DISSERTATION ON

HIGHLY SENSITIVE C - REACTIVE PROTEIN IN THE PATIENTS WITH UNSTABLE ANGINA AND ITS PROGNOSTIC IMPLICATIONS

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CERTIFICATE

This is to certify that this dissertation entitled" **HIGHLY SENSITIVE C - REACTIVE PROTEIN IN THE PATIENTS WITH UNSTABLE ANGINA AND ITS PROGNOSTIC IMPLICATIONS"** Submitted by **Dr.Vijayasekaran.B** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2008 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

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The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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INTRODUCTION

Unstable angina lies in the centre of the spectrum of clinical condition caused by myocardial ischemia. This changes range from Chronic Stable Angina (CSA) to Acute Coronary Syndrome (ACS) . Acute coronary syndrome consists of myocardial infarction associated with electrocardiographic ST segment elevation (STEMI) and Unstable Angina /Non ST segment elevation myocardial infarction (UA/ NSTEMI). STEMI[1] is associated with total coronary occlusion, whereas UA/ NSTEMI are usually associated with partial obstruction in which the lumen is not totally occluded. If partial occlusion is long in duration and greater in severity myocardial necrosis occurs and the patient is classified under non Q wave MI. Unstable Angina is an acute coronary syndrome which is not associated with myocardial necrosis.

The most common cause of UA is rupture or erosion of atherosclerotic plaque which superimposed by non occlusive thrombi. Plaque rupture is predisposed by variable factors including high lipid content, local inflammation causing breakdown of thin

shoulder of plaque, coronary artery constriction, local shear stress factor and platelet activation. Out of which inflammation appears to play a key role in all the stages of atherosclerosis starting from fatty streak involving recruitment of leucocytes by expression of leukocyte adhesion molecule , migration of mononuclear cells, proliferation of smooth muscle cells to thrombotic complication involving physical disruption are associated with inflammation. It is not surprising that there is elevation of inflammatory markers in low grade inflammation and their estimation helps the prediction of severity of inflammation. Some of the markers include fibrinogen, IL-6, IL-1,adhesion molecules like ICAM-1[2,5], TNF, C-reactive protein etc.

Out of these, CRP[3] levels are independently associated with cardiovascular disease in apparently healthy individuals and patients presenting with Acute Coronary Syndrome(ACS). CRP concentrations are higher in patients with ACS and correlate with number of complex lesions in these patients. These findings indicate that serum CRP is a marker of disease activity and this concept is endorsed by studies showing that CRP levels correlate

with cardiovascular risk in ACS patients.CRP is not merely a marker of systemic inflammation but may also play a role in sustaining the inflammation in ACS. Increased serum CRP levels in patients with chronic Stable Angina(CSA) may be a reflection of ongoing inflammation[7] in the atheromatous plaque, which may lead to plaque vulnerability and progress to acute coronary syndromes. It has been recently reported that hs-CRP level correlates with the number of vulnerable atherosclerotic plaques with superficial foam cells, large necrotic cores and thin fibrous cap atheroma.These findings suggest that the increased risk of future coronary events observed in patients with elevated serum CRP is directly related to the increased number of vulnerable plaques prone to rupture, strengthening the role of the CRP as a major risk factor for the development of clinical manifestations of Coronary Artery Disease(CAD). CRP has been shown to actively participate in both atheromatous lesion formation and plaque disruption.

CRP increases the expression of endothelial adhesion molecules and monocyte chemo attractant protein-1 (MCP-1), facilitates native LDL uptake into macrophages[4], promotes

monocyte activation and a procoagulant effect by inducing monocytes to synthesize tissue factor. CRP can also activate the classic pathway of complement activation and has been demonstrated to co localize with terminal complement complexes in established coronary plaques. Recently, it has been reported that several vulnerable plaques other than the “culprit” stenosis can be found in individual patients with MI and that multiple plaque disruption occurs in patients with ACS. These findings are likely to be the result of a diffuse inflammatory process that leads to multifocal plaque instability[6,53]. CRP may thus be a marker of this process.

This study is the measure of the highly sensitive C - reactive protein (hs_CRP) values in patients who were hospitalized for unstable angina and to assess the outcome of these patients and also to correlate between the levels of hs_CRP and various risk factors and clinical, laboratory profile in patient with unstable angina.

AIM OF THE STUDY:

1. To assess the prognostic value of hs_CRP in patients with unstable angina who were hospitalized.

2. To correlate between the elevation of hs_CRP and the occurrence and the severity of recurrent coronary events during the hospital stay.

3. To correlate between hs_CRP elevation and occurrence of complications in unstable angina patients during the hospital stay.

4. To analyse the relationship between various risk factors and elevation of hs- CRP levels in unstable angina patients.

REVIEW OF LITERATURE

DEFINITION:

Unstable Angina is defined as angina pectoris or equivalent ischemic discomfort with at least one of the three features.

