction especially in males and aged above 50 years. Further, this subset of patients may present with history of diabetes mellitus and essential hypertension or hypertension with symptoms of breathlessness and sweating.

Keywords

Anterior wall myocardial infarction; Atypical myocardial infarction; Myocardial infarction;

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INTRODUCTION

Asian Indians have considerably higher prevalence of premature Coronary Artery Disease (CAD) and standardized mortality rates for CAD compared with Europeans, Chinese and Malays.[1] Over the last four decades there has been a 10-fold increase in the prevalence of coronary artery disease in urban area of India. The overall rate of Coronary artery disease was 11.0% in Chennai Urban population.[1]

Myocardial infarction (MI) remains a major clinical problem and the leading causes of mortality in the world. In the United States alone, approximately one million people suffer MI each year. In the UK, the annual incidence of MI (using 2006 CHD mortality data) was estimated to be about 146,000 of all aged individuals (men: ∼87,000 and women: ∼59,000), and the estimated prevalence in those aged >35 years is more than 1.4 million (men: ∼970,000 and women: ∼439,000).[2] MI can be defined by pathology as myocardial cell death due to prolonged ischemia.[3] The most common cause of MI is coronary atherosclerotic plaque rupture or erosion, resulting in the exposure of thrombogenic contents to the blood. This leads to thrombus formation and consequently MI. Several risk factors are associated with MI.[2]

The risk factors include age, gender, low-birth weight, race/ethnicity, genetic factors (non-modifiable risk factors), hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, less physical activity, obesity, and body fat distribution (well-documented and modifiable risk factors) and metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive use, sleep-disordered breathing, migraine headache, hyperhomocysteinemia, elevated lipoprotein(a), elevated lipoprotein-associated phospholipase, hypercoagulability, inflammation, infection (less well-documented or potentially modifiable risk factors).[4]

According to WHO's definition, a myocardial infarction occurs if at least two of three criteria are fulfilled: typical ischaemic chest pain; raised concentrations of creatine kinase-MB in serum; and typical electrocardiographic findings, including development of pathological Q-waves.[5]

The ESC/ACC definition fits with the patient's clinical course. Patients do not present with overt myocardial infarction, but with acute chest pain suggestive of acute coronary pathology, characterised by presence or absence of ST-segment elevation, and by presence or absence of biochemical markers of myocardial injury.[6]

Patients with typical myocardial infarction may have fatigue, chest discomfort and malaise following prodromal symptoms in the days preceding the event. Typical chest pain in acute myocardial infarction is characterized by intense and unremitting for 30-60 minutes, retrosternal and often radiates up to the neck, shoulder, and jaw and down to the ulnar aspect of the left arm and usually described as a substernal pressure sensation that also may be characterized as squeezing, aching, burning, or even sharp. Some patients, the symptoms may be epigastric, with a feeling of indigestion or of fullness and gas.[7]

However, a substantial number of myocardial infarctions (MIs) are asymptomatic or associated with minor and atypical symptoms, and are found accidentally during routine electrocardiogram (ECG) examinations that reveal the existence of abnormal Q waves. The possible causes of blunted MI perception in some patients remain ill defined, but there may be some impairment of the stimulation of cardiac receptors, impulse initiation, or conduction, or of cerebral pain perception.[8] Symptoms are often atypical or even absent, especially in diabetic patients a population particularly at risk for coronary artery disease (CAD).[9] Compared with the frequency of silent myocardial ischaemia, which is defined as evidence of myocardial ischaemia in the absence of signs of angina, the frequency of silent MI, which is unequivocal objective signs of infarction accompanied by unrecognized minimal, atypical symptoms or no symptoms at all, is less well known.[10]

Atypical myocardial infarction is an unrecognized myocardial infarction charcterised by a negative history of chest pain, with ECG evidence of infarction and raised serum enzyme levels.

The atypical myocardial infarction (MI) represents an infamous problem for emergency physicians. Given the overwhelming number of patients that present to the emergency department with symptoms that could be suggestive of an acute coronary syndrome (ACS), the challenge to avoid missing this diagnosis is a daunting task. Heightened awareness among physicians of the atypical MI issue, together with improved technology for diagnosis of cardiac ischemia, has contributed to reducing the percentage of atypical MIs.

Nonetheless, atypical MI remains one of the greatest sources of litigation against physicians. In addition, there is a paucity of studies that have described the characteristics of atypical myocardial infarction in our country. Also, the statistical data of patients having atypical myocardial infarction varies because of lack of appreciation of symptoms like chest pain. Early diagnosis and intensive therapy can save many sudden cardiac deaths and improve the prognosis of patients having atypical myocardial infarction. Hence the present study was undertaken to assess the prevalence of atypical MI so as to elaborate the clinical and diagnostic characteristics of the same.

OBJECTIVES

The objective of the present study was to assess prevalence of atypical myocardial infarction.

REVIEW OF LITERATURE

Coronary heart disease (CHD) is the number one cause of death in the Western world and as such constitutes an immense public health problem. While CHD mortality declined in the last four decades in the USA as life expectancy increased, the use of age-adjusted rates to describe the CHD mortality obscures the fact that the decline largely represents the postponement of CHD deaths until older age. Thus, the burden of CHD is increasing in parallel with the increase in life expectancy.[11]

As more persons live with heart disease, the burden of prevalent disease with its assorted comorbid complications is increasing. Thus, the matter of identifying persons with heart disease, measuring the incidence of disease and its outcome and how these may have changed over time becomes essential as multifaceted approaches to reduce the burden of disease including drug discovery, clinical trials and policies have shaped the practice of cardiology for decades and will likely continue to do so in the future. In this context, myocardial infarction occupies a central role in the assessment of the burden of heart disease.[11]

Acute myocardial infarction (AMI) is a common disease with serious consequences resulting in mortality, morbidity, and financial burden to the society. Coronary atherosclerosis plays a pivotal role as the underlying substrate in many patients. About 50% deaths associated with acute myocardial infarction occur within one hour of the event and are attributable to arrhythmia, most commonly ventricular fibrillation.

Coronary artery anatomy

Epicardial coronary artery system consists of the left and right coronary arteries, which normally arise from the ostia located in the left and right sinus of valsalva, respectively. The main arteries and major rami are usually subepicardial but those in the atrioventricular and interventricular sulci are deeply sited. Portions of epicardial coronary arteries may dip into the myocardium and be covered by ventricular muscle (myocardial bridge)

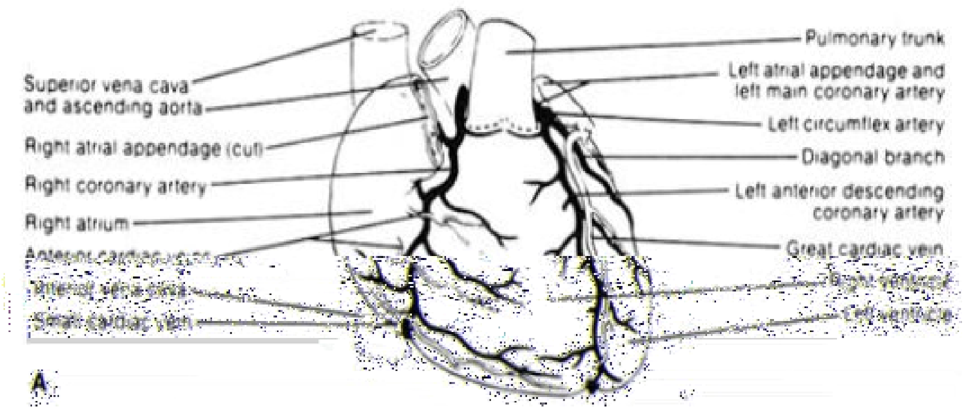


Figure 1. Coronary artery anatomy anterior view

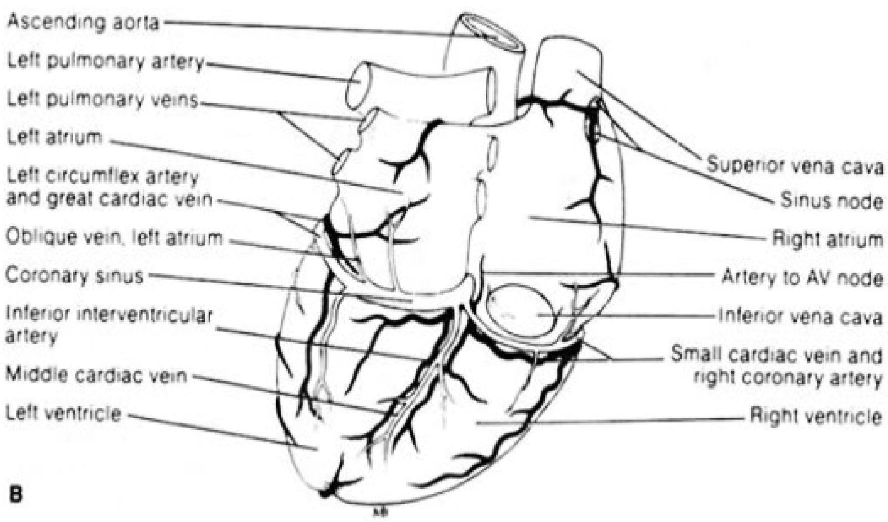


Figure 2. Coronary artery anatomy Posterior view

Left coronary artery (LCA)

Left main coronary artery (LMCA)

It arises from the left coronary sinus. The diameter ranges from 2.0 – 5.5 mm (mean 4 mm). It bifurcates into left anterior descending (LAD) and left circumflex (LCX) arteries.

Left anterior descending artery (LAD)

It passes down the anterior interventricular groove towards the cardiac apex. Luminal diameter ranges from 2 – 5 mm (mean 3.6 mm). It measures from 10 – 13 cm in length.

The branches are first diagonal, first septal perforator, right ventricular (not always seen in normal heart), other septal perforators (3 – 5 including the first), other diagonals (2 – 6 including the first). A left conus artery frequently leaves LAD artery near its start, anastomosing on the conus with that of RCA and vas vasorum of pulmonary artery and aorta. The first diagonal may arise separately from the left main. The septal branches leave LAD artery at 90º and plunge deeply into ventricular septum, supplies ventral two-thirds of the septum.

The LAD and its branches supply blood to ventricular septum, the anterior, lateral and apical wall of the left ventricle, most of the right and left bundle branches and anterolateral papillary muscle. The LAD can also provide collaterals to the anterior right ventricle via the circle of Vissuens, to the posterior ventricular septum by septals and to the posterior descending artery from distal LAD or diagonal branch.

Left circumflex (LCX)

It originates at the bifurcation of LMCA and passes down the left atrioventricular groove. Luminal diameter ranges from 1.5 – 5.5 mm and measures about 6 – 8 cm in length. The branches of LCX are variable. It gives sinus nodal artery in 40 -50%, left atrial circumflex branch, anterolateral, obtuse marginal, distal circumflex, posterior descending in 10 – 15%. The obtuse marginal is the largest branch and is directed along the anterolateral wall towards the apex.

The regions supplied by left circumflex include the left atrial wall, the posterior and lateral left ventricle, the anterolateral papillary muscle, the sinus node (in 40 -50%) and when dominant (10 – 15%) AV node, proximal bundle branches, inferoposterior LV wall, posterior basilar ventricular septum.

Right coronary artery (RCA)

It arises from right aortic sinus at a point somewhat lower than the origin of LCA. If dominant, it measures 12 – 14 cm in length. The branches are – conus artery, artery to sinus node, anterior right ventricular branches, right atrial branches, acute marginal branch, posterior descending artery, artery to AV node. RCA before the right ventricular branch is called the proximal, thereafter the distal RCA. Occlusion of the proximal RCA leads to right ventricular infarction, with diminished function of the RV, possibly leading to under filling of the LV with hypotension and cardigenic shock. In proximal RCA occlusion there is also a high incidence of high degree AV nodal conduction disturbances.

With this anatomical description, we can conclude that the blood supply of the human myocardium is regional and each major branch of the coronary arteries supplies a specific segment of myocardium. Clinical studies of regional myocardial infarction in humans confirm the importance of occlusion of the subtending (infarct related) artery.

Variability in coronary circulation

Despite the position of the heart within the chest and the position of the great arteries as they arise from the heart, aortic and pulmonary valves normally have a single point of contact, with commissural apposition at this point. Coronary arteries almost always arise normally from the "facing" sinuses of Valsalva on either side of this point of commissural contact. Coronary arteries do not normally arise from "nonfacing" or most distant sinus; however, variations in coronary anatomy are common. Variations that occur in less than 1% of the general population may be considered abnormal or anomalies.[12]

Four percent of people have a third, the posterior coronary artery. In rare cases, a person will have one coronary artery that runs around the root of the aorta. Occasionally, a coronary artery will exist as a double structure (i. e. there are two arteries, parallel to each other, where ordinarily there would be one). In 51 (1.2%) of 4,250 patients studied by selective coronary arteriography, one or more major elements of the coronary arterial system originated from the sinuses of Valsalva in an ectopic manner. The majority of variations involved the left coronary artery. The majority of ectopic ostia were located in the right sinus of Valsalva. Failure to recognize variations in coronary arterial origin can prolong arteriography procedures and lead to errors in interpretation of coronary artery anatomy and pathology. It is concluded from this experience that the incidence and location of major variations in coronary arterial origin are relatively predictable. The data are useful in expediting coronary arteriography procedures and thus improving patient care.[13]

Coronary artery dominance

The artery that supplies the posterior descending artery (PDA) determines the coronary dominance.[14] If the posterior descending artery (PDA) is supplied by the right coronary artery (RCA), then the coronary circulation can be classified as "right- dominant". If the posterior descending artery (PDA) is supplied by the circumflex artery (CX), a branch of the left artery, then the coronary circulation can be classified as "left-dominant". If the posterior descending artery (PDA) is supplied by both the right coronary artery (RCA) and the circumflex artery, then the coronary circulation can be classified as "co-dominant".

Approximately 70% of the general population are right-dominant, 20% are co- dominant, and 10% are left-dominant. A precise anatomic definition of dominance would be the artery which gives off supply to the AV node i.e. the AV nodal artery. Most of the times this is the Right Coronary Artery.

Blood supply of the papillary muscles

The anterolateral papillary muscle more frequently receives two blood supplies: left anterior descending (LAD) artery and the left circumflex artery (LCX). It is therefore more frequently resistant to coronary ischemia (insufficiency of oxygen-rich blood). On the other hand, the posteromedial papillary muscle is usually supplied only by the PDA. This makes the posteromedial papillary muscle significantly more susceptible to ischemia. The clinical significance of this is that a myocardial infarction involving the PDA is more likely to cause mitral regurgitation.[15]

Coronary arterial flow

During contraction of the ventricular myocardium (systole), the subendocardial coronary vessels (the vessels that enter the myocardium) are compressed due to the high intraventricular pressures. However, the epicardial coronary vessels (the vessels that run along the outer surface of the heart) remain patent. Because of this, blood flow in the subendocardium stops. As a result most myocardial perfusion occurs during heart relaxation (diastole) when the subendocardial coronary vessels are patent and under low pressure. This contributes to the filling difficulties of the coronary arteries. Compression remains the same. Failure of oxygen delivery caused by a decrease in blood flow in front of increased oxygen demand of the heart results in tissue ischemia, a condition of oxygen debt. Brief ischemia is associated with intense chest pain, known as angina. Severe ischemia can cause the heart muscle to die from hypoxia, such as during a myocardial infarction. Chronic moderate ischemia causes contraction of the heart to weaken, known as myocardial hibernation.

In addition to metabolism, the coronary circulation possesses unique pharmacologic characteristics. Prominent among these is its reactivity to adrenergic stimulation. The majority of vasculature in the body constricts to norepinephrine, a sympathetic neurotransmitter the body uses to increase blood pressure. In the coronary circulation, norepinephrine elicits vasodilatation, due to the predominance of beta-adrenergic receptors in the coronary circulation. Agonists of alpha-receptors, such as phenylephrine, elicit very little constriction in the coronary circulation.

Anastomoses

When two arteries of the coronary circulation join, dual blood flow to a certain area of the myocardium occurs. These junctions are called anastomoses. If one coronary artery is obstructed by an atheroma, the second artery is still able to supply oxygenated blood to the myocardium. However this can only occur if the atheroma progresses slowly, giving the anastomoses a chance to proliferate. Under the most common configuration of coronary arteries, there exist two anastomoses on the posterior side of the heart. More superiorly, there is an anastomosis between the circumflex artery (a branch of the left coronary artery) and the right coronary artery. More inferiorly, there is an anastomosis between the anterior interventricular artery (a branch of the left coronary artery) and the posterior interventricular artery (a branch of the right coronary artery).

Acute myocardial infarction

Acute myocardial infarction (MI) portends important and substantial consequences. Angioplasty or fibrinolytic therapy to open the blocked coronary artery is proven to improve the patient’s chances of surviving without consequent morbidity or death. But the diagnosis is not always straightforward. The presentation of acute MI can vary widely, and a number of other conditions—many of them equally serious emergencies—can mimic its symptoms, electrocardiographic signs, and biomarker patterns.[16]

In an attempt to improve the accuracy of the diagnosis of MI, a multinational task force met in 1999 under the auspices of the European Society of Cardiology and the American College of Cardiology. The goal was to develop a simple, clinically oriented definition of MI that could be widely adopted. A document was created and published simultaneously in 2000.[17] These organizations updated their paper in 2007 with a new definition of acute MI to account for advances in diagnosis and management.[18]

Acute myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide. Myocardial infarction occurs when myocardial ischemia, a diminished blood supply to the heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death.

Critical myocardial ischemia can occur as a result of increased myocardial metabolic demand, decreased delivery of oxygen and nutrients to the myocardium via the coronary circulation, or both. An interruption in the supply of myocardial oxygen and nutrients occurs when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion.[19]

A high-grade (>75%) fixed coronary artery stenosis caused by atherosclerosis or a dynamic stenosis associated with coronary vasospasm can also limit the supply of oxygen and nutrients and precipitate an MI. Conditions associated with increased myocardial metabolic demand include extremes of physical exertion, severe hypertension (including forms of hypertrophic obstructive cardiomyopathy), and severe aortic valve stenosis. Other cardiac valvular pathologies and low cardiac output states associated with a decreased mean aortic pressure, which is the prime component of coronary perfusion pressure, can also precipitate MI.[19]

Myocardial infarction can be subcategorized on the basis of anatomic, morphologic, and diagnostic clinical information. From an anatomic or morphologic standpoint, the two types of MI are transmural and nontransmural. A transmural MI is characterized by ischemic necrosis of the full thickness of the affected muscle segment(s), extending from the endocardium through the myocardium to the epicardium. A nontransmural MI is defined as an area of ischemic necrosis that does not extend through the full thickness of myocardial wall segment(s). In a nontransmural MI, the area of ischemic necrosis is limited to the endocardium or to the endocardium and myocardium. It is the endocardial and subendocardial zones of the myocardial wall segment that are the least perfused regions of the heart and the most vulnerable to conditions of ischemia. An older subclassification of MI, based on clinical diagnostic criteria, is determined by the presence or absence of Q waves on an electrocardiogram (ECG). However, the presence or absence of Q waves does not distinguish a transmural from a nontransmural MI as determined by pathology.[19]

A consensus statement was published to give a universal definition of the term myocardial infarction. The authors stated that MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with MI. Myocardial infarction was then classified by the clinical scenario into various subtypes. Type 1 is a spontaneous MI related to ischemia from a primary coronary event (e.g., plaque rupture, thrombotic occlusion). Type 2 is secondary to ischemia from a supply-and-demand mismatch. Type 3 is an MI resulting in sudden cardiac death. Type 4a is an MI associated with percutaneous coronary intervention, and 4b is associated with in-stent thrombosis. Type 5 is an MI associated with coronary artery bypass surgery.[20]

Prevalence and risk factors

Myocardial infarction is the leading cause of death in the United States and in most industrialized nations throughout the world. Approximately 450, 000 people in the United States die from coronary disease per year. The survival rate for U.S. patients hospitalized with MI is approximately 95%. This represents a significant improvement in survival and is related to improvements in emergency medical response and treatment strategies.[19]

The incidence of MI increases with age; however, the actual incidence is dependent on predisposing risk factors for atherosclerosis. Approximately 50% of all MIs in the United States occur in people younger than 65 years. However, in the future, as demographics shift and the mean age of the population increases, a larger percentage of patients presenting with MI will be older than 65 years.[19]

Six primary risk factors have been identified with the development of atherosclerotic coronary artery disease and MI: hyperlipidemia, diabetes mellitus, hypertension, tobacco use, male gender, and family history of atherosclerotic arterial disease. The presence of any risk factor is associated with doubling the relative risk of developing atherosclerotic coronary artery disease.[19]

Dyslipidemia

Elevated levels of total cholesterol, LDL, or triglycerides are associated with an increased risk of coronary atherosclerosis and MI. Levels of HDL less than 40 mg/dL also portend an increased risk.[21]

Diabetes Mellitus

Patients with diabetes have a substantially greater risk of atherosclerotic vascular disease in the heart as well as in other vascular beds. Diabetes increases the risk of MI because it increases the rate of atherosclerotic progression and adversely affects the lipid profile. This accelerated form of atherosclerosis occurs regardless of whether a patient has insulin-dependent or non–insulin-dependent diabetes.[19]

Hypertension

High blood pressure has consistently been associated with an increased risk of MI. This risk is associated with systolic and diastolic hypertension. The control of hypertension with appropriate medication has been shown to reduce the risk of MI significantly.[22]

Tobacco Use

Certain components of tobacco and tobacco combustion gases are known to damage blood vessel walls. The body's response to this type of injury elicits the formation of atherosclerosis and its progression, thereby increasing the risk of MI. A small study in a group of volunteers showed that smoking acutely increases platelet thrombus formation. This appears to target areas of high shear forces, such as stenotic vessels, independent of aspirin use.[23]

Male Gender

The incidence of atherosclerotic vascular disease and MI is higher in men than women in all age groups. This gender difference in MI, however, narrows with increasing age.[19]

Family History

A family history of premature coronary disease increases an individual's risk of atherosclerosis and MI. The cause of familial coronary events is multifactorial and includes other elements, such as genetic components and acquired general health practices (e.g. smoking, high-fat diet).[19]

Pathophysiology and Natural history

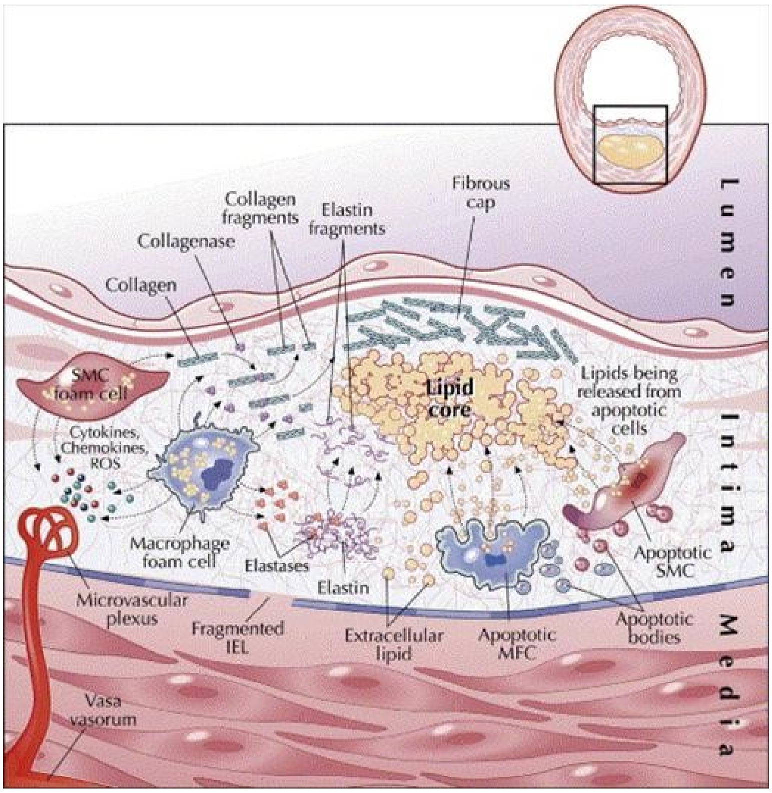


Figure 3. Atherosclerotic plaque

Most myocardial infarctions are caused by a disruption in the vascular endothelium associated with an unstable atherosclerotic plaque that stimulates the formation of an intracoronary thrombus, which results in coronary artery blood flow occlusion. If such an occlusion persists for more than 20 minutes, irreversible myocardial cell damage and cell death will occur. The development of atherosclerotic plaque occurs over a period of years to decades. The two primary characteristics of the clinically symptomatic atherosclerotic plaque are a fibromuscular cap and an underlying lipid-rich core. Plaque erosion can occur because of the actions of matrix metalloproteases and the release of other collagenases and proteases in the plaque, which result in thinning of the overlying fibromuscular cap. The action of proteases, in addition to hemodynamic forces applied to the arterial segment, can lead to a disruption of the endothelium and fissuring or rupture of the fibromuscular cap. The loss of structural stability of a plaque often occurs at the juncture of the fibromuscular cap and the vessel wall, a site otherwise known as the *shoulder region.* Disruption of the endothelial surface can cause the formation of thrombus via platelet-mediated activation of the coagulation cascade. If a thrombus is large enough to occlude coronary blood flow, an MI can result.[19]

The death of myocardial cells first occurs in the area of myocardium most distal to the arterial blood supply: the endocardium. As the duration of the occlusion increases, the area of myocardial cell death enlarges, extending from the endocardium to the myocardium and ultimately to the epicardium. The area of myocardial cell death then spreads laterally to areas of watershed or collateral perfusion. Generally, after a 6- to 8-hour period of coronary occlusion, most of the distal myocardium has died. The extent of myocardial cell death defines the magnitude of the MI. If blood flow can be restored to at-risk myocardium, more heart muscle can be saved from irreversible damage or death.[19]

The severity of an MI depends on three factors: the level of the occlusion in the coronary artery, the length of time of the occlusion, and the presence or absence of collateral circulation. Generally, the more proximal the coronary occlusion, the more extensive the amount of myocardium that will be at risk of necrosis. The larger the myocardial infarction, the greater the chance of death because of a mechanical complication or pump failure. The longer the period of vessel occlusion, the greater the chances of irreversible myocardial damage distal to the occlusion.[19]

STEMI is usually the result of complete coronary occlusion after plaque rupture. This arises most often from a plaque that previously caused less than 50% occlusion of the lumen. NSTEMI is usually associated with greater plaque burden without complete occlusion. This difference contributes to the increased early mortality seen in STEMI and the eventual equalization of mortality between STEMI and NSTEMI after 1 year.[19]

Clinical classification

The new classification scheme of the different types of MI is as below.[18]

Type 1: Spontaneous myocardial infarction (MI) related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a: MI associated with percutaneous coronary intervention

Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy

Type 5: MI associated with coronary artery bypass grafting

The new classification scheme does not include myocardial necrosis from mechanical manipulation of the heart during open heart surgery, from cardioversion, or from toxic drugs. As clinicians are aware, it is not unusual to see elevated biomarker levels in a host of conditions unrelated to acute myocardial ischemia or MI. The new classification of acute MI is most helpful in this regard. It will likely be even more helpful in guiding treatment and management when new ultrasensitive troponin assays are widely introduced into clinical practice.[18]

The new classification also negotiates the controversy regarding elevated biomarker levels following percutaneous coronary intervention. In brief, elevation of biomarkers is not entirely avoidable even with a successful percutaneous coronary intervention, and furthermore, there is no scientific cutoff for biomarker elevations. So, by arbitrary convention, the troponin level must rise to more than three times the 99th percentile upper reference limit to make the diagnosis of type 4a MI. A separate type 4b MI is ascribed to angiographic or autopsy-proven stent thrombosis.[18]

Clinical features

Sir William Osler said, “Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.”[16]

Just so, patients with acute MI display a wide variety of presentations, from no symptoms (about 25%) to severe, crushing chest pain. Discomfort may occur in the upper back, neck, jaw, teeth, arms, wrist, and epigastrium. Shortness of breath, diaphoresis, nausea, vomiting, and even syncope may occur. Unlike in acute aortic dissection, the discomfort is not usually maximal at its onset: it builds up in a crescendo manner. It is not usually changed by position, but can lessen in intensity upon standing. The discomfort in the chest is deep and visceral, and typically not well localized. A pressure sensation, air hunger, or “gas buildup” can be described. The only symptom may be shortness of breath or severe diaphoresis. The symptoms can last from minutes to hours. Atypical or less-prominent symptoms may make the diagnosis more difficult in the elderly, patients with diabetes mellitus, and women.[16]

The physical examination during acute MI usually finds no clear-cut distinguishing features. The patient may appear pale and diaphoretic, and the skin cool to the touch. Heart sounds are generally soft. A fourth heart sound may be audible. Blood pressure may be high, but it can vary widely. In view of the wide variation in presentations, the history and physical findings can raise the suspicion of acute MI, but sequential electrocardiograms and measurements of biomarkers (troponin) are always necessary.[16]

Atypical myocardial infarction

Silent myocardial ischemia is defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents. Since its original description in the 1970s, it has undergone intensive investigation, and its clinical significance is now well established.[24]

Chest pain has been reported as a cardinal clinical feature among the patients with acute coronary syndrome (ACS). However, several patients exhibit the atypical or no symptom on initial evaluation. Atypical symptom was defined as the absence of chest pain before or during admission, and may have included gastrointestinal or respiratory symptoms such as dyspnea, nausea, vomiting, and abdominal discomfort. Patients who present without chest pain are frequently misdiagnosed, and less likely to receive optimal treatment for ACS. Consequently, greater in-hospital morbidity, and mortality are noted. Therefore, understanding the factor associated with atypical presentations may help in the earlier detection and treatments in patients with ACS. Prior to discussing the risk factor, clarifying the concept of symptom in patients with ACS is needed to figure out this theme. In this manuscript, atypical presentation is used interchangeably 1 or 1+2 in figure 1 according to each reference.[24]

Definition of clinical presentation

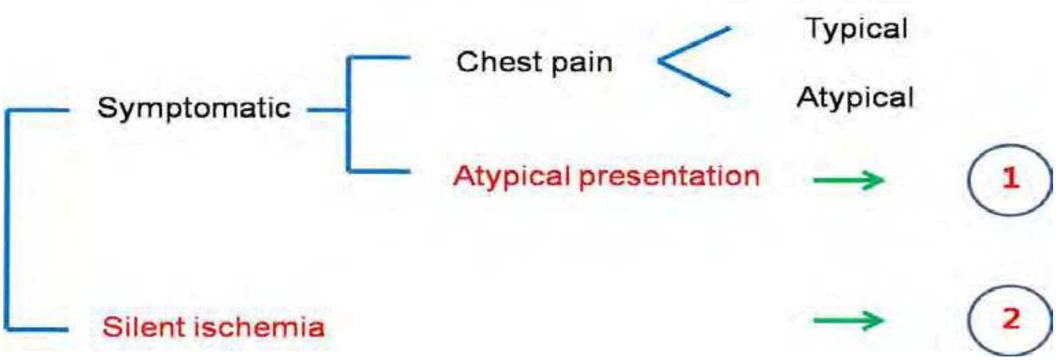


Figure 4. Definition of atypical presentation; 1 or 1+2[24]

<u>Ischemic chest pain</u>

There are several features that tend to distinguish ischemic chest pain from non-cardiac pain.[24]

Quality

Patients with ischemic pain often describe more as a discomfort than pain. Typical pain is expressed by terms include squeezing, tightness, pressure, constriction, strangling, burning, heavy weight on chest. It is not generally described as sharp, knife- like, stabbing, and pins.[24]

Site

Ischemic pain is a diffuse discomfort that may be difficult to localize. The sensation is often located in the retro-sternal area but may be felt in the epigastrium, back, arms, or jaw. Pain radiating to the upper extremities is highly suggestive of ischemic pain.[24]

Onset

Ischemic pain is described as having a crescendo pattern (wax and wane), and is typically gradual in onset.[24]

Provocation and relieving factors

Ischemic pain is usually developed by situations such as exercise, emotional stress which increases cardiac oxygen demands. Chest pain that is reproduced on respiration, coughing, position change, palpation is often associated with not-ACS disease. Relief of pain after administration of nitroglycerin or gastro-intestinal cocktails (GI cocktails; viscous lidocaine and antacid) could not guarantee the cardiac or gastric origin pain.[24]

Atypical chest pain and presentation

The following characteristics were considered as more non-ischemic chest discomfort.[24]

- Sharp or knife like pain related to respiration, coughing
- Reproduced pain by movement or palpation
- Localized pain with one finger
- Radiating pain into the lower extremities or above the mandible
- Pain lasting for days or a few seconds

Atypical presentation was defined as the absence of chest pain before or during admission, and may have included gastrointestinal or respiratory symptoms such as dyspnea, nausea, vomiting, and abdominal discomfort. The prevalence of this presentation was 8.4% in the Global Registry of Acute Coronary Events (GRACE),[25] 33% in the National Registry of Myocardial Infarction 2 (NRMI-2)[26] and the dominant symptoms in these patients were dyspnea, nausea, syncope.[24]

Clinical characteristics and prognosis with atypical symptom

In NRMI-2 report,[26] patients with atypical presentation had a longer delay before hospital seek (mean, 7.9 vs. 5.3 hours), were less likely to be diagnosed with a myocardial infarction on admission (22% vs. 50%), and were less likely to be treated with optimal medical therapy [aspirin (60% vs. 85%), β-blocker (28% vs. 48%), heparin (53% vs. 83%)] and to receive thrombolytic therapy or primary percutaneous coronary intervention (25% vs. 74%).6 Its results were similar with GRACE report.[25] Not surprisingly, in-hospital mortality rates were much higher in patients with atypical presentation in both registry data (NRMI-2,[26] 23% vs. 9%; GRACE[25] 13% vs. 4%). Moreover, in-hospital complications were developed more in atypical presentation group.

Classification

SMI contributes to an already complex spectrum of elusive ischaemic mechanisms. In 1912, James Herrick discovered that myocardial ischaemia and pain were not synonymous in nature; rather, pain was a discriminate and unpredictable feature of myocardial ischaemia that could propose a threat for patients and their physicians.[27] Research papers that followed reported similar notions with major difficulties in the classification, recognition, diagnosis and treatment of myocardial ischaemia.[28]

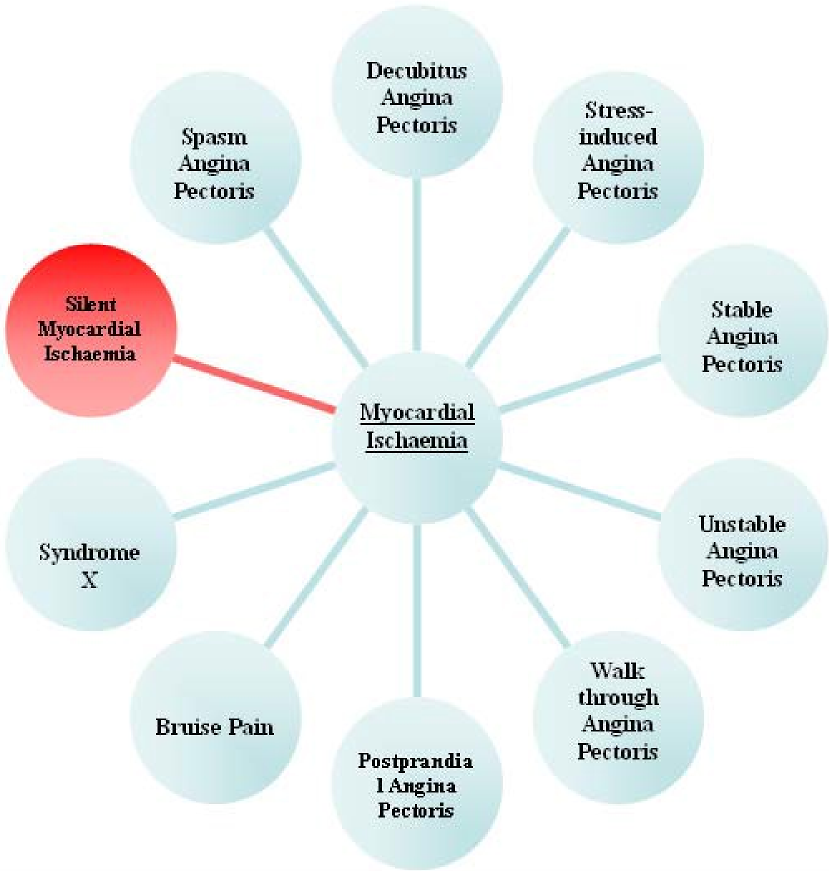


Figure 5. Spectrum of Myocardial Ischaemia[28]

SMI is not exclusive to populations with symptomatic Coronary Artery Disease (CAD). In fact, patients with no history of myocardial infarction or angina pectoris, have been found to exhibit characteristic ST segment changes and T-wave abnormalities during exercise stress testing without the usual complaint of pain.[29] Considering its variability in nature and the likely prognostic differences for each sub-group of patients, Cohn recommended that SMI be classified under three patient presentations.[29] It is important to note however that each clinically defined group gives rise to subgroups that will naturally have an increased risk and others with a lower risk for silent ischaemia and adverse outcome.[30]

Type 1

Silent Myocardial Ischaemia The literature suggests that SMI may well affect between 2.5% to 10% of the population before they are symptomatically aware of any underlying coronary artery malformations.[24,31-35] However, a study by Anand et al.[36] investigated 864 asymptomatic individuals with the use of electron beam tomography coronary calcium imaging and found that 18% of patients with moderate and 45% with severe atherosclerosis experienced episodes of silent ischaemia. This increase may reflect the differing risk factor profiles of sample populations, whereby, the mean number of risk factors may have been significantly higher in this study.[28]

Type 2

Silent Myocardial Ischaemia SMI is a significant predictor of death and re-infarction in post myocardial infarction patients.[37-39] Ouyang et al.[38] investigated 59 uncomplicated post infarction patients that underwent electrocardiography monitoring 4 days after admission, and found that 46% of these patients experienced asymptomatic daily life ischaemia. Fifty-two percent of patients experienced further cardiac events (death or post infarction angina or acute pulmonary oedema), while in comparison only 22% of patients without silent ischaemia experienced cardiac related events. Angiography revealed similar degrees of CAD in both populations. Narins et al.[40] went on to make the comparison that patients with painless ischaemic episodes during stress testing 1 to 6 months post coronary event (unstable angina or myocardial infarction) had superior left ventricular wall function and fewer recurring cardiac events than those with symptomatic ischaemia.

Type 3

Silent Myocardial Ischaemia The incidence of SMI in patients who experience regular episodes of angina pectoris varies considerably in the literature from 40% to 90%.[41-47] In addition, Deedwania and Carbajal highlighted that from 107 stable angina patients who underwent ambulatory electrocardiography monitoring, SMI was the most powerful and independent predictor of cardiac mortality and poor prognostic outcome.[48] It is also important to note that the majority of ischaemic episodes in this population manifest silently.[43]

Risk factors of atypical presentation

In NRMI-2 registry, Variables such as older age, gender, race, and co-morbidities (diabetes, stroke, heart failure) were considered as a risk factor for atypical symptom, and many studies have described the association of aging, gender, and diabetes mellitus.[26]

Independent risk factors for atypical presentation[26]

Variables	Odds ratio (95% CI)
Non white	1.05 (1.03-1.07)
Women	1.06 (1.04-1.08)
Diabetes mellitus	1.21 (1.19-1.23)
Age (10 year interval)	1.28 (1.26-1.28)
Prior stroke	1.43 (1.40-1.47)
Prior heart failure	1.77 (1.74-1.81)

Women

Atypical presentation in ACS was observed more commonly in women than men in large cohort studies. Women with coronary heart disease are older by 10 years and have more risk factors than men. It might be due to lack of early recognition and management.[24]

There are several differences between men and women in presentation. Women were less likely to have typical angina, rated their pain as more intense, used different words to describe it (more burning, sharp), and reported more non-pain-related symptoms than men. They experienced pain and other sensations in the neck area more frequently. Another feature of chest pain in women is that angina being induced by rest, sleep, mental stress instead of or addition to physical exertion. Psychosocial factors might also affect symptom presentation and diagnostic approach in women. For example, a history of anxiety disorders is associated with a lower probability of significant angiographic disease among women with chest pain symptoms. As women underestimate their own risk of coronary artery disease, diagnostic approach by physician could be altered less aggressively than men. Compared with men, women are less likely to perform cardiac monitoring, cardiac enzyme measurement, electrocardiogram, cardiac consultation, admission to a coronary care unit, undergo less coronary angiography, angioplasty, and bypass surgery.[24]

Prevalence of atypical presentation in large cohort[24]

Study	Year	Sample size	Mean	Women
GRACE[25]	1999-2002	20881	7.3%	10.6%
NRMI-2[26]	1994-1998	434877	28.6%	38.6%
Alabama UA Registry	1993-1999	4167	50.2%	53.0%
United Kingdom	1995	2096	17.6%	24.6%
Worcester MI Study	1986-1988	1360	18.0%	23.0%
Worcester MI Study	1997-1999	2073	30.9%	45.8%
26 hospitals CCU	2000	2113	18.7%	29.7%
Croatia	1990-1992	1996	12.4%	20.3%
Olmsted county	1985-1992	2271	25.0%	19.0%

Diabetes mellitus

Some patients with diabetes mellitus (DM) have a blunted perception of ischemic chest pain, which could result in atypical presentation. The suggested mechanisms of this phenomenon are as follows; 1) autonomic neuropathy, 2) prolongation of the anginal perceptual threshold.[24]

Sympathetic denervation diabetic patients have evidence of a significant reduction in MIBG uptake, most likely on the basis of autonomic dysfunction. Furthermore, diabetic patients with silent myocardial ischemia have evidence of a diffuse abnormality in metaiodobenzylguanidine (MIBG) uptake, suggesting that abnormalities in pain perception may be linked to sympathetic denervation. Similar finding has also been observed with positron emission tomography. Moreover, regional heterogeneity in sympathetic denervation could result in potentially life-threatening myocardial electrical instability that may lead to life-threatening arrhythmias.[24]

Another mechanism of abnormal perception is prolongation of the angina perceptual threshold during exercise. Anginal perceptual threshold (the time from onset of 0.1 mV of ST segment depression to onset of angina during treadmill exercise) is prolonged in diabetic patients with coronary artery disease. The permissive effect of a prolonged anginal perceptual threshold on exercise capacity is undesirable as reflected by its correlation with ischemia at peak exercise (r = 0.6, p less than 0.001): the longer the threshold, the greater the exercise capacity and the more severe the ischemia.[24]

Age and atypical presentation

Advanced age is an important predictor of atypical presentation and poor prognosis. Recent study in Korea examined and compared the risk factor associated with atypical presentation according to the age parameter. In this study, diabetes and hyperlipidemia significantly predicted atypical symptom in relatively young (<70 years) age group. Otherwise, co- morbid conditions such as stroke or chronic obstructive pulmonary disease were the positive predictors in relatively old age group (>70 years).[24]

Predicting factors of atypical presentation in younger and older patients[24]

Risk factors	Younger			Older		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Female gender	0.861	0.576-1.769	0.069	0.721	0.780-2.599	0.385

Hypertension	0.740	0.712-1.875	0.352	0.628	0.780-2.599	0.208
Diabetes	2.494	1.108-4.014	0.023	0.841	0.416-1.515	0.719
Hyperlipidemia	0.486	0.285-0.828	0.006	0.840	0.438-1.611	0.465
Co-morbidity	2.029	0.889-4.633	0.093	3.315	1.357-8.729	0.001
Smoking	0.595	0.345-1.025	0.061	0.575	0.255-1.297	0.157
ACS type	1.243	0.675-1.235	0.883	1.041	0.744-1.417	0.877

Pathophysiology

No discussion of silent ischemia is complete without consideration of the cardiac pain mechanism. Although much has been learned about this subject, much is still uncertain. The afferent fibers that run in the cardiac sympathetic nerves are usually thought of as the essential pathway for the transmission of cardiac pain.[49]

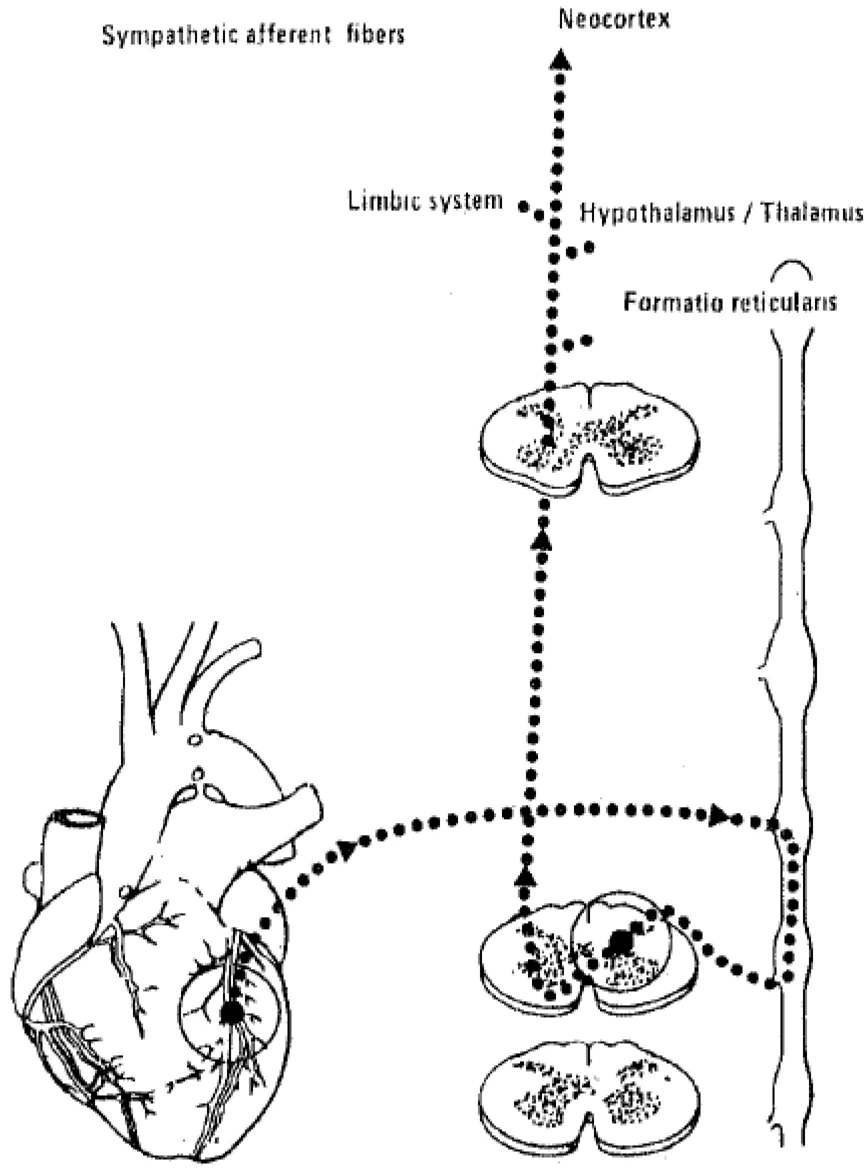


Figure 6. Mechanisms of cardiac pain. From Droste and Roskamm[50]

The atria and ventricles are abundantly supplied with sympathetic sensory innervation; from the heart, the sensory nerve endings connect to afferent fibers in cardiac nerve bundles, which in turn connect to the upper 5 thoracic sympathetic ganglia and the upper 5 thoracic dorsal roots of the spinal cord. Within the spinal cord, impulses mediated by this sympathetic afferent route probably converge with impulses from somatic thoracic structures onto the same ascending spinal neurons.

This would be the basis for cardiac pain referred to the chest, wall, arm, back etc. In addition to this “convergence-projection theory,” the contribution of vagal afferent fibers must be acknowledged for an explanation of cardiac pain referred to the jaw and neck. How these vagal fibers are activated remains unclear. Furthermore, somatic localization of ischemic pain cannot predict the site of myocardial ischemia (anterior, inferior, or lateral) from one patient to the next.[49]

The actual “trigger” that stimulates the sensory nerve endings remains elusive. If a chemical pain stimulus is involved, the substance that has been most recently linked to the production of angina-like chest pain is adenosine.[49]

Sylven et al[51] observed that an adenosine infusion resulted in chest pain even in patients without obstructive coronary artery disease. Subsequently, they gave varying amounts to healthy volunteers and caused dose-dependent chest pain in all of the volunteers. Concomitant dipyridamole administration (which reduces cellular uptake of adenosine) increased the pain response, whereas theophylline (a nonspecific adenosine antagonist) reduced the pain response.

When Crea et al[52] gave adenosine via intracoronary infusion to 22 angina patients, it reproduced chest pain significantly in 20 of 22 patients but without electrocardiographic evidence of ischemia. When the drug was infused into the right atrium, it failed to reproduce the pain. From these studies and others, it appears that adenosine is a mediator of cardiac and muscular ischemic pain. At one time, a mechanical stimulus (stretching of the coronary arteries) was also proposed as a cause of pain even when ischemia itself was not induced. This was suggested after watching the behavior of laboratory animals whose coronary arteries were stretched.

This theory has received increased support because of the observation that during percutaneous transluminal coronary angioplasty (PTCA) in humans, the greater the balloon inflation pressure, the more intense pain in the same individual.[53]

The pioneering somatic pain threshold studies of Droste and Roskamm[50] suggested differences between coronary patients either with or without angina during a positive exercise test. They studied 3 different modalities of somatic pain perception. When pain perception was determined by an electrical current applied to the thigh, asymptomatic patients had a significantly higher threshold. Subsequent studies from other laboratories confirmed their findings.

A central mechanism was suggested in 1996, by Rosen et al,[54] using PET scanning to measure cerebral blood flow in patients with and without silent ischemia. On the basis of their data, the authors postulated that abnormal central processing of afferent cardiac pain signals could be involved in the pathophysiology of this syndrome.

A possible role for endorphins in cardiac pain responses also has been studied. Varying concentrations of these opioid- like substances exist in plasma and cerebrospinal fluid and may be important in mediating pain sensitivity. The issue is not clear cut, as different laboratories that have measured plasma endorphin levels during and after exercise tests have produced conflicting results, and considerable overlap exists in values between patients with and those without silent ischemia.[49]

Data from PTCA studies by Falcone et al[55] have suggested a link between endorphin levels and symptoms, but Oldroy et al[56] found endorphin release to be common during both spontaneous and provoked acute myocardial ischemia and to have no correlation with intensity of chest pain. Thus, the evidence linking endorphins to silent myocardial ischemia is suggestive but not conclusive. This is true in nondiabetics as well as diabetics. Diabetics also have overt neuropathy as an additional contributing factor to their silent ischemia, although in many instances the neuropathy is subclinical and can only be detected by demonstration of autonomic impairment. According to a study,[57] the combination of microalbuminuria and silent ischemia in asymptomatic diabetics identifies a particularly high-risk subgroup for future cardiac events.

Benzodiazepines have been shown to interact with opioid antinociception. Considering the importance of inflammation and leukocytes in myocardial ischemia, could the expression of peripheral benzodiazepine receptors on leukocytes be different in patients with and without angina during myocardial ischemia? This is the question Mazzone et al[58] asked recently in a study of 57 patients. They found that the expression of these receptors was indeed higher in patients with silent ischemia. This same group of investigators also studied production of inflammatory cytokines in a similar patient population and reported that an “anti-inflammatory pattern” of cytokine production was observed in the patients with silent ischemia.[59] The authors concluded that the activation of the immune-inflammatory system may be crucial for production of anginal symptoms.

Hemodynamic Abnormalities

During Silent Ischemia Unlike the endorphin controversy, this is an area where increasing data have proven useful in clarifying physiological mechanisms. To begin with, PTCA has allowed the sequence of ischemic events to be precisely defined in a controlled setting. In their classic study, Sigwart et al[60] placed a catheter in the pulmonary artery and a high-fidelity micromanometer in the left ventricle via the transseptal approach in 12 patients. Based on their findings and those of others in subsequent studies, it is apparent that hemodynamic abnormalities occur first and that pain follows electrocardiographic changes and is the final event in the sequence of events that characterizes an episode of myocardial ischemia. The amount of myocardium rendered ischemic in humans is difficult to quantify, but comparisons between symptomatic and silent ischemia have been attempted using a variety of techniques.

For example, Hirzel et al[61] reported on both wall-motion disorders and hemodynamic changes in their series of 36 patients with exercise-induced ischemia. Under similar exercise conditions, comparable hemodynamic and wall-motion abnormalities indicative of ischemia were ob- served in patients with and without angina. Most, but not all, subsequent studies agreed with their findings. Some myocardial perfusion studies using radionuclear agents also tend to refute the hypothesis that lesser amounts of myocardium are injured during painless ischemia.[62]

Holter monitoring has also proven useful in clarifying pathophysiologic mechanisms during silent ischemia. Early studies of ambulatory ischemia noted that almost 80% of total ischemic episodes were silent and that most of the asymptomatic episodes were short, whereas the symptomatic ones were just as likely to be long as short.[63,64]

As more and more studies using the Holter monitor have been published, it is apparent that there is a circadian variation in ischemic episodes, with most coming after arousal in the morning, or waking and rising at night. This circadian variation is the same in both men and women. What triggers myocardial ischemia during certain activities and not during others? This is a question to which ambulatory ECG monitoring has helped provide answers by correlating ECG data to diaries of daily events, concurrent drawing of blood catecholamines, etc. A relation to enhanced platelet aggregation or variations in vascular tone has been suggested. The importance of physical exertion, anger, smoking, and mental stress have all been well documented with the latter receiving special attention.

Kop et al[64] measured heart rate variability using Holter monitoring 60 minutes before and after each of 68 ischemic events, most of which were silent. They concluded that “autonomic change consistent with vagal withdrawal can act as a precipitating factor for daily life ischemia in episodes triggered by mental activity.” One of the most intriguing physiological observations has been the steady increase in heart rate preceding the ischemic episode.[49]

Even when not frankly tachycardia, this increased heart rate varies suggests more of a “demand” than “supply” imbalance as a basis for many of the episodes that were once thought to be vasospastic in origin. Documenting silent ischemia in patients with true variant angina represents a unique problem because in its purest form ST elevation is the predominant finding. Criteria for ST elevation on the ambulatory ECG are not as well developed as for ST depression, but it is generally accepted that the abnormality should be profound (2 mm) to be considered significant.[49]

Overall, silent myocardial ischaemia is a common entity and has been closely studied in recent times. The mechanisms underlying its presence are becoming increasingly understood. Many ischaemic episodes are silent because they are either not severe enough or long enough to fully stimulate the anginal pain pathway. However, more prolonged severe episodes of angina can also be silent. This may be due to gating mechanisms at the level of the thalamus. These appear to vary with personality type and levels of endogenous endorphins, causing variation in pain threshold between individuals. In diabetic subjects cardiac autonomic neuropathy is also implicated resulting in interruption of the pain pathway.

METHODOLOGY

This one year cross-sectional study was undertaken at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013.

Study design and duration

The study design was a one year hospital based cross-sectional study.

Study period

This study was carried out from January 2013 to December 2013.

Source of Data

Patients with suspicion of atypical myocardial infarction at Department of Medicine and Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were enrolled.

Sample size

All the patients presenting with atypical myocardial infarction during the study were enrolled.

Selection criteria

Inclusion Criteria

- Patients presenting with suspected atypical myocardial infarction

Exclusion Criteria

- Patients with symptomatic myocardial infarction

Ethical clearance

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum.

Informed consent

The patients were screened for eligibility and those who fulfilled selected selection criteria were informed about the nature of study and included after obtaining a written informed consent (Annexure–I).

Data collection

Demographic data, history of other comorbid conditions and personal history were noted. The patients underwent clinical examination and systemic examination. These findings were noted on a predesigned and pretested proforma (Annexure-II).

Investigations

The patients underwent following investigations

- Electrocardiography
- CK MB
- Troponin I

- Random blood sugar

Statistical methods

The data obtained was coded and entered into the Microsoft Excel Spreadsheet (Annexure III). The categorical data was expressed in terms of rates, ratios and percentages and continuous data was expressed as mean ± standard deviation.

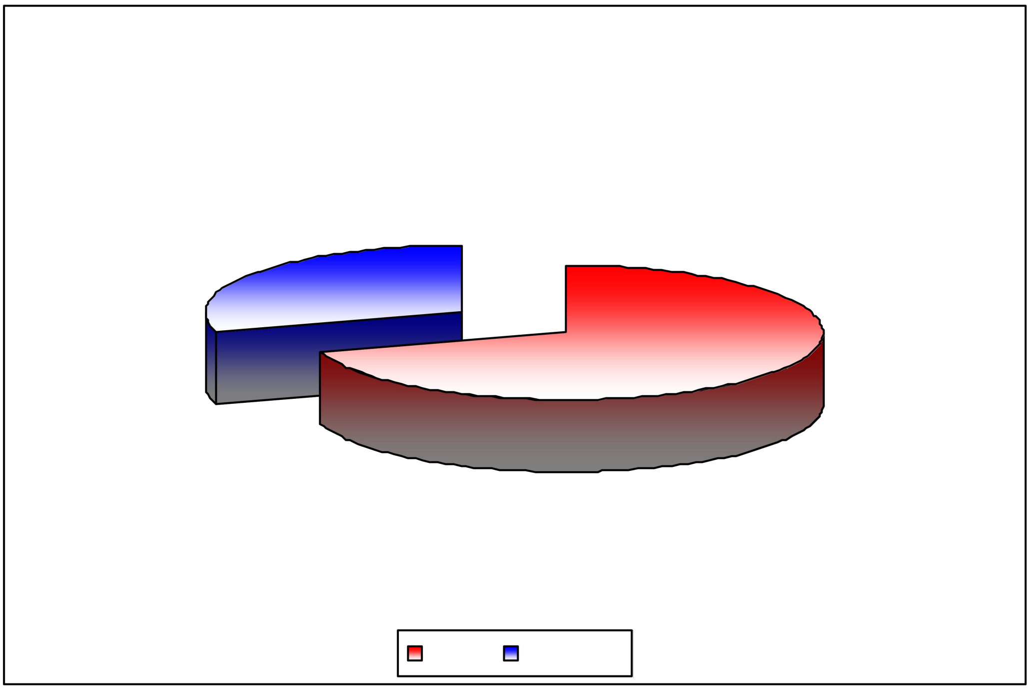
RESULTS

The present one year hospital based cross-sectional study was carried out at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013.

During the study period there were 526 patients admitted with acute myocardial infarction. Of these 64 patients presented with atypical acute myocardial infarction hence the prevalence of atypical myocardial infarction was 12.16%.

Table 1. Sex distribution

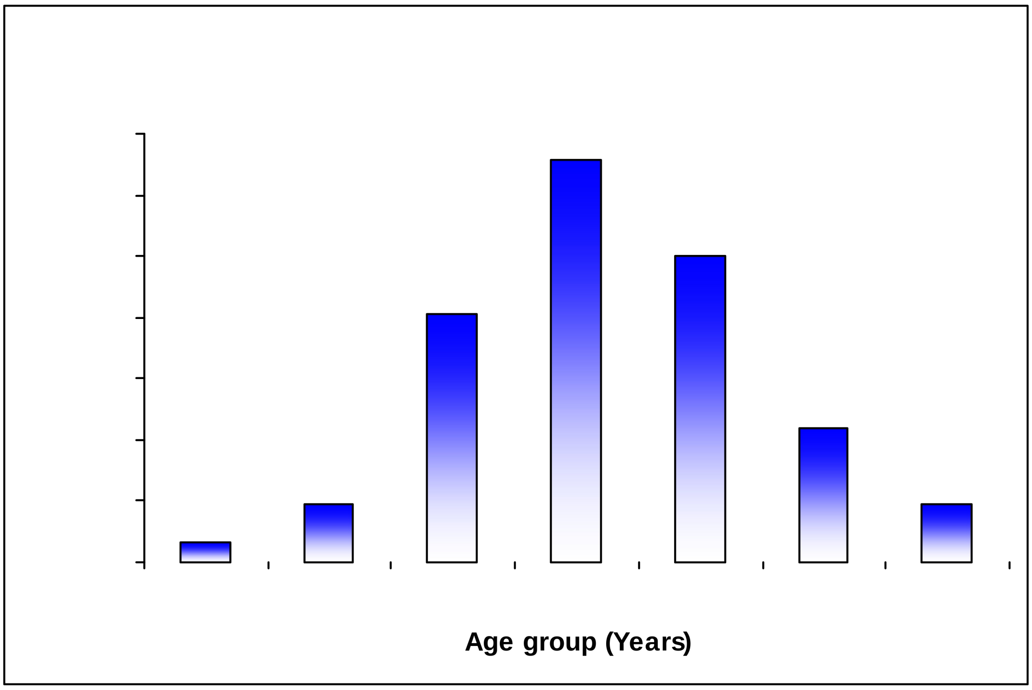
Sex	Distribution (n=64)	
	Number	Percentage
Male	45	70.31
Female	19	29.69
Total	**64**	**100.00**



In the present study 70.31% of the patients were males and 29.69% were females. The male to female ratio was 2.36:1

Table 2. Age distribution

Age group (Years)	Distribution (n=64)	
	Number	**Percentage**
≤ 30	1	1.56
31 - 40	3	4.69
41 - 50	13	20.31
51 - 60	21	32.81
61 - 70	16	25.00
71 - 80	7	10.94
> 80	3	4.69
Total	**64**	**100.00**

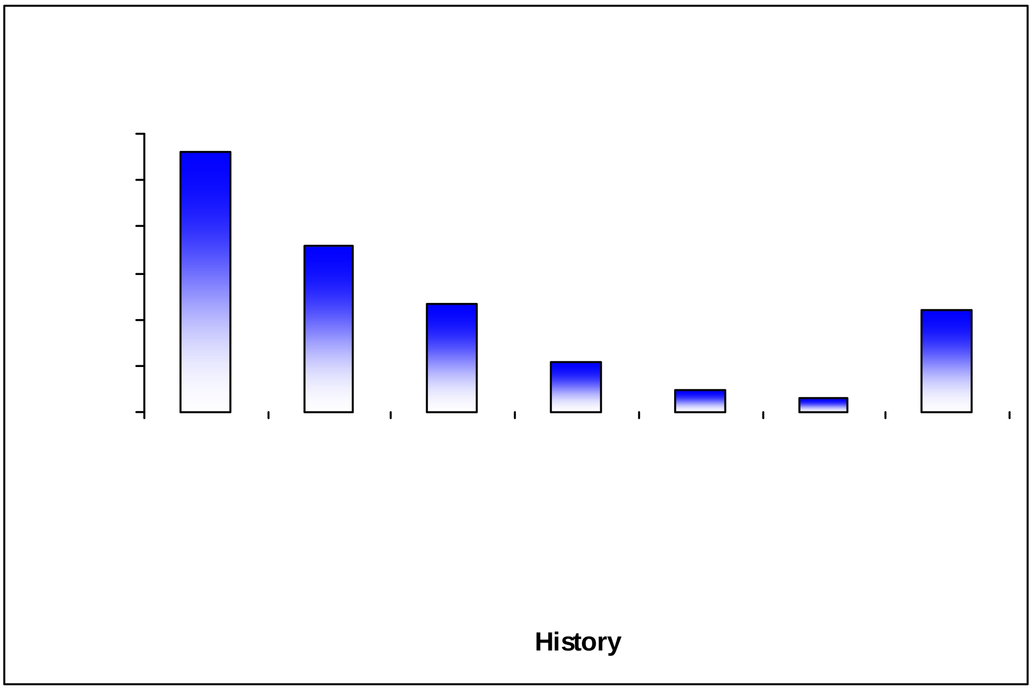


In this study most of the patients were aged between 51 to 60 years (32.81%). The age distribution of other patients is as shown in table 2 and graph 2. The mean age was 58.28 ± 12.55 years.

Table 3. History

History	Distribution (n=64)	
	Number	Percentage
Diabetes mellitus	36	56.25
Essential hypertension	23	35.94
Ischemic heart disease	15	23.44
Chronic kidney disease	7	10.94
Other heart disease	3	4.69
Cerebrovascular accident	2	3.13
Others	14	21.88

Multiple presentations hence total not shown

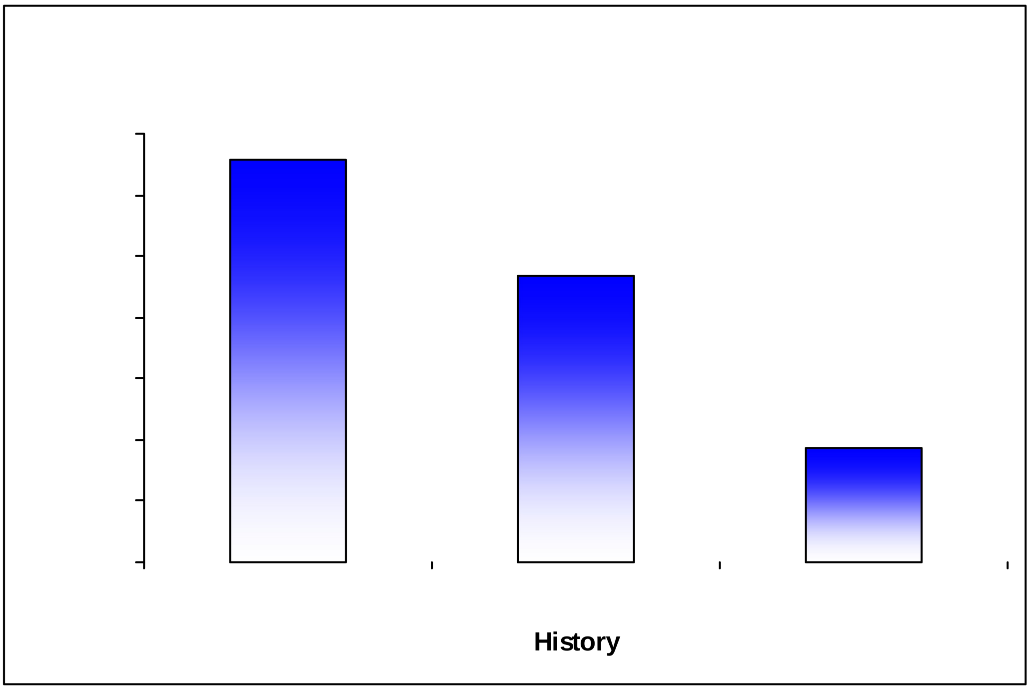


In the present study most of the patients (56.25%) reported history of diabetes mellitus followed by hypertension (35.94%), cerebrovascular accident (23.44%), chronic kidney disease (10.94%).

Table 4. Personal history

History	Distribution (n=64)	
	Number	Percentage
Smoking	21	32.81
Alcohol consumption	15	23.44
Tobacco chewing	6	9.38

Multiple presentations hence total not shown



In this study personal history of smoking, alcohol consumption and tobacco chewing was present in 31.81%, 23.44% and 9.38%.

Table 5. Family history

Family history	Distribution (n=64)	
	Number	Percentage

Diabetes mellitus	15	23.44
Iscahemic heart disease	13	20.31
Essential hypertension	8	12.50
Diabetes and IHD	5	7.81
Essential hypertension and IHD	2	3.13
Diabetes and hypertension	1	1.56
Not contributing	20	31.25

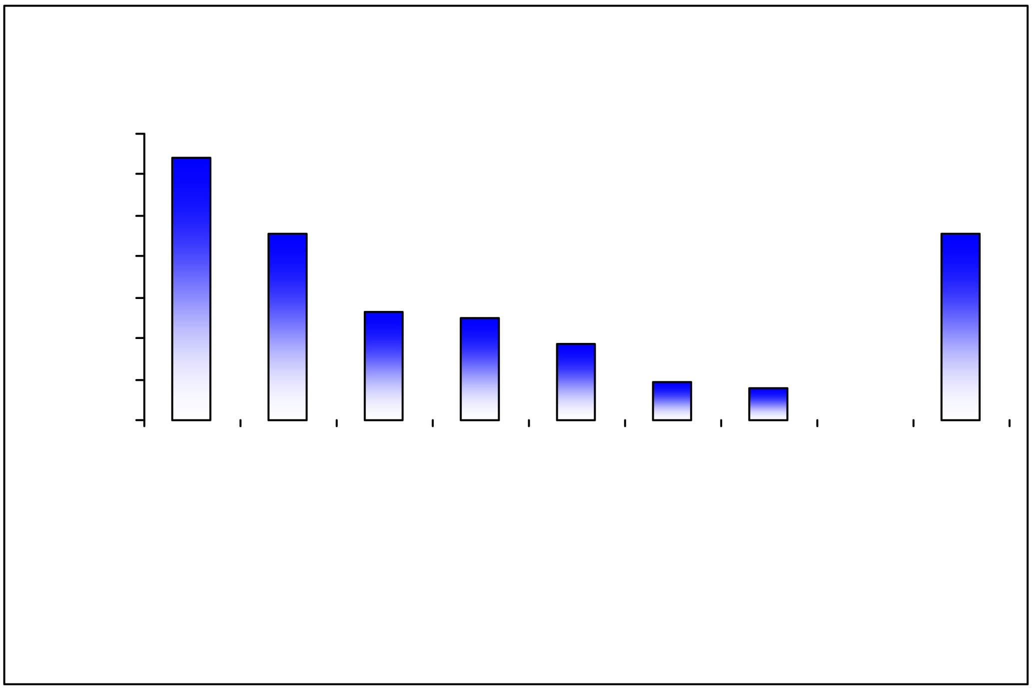
In this study the family history was reported by 68.75% of the patients and diabetes and ischaemic heart disease were noted in 23.44% and 20.31% of the patients.

Table 6. Clinical presentation

Presentation	Distribution (n=64)	
	Number	Percentage
Breathlessness	41	64.06
Sweating	29	45.31

Abdominal pain	17	26.56
Vomiting	16	25.00
Palpitation	12	18.75
Headache	6	9.38
Syncope	5	7.81
Chest pain	0	0.00
Other complaints	29	45.31

Multiple presentations hence total not shown



In this study breathlessness was the commonest clinical presentation (64.06%). The other presentations are as shown in table 6 and graph 5.

Table 7. Clinical examination findings

Vitals	**Distribution (n=64)**		**Distribution (n=64)**	
	Mean	**SD**	**Median**	**Range**

Pulse rate (/Minute)	88.20	25.81	84	0-192
Temperature	98.1	6.41	98.6	98.4-105
Systolic BP (mm Hg)	104.1	33.27	110	0-190
Diastolic BP (mm Hg)	60	29.6	70	0-110

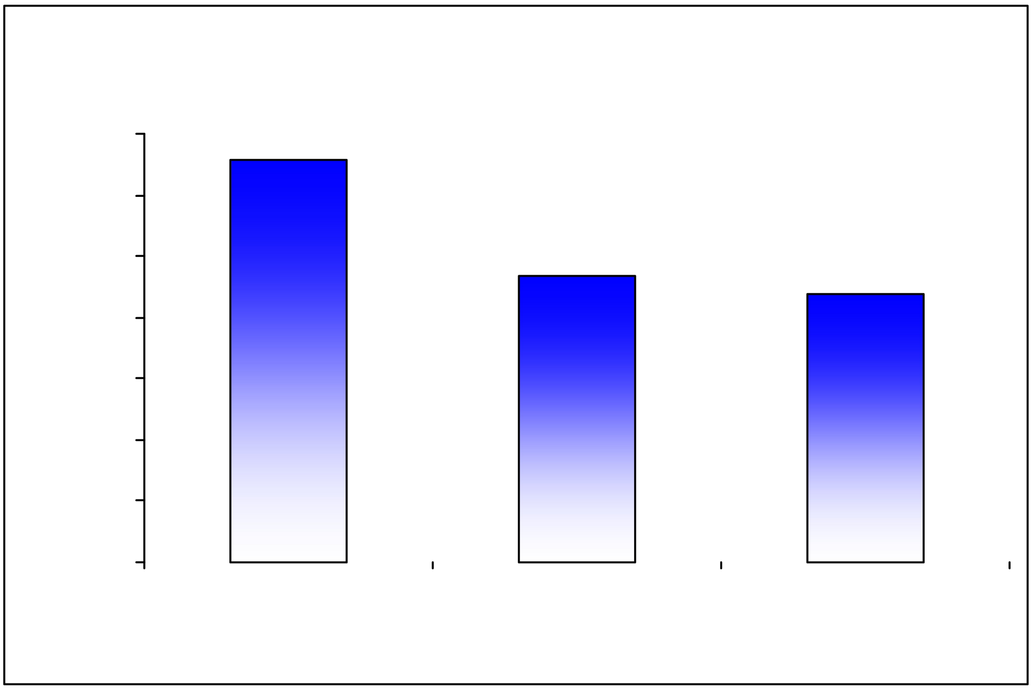
The mean and median pulse rate, temperature, systolic and diastolic blood pressure are as shown in table 7.

Table 8. Clinical signs

Signs	Distribution (n=64)	
	Number	Percentage
Signs of heart failure	21	32.81
Pallor	15	23.44

Pedal oedema	14	21.88

Multiple presentations hence total not shown



In this study the commonest clinical signs was heart failure (32.81%). However, pallor and oedema were present in 23.44% and 21.88%.

Table 9. Systemic examination findings in cardiovascular system

Findings	Distribution (n=64)	
	Number	Percentage
Normal	60	93.75
Pansystolic murmur	2	3.13
Mid diastolic murmur	1	1.56

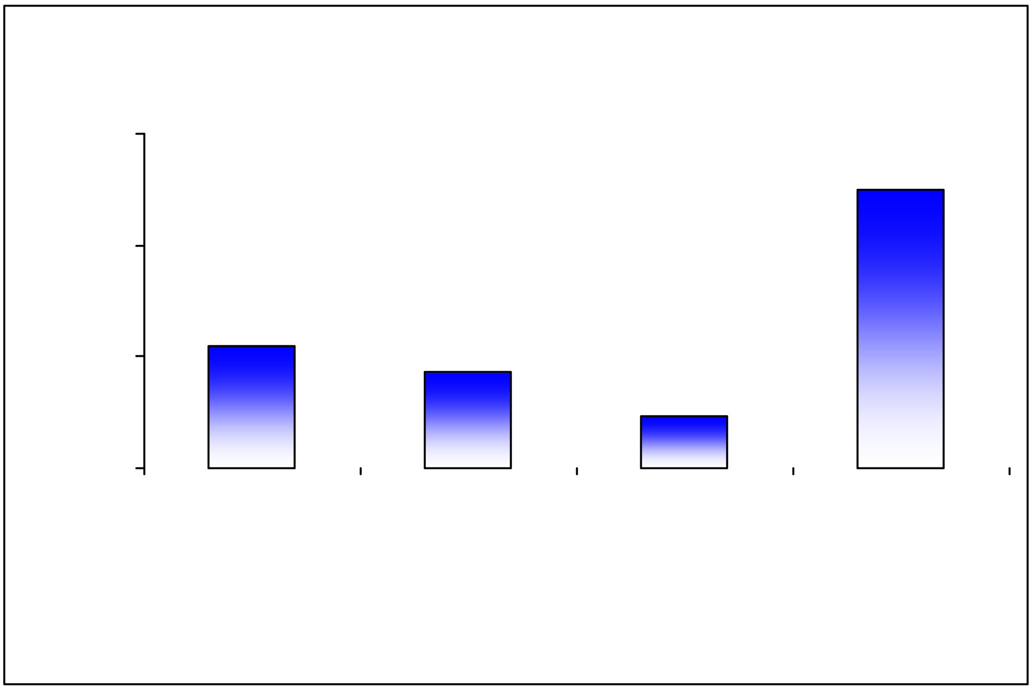
Multiple presentations hence total not shown

In the present study cardiovascular system findings revealed Pansystolic murmur (3.13%) and mid diastolic murmur (1.56%).

Table 10. Systemic examination findings CNS

Findings	Distribution (n=64)	
	Number	Percentage
Sensory neuropathy	14	21.87
Altered sensorium	11	17.18
Hemiplegia	6	9.37
Normal	32	50.00

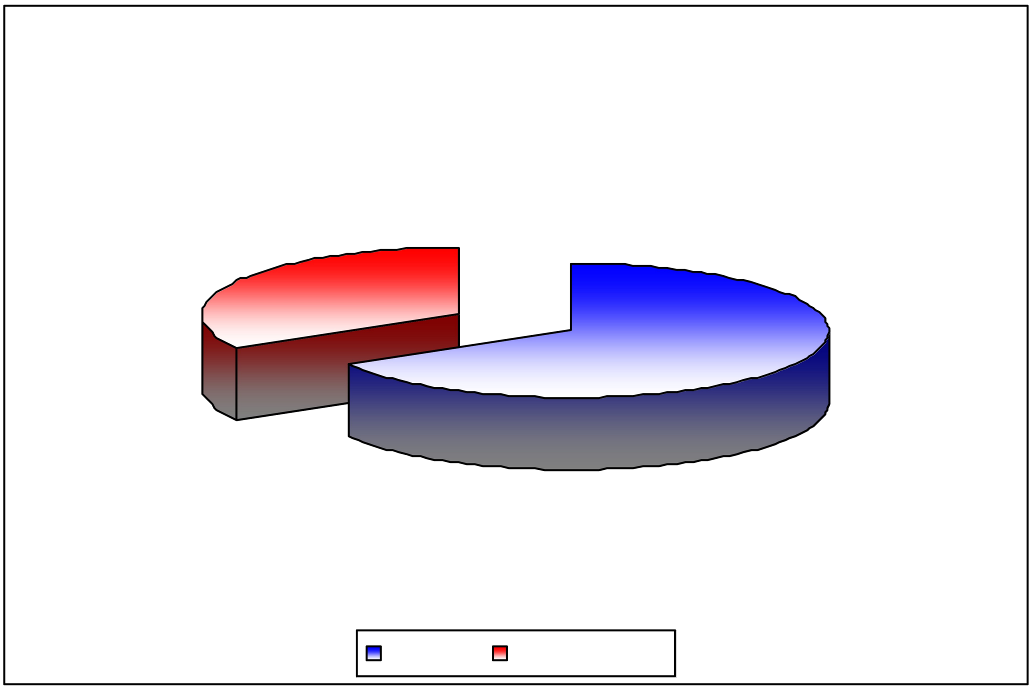
Multiple presentations hence total not shown



In this study CNS findings revealed most of the patients with sensory neuropathy (21.87%).

Table 11. Random blood sugar

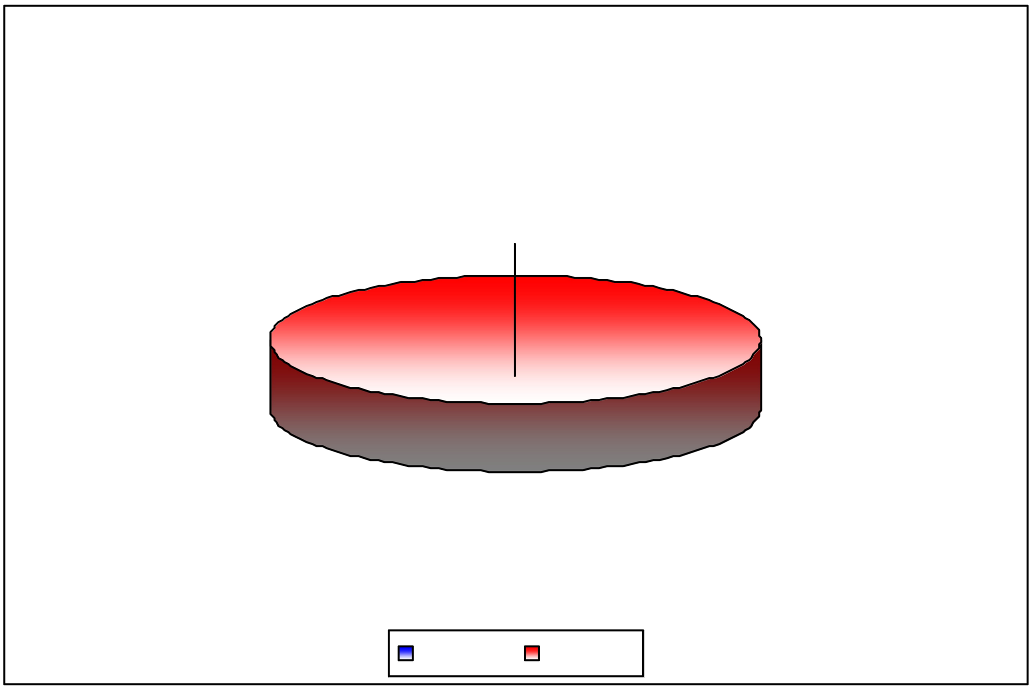
Random blood sugar (mg/dL)	Distribution (n=64)	
	Number	**Percentage**
Normal (<200)	45	65.60
200 or more	21	32.80
Total	**64**	**100.00**



In the present study 32.80% of the patients presented with random blood sugar levels of ≥ 200 mg/dL.

Table 12. Troponin I

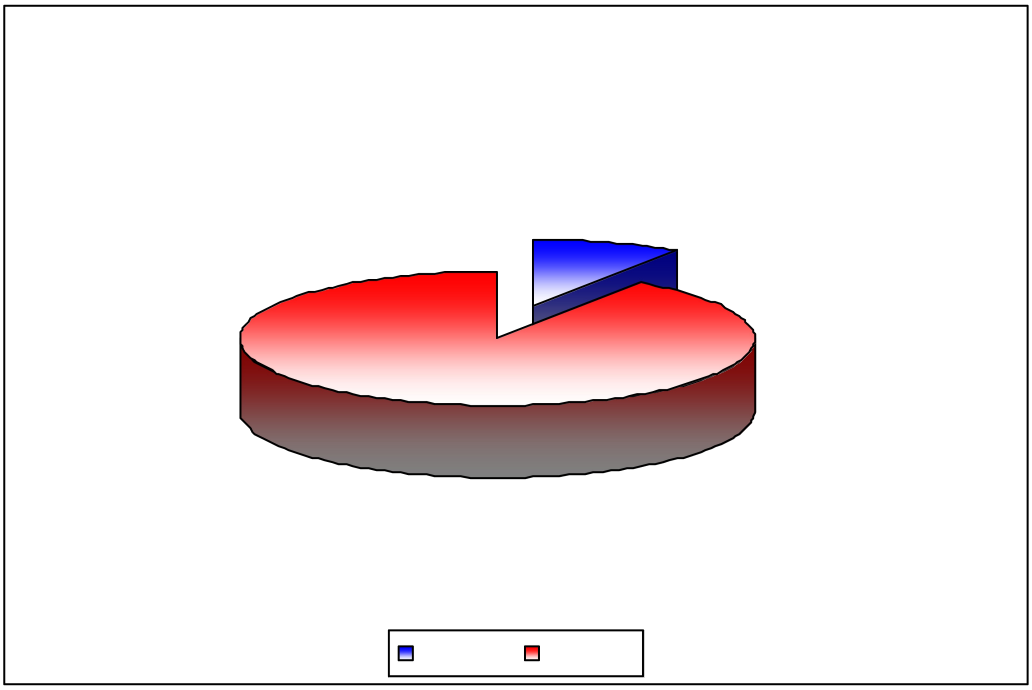
Troponin I	Distribution (n=64)	
	Number	Percentage
Normal (≤0.04)	0	0.00
Raised (> 0.04)	64	100.00
Total	**64**	**100.00**



In this study raised troponin I was noted in all the patients (100%).

Table 13. CK MB

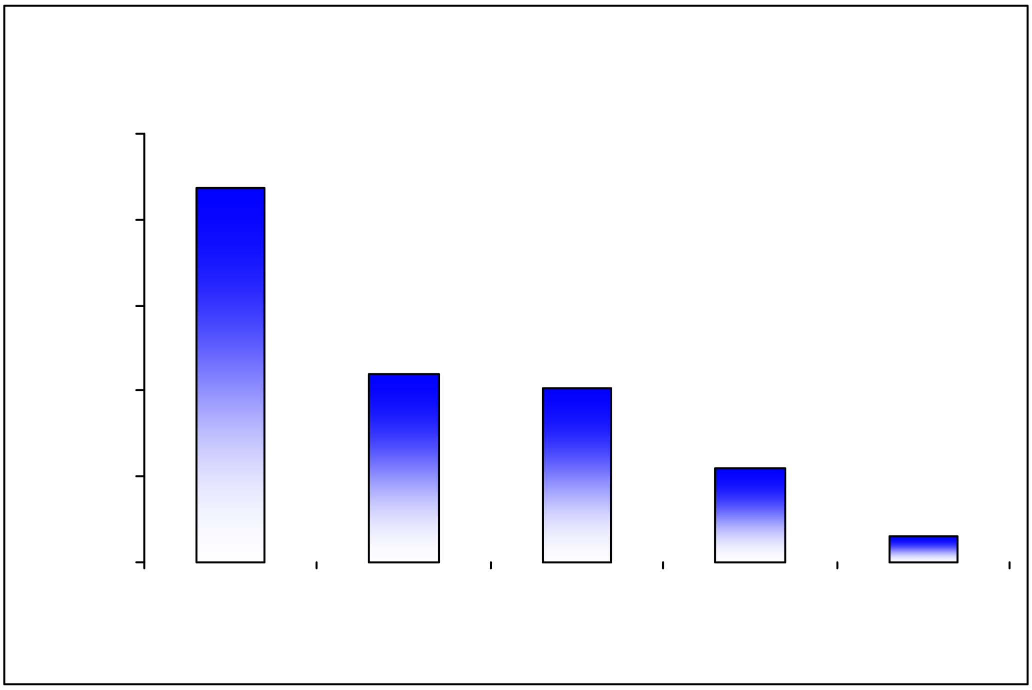
CK MB	Distribution (n=64)	
	Number	Percentage
Normal (≤25)	6	9.38
Raised (>25)	58	90.62
Total	**64**	**100.00**



In the present study raised CK MB (> 25) were noted in 90.62% of the patients.

Table 14. Diagnosis

Diagnosis	Distribution (n=64)	
	Number	**Percentage**
Anterior wall MI	28	43.75
Anteroseptal MI	14	21.88
Inferior wall MI	13	20.31
Non ST elevation MI	7	10.93
High lateral wall MI	2	3.13
Total	**64**	**100.00**



In this study 43.75% of the patients were diagnosed to have anterior wall myocardial infarction followed by ASMI in 21.88% and IWMI in 20.31%.

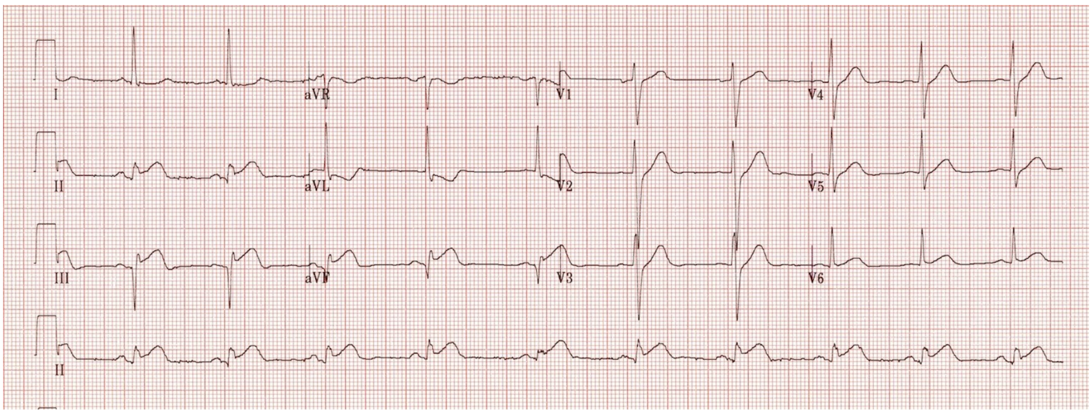


Figure 7. ECG showing acute inferior wall myocardial infarction

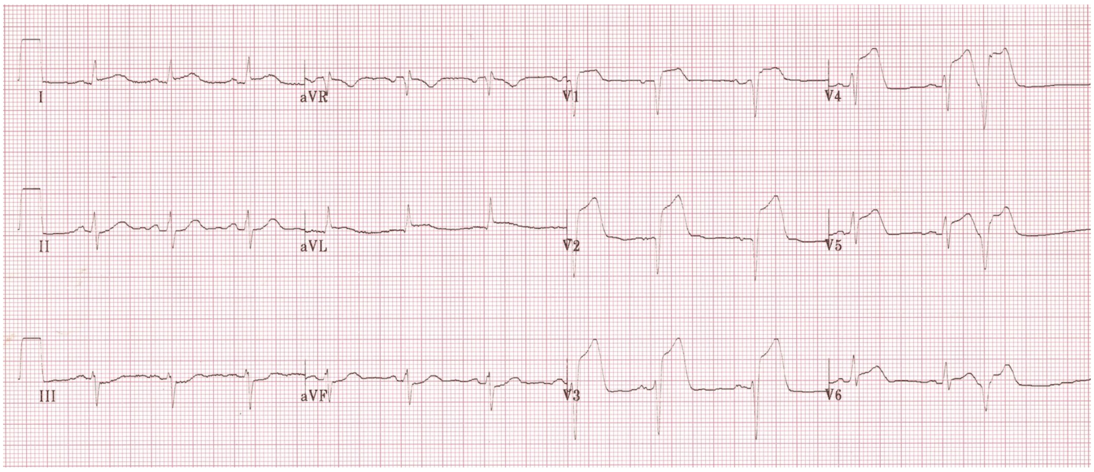


Figure 8. ECG showing ST Elevation anterior wall myocardial infarction

DISCUSSION

Acute myocardial infarction is the major cause of death and disability worldwide. After three decades of unparalleled research, multiple highly effective treatments for acute myocardial infarction have been documented in largescale clinical trials, including early coronary revascularization, antithrombotic therapy, and secondary prevention. These therapies have led to a substantial reduction in mortality. Two groups of acute myocardial infarction patients have not, however, been able to benefit from these advances: patients in whom acute myocardial infarction results in immediate sudden death and patients with atypical myocardial infarction, in whom the patient or his environment do not recognize the occurring event in the acute phase due to absence of chest pain.[65]

Little is known about the phenomenon of silent myocardial infarction. Atypical myocardial infarction is characterized by lack of unequivocal objective signs of myocardial infarction and minimal, atypical, no chest pain or no symptoms at all. Compared with the prevalence of typical acute myocardial infarction, the prevalence of atypical myocardial infarction is less well known. Atypical myocardial infarctions represent missed opportunities for the early initiation of the highly effective and extensively documented treatment with thrombolytic agents and anticoagulants and initiating preventive measures such as antiplatelet therapy and high-dose statins. Currently, atypical myocardial infarction is most often diagnosed using the 12-lead electrocardiogram (ECG) for screening purposes. However, the ECG has a very low sensitivity. Newer imaging techniques such as myocardial perfusion single photon emission computed tomography (myocardial perfusion

SPECT [MPS]) or cardiac magnetic resonance offer better diagnostic capability, particularly test sensitivity.[65] The present study was undertaken to assess the prevalence of atypical MI.

This one year hospital based cross-sectional study was done under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013.

Chest pain has been reported as the cardinal feature in patients with AMI. The WHO requires the presence of chest pain as one of the cornerstone feature for the diagnosis of chest pain.[66] In the present study, during the study period a total of 526 patients were admitted with acute myocardial infarction. Among them 64 patients had atypical acute myocardial infarction and the prevalence was as high as 12.16%. Nearly two thirds of the study population presented with breathlessness (64.06%). The next common presentation was sweating (45.31%) followed by abdominal pain (26.56%), vomiting (25%), palpitation (18.75%), headache (9.38%) and syncope (7.81%). On clinical examination the commonest clinical sign was evidence of heart failure (32.81%) followed by pallor (23.44%) and oedema (21.88%). On systemic examination, central nervous system examination revealed sensory neuropathy in 21.87% of the patients. The literature suggests that atypical MI may well affect between 2.5% to 10% of the population before they are symptomatically aware of any underlying coronary artery malformations.4-8 Results from other population studies have shown that 20–60% of all MI are presented with atypical symptoms. In the Reykjavik study,[66] approx 30% of MI patients presented with atypical symptoms. However, a study by Anand et al. investigated 864 asymptomatic individuals with the use of electron beam tomography coronary calcium imaging and found that 18% of patients with moderate and 45% with severe atherosclerosis experienced episodes of silent ischaemia.[36]

In the present study atypical myocardial infarction was seen more commonly among males (70.31%) as the male to female ratio was 2.36:1 suggesting male preponderance. These findings were similar to the observations made by Muller RT et al.[67] Comparison of data from the Reykjavik study[66] for male and female cohorts indicated higher incidence rates in relatively young male subjects than in their female counterparts.[68] A study[69] from Mangalore also documented a pronounced gender difference with females far outnumbering males in the incidence of painless infarction.

Advanced age is an important predictor of atypical presentation and poor prognosis. In this study the commonest age group was 51 to 60 years comprised of 32.81% and mean age was 58.28 ± 12.55 years. These findings suggest that acute myocardial infarction was more common among elderly. According to Canto and Shlipak,[70] patients presented with atypical symptoms were older and were women. Reykjavik[66,68,71] and Honolulu cohorts, a direct relationship was found between age and the incidence of atypical MI. A study[69] from Mangalore also reported an increase in the proportion of atypical MI with advancing age but the same was not true statistically although it was not commonly seen before the age of 55. There was a slight increase in the incidence of painless infarction with increasing age. In the group between 55 and 64 years, 25% patients presented with atypical symptoms and 31% in 65–74 years age group. These findings were comparable with Kennel and others,[72] where the values were 27% and 31%, respectively. In contrast to earlier studies in which patients who were 70 years or older were more likely to present without chest pain, in this study only one patient out of six presented with atypical symptoms.

Patients with diabetes mellitus (DM) have a blunted perception of ischemic chest pain, which could result in atypical presentation. The suggested mechanisms of this phenomenon are as follows; 1) autonomic neuropathy, 2) prolongation of the anginal perceptual threshold. In the present study more than half of the study population (56.25%) presented with history of diabetes. The other comorbid conditions noted were hypertension in 35.94%, ischaemic heart disease in 23.44% and chronic kidney disease in 10.94%. This supports the Honolulu Hawai Heart program study[73] in which the patients with atypical symptoms were more likely to be hypertensive, to have diabetes or impaired glucose tolerance but they were less likely to have angina pectoris. A greater prevalence of hypertension and diabetes in the atypical MI group was also noted in Framingham study[74] and study by John G Canto.[70]

In NRMI-2 registry,[26] Variables such as older age, gender, race, and co-morbidities (diabetes, stroke, heart failure) were considered as a risk factor for atypical symptom, and many studies have described the association of aging, gender, and diabetes mellitus which are in agreement with the present study.

In this study most of the patients were diagnosed to have anterior wall myocardial infarction (43.75%). The next common diagnosis was ASMI in noted among 21.88% of the patients and IWMI in 20.31% of patients. These findings implicate higher prevalence of atypical presentation in patients with anterior wall MI. A study from Manipal reported higher percentage (50%) of inferior-wall MI patients presented with atypical symptoms which was noted among 20.31% of the patients in this study. The Honolulu Hawai Heart Program Study[73] also demonstrated a pronounced increase in painless infarction with inferior-wall MI patients (51%). A higher proportion of inferior-wall MI tends to cause atypical symptoms, such as epigastric pain or abdominal distress, which would be failed to be recognized as MI. However, the study by Kennel[72] and others showed that there was no fact between those with atypical and typical symptoms of MI. In the Framingham Study[74] also, the proportion of atypical MI did not appear to vary with electrographic location of the infarct.

CONCLUSION

The present study showed prevalence of atypical myocardial infarction as high as 12.16%. Higher prevalence was noted among males and aged above 50 years. Patients with atypical myocardial infarction are likely to present with history of diabetes or hypertension and symptoms of breathlessness and sweating. Further, these patients may likely diagnose to have anterior wall myocardial infarction.

SUMMARY

Atypical myocardial infarction is characterized by lack of unequivocal objective signs of myocardial infarction and minimal, atypical, or no symptoms at all. However, there is limited data and little is known about the phenomenon. The present study was undertaken to assess the prevalence of atypical MI.

This one year hospital based cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients presenting with atypical myocardial infarction. Patients were assessed for clinical signs and symptoms, and were subjected to ECG for the diagnosis of atypical myocardial infarction.

During the study period that is, from January 2013 to December 2013 there were 526 admissions with acute myocardial infarction. Of these, 64 patients had atypical acute myocardial infarction and the prevalence was 12.16%. Atypical myocardial infarction was seen more commonly among males (70.31%; male to female ratio was 2.36:1) and in the age group between 51 to 60 years (32.81%) and mean age was 58.28 ± 12.55 years. More than half of the study population that is, 56.25% of the patients presented with history of diabetes mellitus and personal history of smoking was noted in 31.81%. Breathlessness was the commonest clinical presentation noted in 64.06% and commonest clinical sign was heart failure present in 32.81%. The investigations revealed raised random blood sugar levels in 65.60%, raised CK MB in 90.62%, and troponin I was found to be raised in all the patients

(100%). Most of the patients were diagnosed to have anterior wall myocardial infarction (43.75%) followed by anteroseptal MI (21.88%).

Overall the present study showed higher prevalence of atypical myocardial infarction especially in males and aged above 50 years. Further this subset of patients may present with history of diabetes mellitus and essential hypertension or hypertension with symptoms of breathlessness and sweating.

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ANNEXURE I – CONSENT FORM

Objective and purpose of the study

This research is intended to study the prevalence of acute myocardial infarction with atypical presentation. The principal investigator of the study is Dr. **** ***** under the guidance of Dr. **** ******.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood for the necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part now, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing. If you/your relative have/has any questions about this study, you/your relative may contact Dr. **** ******, Ph. +91 **** ******, Dr. **** *****, Professor, Department Of Medicine, Ph. +91 *********** or Dr. **** *****, Chairperson, Institutional Ethical Committee for Human Subjects Research, Jawaharlal Nehru Medical College, Belgaum, Ph. +91 **** *****. You/your relative will be given a copy of this consent form for your/your relative's information and for your/your relative's records.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

In case of the queries during study or in future you may contact following person.

Principal investigator : Dr. **** ******

Guide : Dr. **** ******

Name of the Participant: ____________________________

Signature / Thumb print: ____________________________

Name of the Witness ____________________________

Signature ____________________________

Name of the investigator __________________________

Signature __________________________

Date: Place:

ANNEXURE II – PROFORMA

Name : Sex :

Age : IP No. :

Address :

Date of admission: Date of discharge:

Occupation:

Chief complaints

Chest pain :

Breathlessness :

Sweating :

Palpitation :

Vomiting :

Abdominal pain :

Syncope :

Headache :

Other complaints :

Past history

- History of Ischaemic heart disease-
- History of Non Ischaemic heart disease-
- History of Diabetes mellitus-
- History of Hypertension-
- History of Cerebro vascular accident(CVA)-
- History of Other diseases-

Personal history

Alcohol consumption-

Smoking-

Tobacco chewing-

On examination:

Pulse rate (/Min) :

Temperature :

Heart rate (/Min) :

Blood pressure

Systolic : mm Hg

Diastolic : mm Hg

Pedal Edema :

Signs of Heart Failure :

Pallor :

Systemic examination

Cerebrovascular system:

Peripheral :

Central :

Respiratory system :

Per abdomen :

Central nervous system:

Investigations

Cardiac enzymes

CK MB :

Troponin I :

Random blood sugar :

E.C.G -

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
AB	-	Absent
APH	-	Aphasia
AS	-	Altered sensorium
ASC	-	Ascites
ASMI	-	Anteroseptal myocardial infarction
AWMI	-	Anterior wall myocardial infarction
AX	-	Anxiety
B/L	-	Bilateral
BC	-	Backache
BP	-	Bells palsy
BP	-	Blood pressure
BRN	-	Burn
BV	-	Blurring of vision
C	-	Crepts
CGH	-	Cough
CK MB	-	Creatine kinase MB
CKD	-	Chronic kidney disease
CL	-	Clubbing
CLD	-	Chronic liver disease
COPD	-	Chronic obstructive pulmonary disease

CVS	-	Cardiovascular system
CYN	-	Cyanosis
DM	-	Diabetes mellitus
DOG	-	Dog bite
EPI TEND	-	Epigastric tenderness
FV	-	Fever
G	-	Female
GM	-	Gum bleeding
GW	-	Generalised weakness
HEMI	-	Hemiparesis
HLWMI	-	High lateral wall myocardial infarction
HPOTHP	-	Hypothyroidism
HTN	-	Hypertension
IHD	-	Ischaemic heart disease
IWMI	-	Inferior wall myocardial infarction
LBP	-	Low backache
LOC	-	Loss of consciousness
LS	-	Loose stools
LWK	-	Left sided weakness
M	-	Male
MDM	-	Middiastolic murmur
mm Hg	-	Millimeter of mercury
MR	-	Mitral regurgitation
N	-	Normal
NSTEMI	-	Non ST elevation myocardial infarction

OCP	-	Organophosphorous compound poisoning
PHTN	-	Portal hypertension
PSM	-	Pansystolic murmur
PSRH	-	Pain in right hand
R	-	Rhonchi
r	-	Right
RBS	-	Retrosternal burning
RWK	-	Right sided weakness
SENN	-	Sensory neuropathy
SW LOA	-	Swelling of both legs
SZR	-	Seizure
TEN HPT	-	Tender hepatomegaly
TEND	-	Tenderness