1) It occurs at rest (or with minimal exertion) usually lasting more than 10 minutes.
2) It is severe and of new onset (i.e. with prior to 4 to 6 weeks) and/or.
3) It occurs with crescendo pattern (i.e. distinctly more severe, prolonged or frequently than previously episode**).**

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA:

(According to characteristics of anginal pain and the underlying cause)

CLASS	**CHARACTERISTICS**
I	**EXERTIONAL ANGINA**
	New onset, severe or accelerate angina .No rest angina in last 2 Months
II	**REST ANGINA, SUBACUTE**

Rest angina within the last month but none within 48 hours

III REST ANGINA, ACUTE

Rest angina within 48 hours of presentation

CLINICAL CIRCUMSTANCES

A SECONDARY UNSTABLE ANGINA

Caused by no cardiac condition, such as anemia, Infection, thyrotoxicosis or hypoxemia

B PRIMARY UNSTABLE ANGINA

C POST INFARCTION UNSTABLE ANGINA

Within 2 weeks of documented myocardial infarction (MI).

INTENSITY

- Occurrence of unstable angina in the absence of treatment for chronic stable angina (CSA)
- During standard treatment for chronic stable angina
- Despite maximal anti-ischemic drug therapy

ECG CHANGES

- With ischemic ST/T changes during pain

- Without ischemic ST/T changes during pain

PATHOPHYSIOLOG Y OF UNSTABLE ANGINA

Unstable angina accounts for more than 1 million hospital admissions annually; 6 to 8 percent of patients with this condition have nonfatal myocardial infarction or die within the first year after diagnosis. Recently, the term “Acute Coronary Syndromes “has been used to describe the spectrum of conditions that includes unstable angina, non-Q-Wave myocardial infarction (which generally presents without ST-segment elevation), and Q-wave myocardial infarction (which generally presents with ST-segment elevation). Patients with unstable angina and those with non- Q-wave myocardial infarction often present in a similar manner, and the distinction between the two conditions can be made only many hours or days latter, when the results of cardiac- enzyme tests become available.

PATHOGENESIS

Initiation of the Cascade of Plaque Fissure and Rupture Disruption of a formed plaque is a complex pathologic process that is central to the initiation of the acute coronary syndromes. Sudden total or near-total arterial occlusion frequently develops in arteries that previously appeared to have minimal stenosis. Two thirds of arteries with plaques that rupture and in which a totally occlusive thrombus subsequently develops have stenosis of 50 percent or less before plaque rupture, and in 97 percent of patients, stenosis is initially less than 70 percent. The arterial lesions of patients with unstable angina frequently have complex, eccentric morphologic features on coronary angiography; such features have been found to represent ruptured plaque with superimposed thrombus.

Mature plaques are made up of two main components:

A lipid-rich core and a meshwork of extra cellular- matrix proteins that form a fibrous cap[8]. The presence of large, eccentric lipid pools and infiltration of foam cells are the characteristics of the lipid core most frequently associated with fissured or ruptured plaques. The majority of these lesions rupture at the sites of greatest

mechanical stress, notably the junction of the plaque cap and the adjacent normal intima or the shoulder regions of the lipid pool. Fissures occurring at weak cap sites and not at sites subject to the greatest mechanical stresses are thought to be initiated by proteinases secreted by macrophages that enzymatic ally degrade the fibrous cap.

Acute Thrombosis and Platelet Aggregation[9,10.11]

Local thrombosis occurring after plaque disruption results from complex interactions among the lipid core, smooth-muscle cells, macrophages, and collagen. The lipid core is the most potent substrate for platelet-rich thrombus formation, and both smooth-muscle and foam cells within the core correlate with the expression of tissue factor in unstable plaques. Once exposed to blood, tissue factor interacts with factor VIIa to initiate a cascade of enzymatic reactions resulting in the local generation of thrombin and deposition of fibrin. Because of the delicate equilibrium between

thrombosis and endogenous thrombolysis, some acute vascular lesions resolve when fissures are repaired.As part of the response to any type of disruption of the endothelial wall, platelets aggregate and release granular contents that further propagate platelet aggregation, vasoconstriction, and thrombus formation

Systemic factors and inflammation also contribute to alterations in the hemostatic and coagulation pathways and may play a part in the initiation of the intermittent thrombosis that is characteristic of unstable angina. Inflammatory acute-phase reactants, cytokines, chronic infections, and catecholaminergic surges may provide a systemic stimulus for enhancing production of tissue factor, procoagulant activity, or platelet hyper agreeability.

Coronary Vasospasm

Although not central to the underlying pathogenesis of the acute coronary syndromes, episodic vasospasm may contribute to vascular instability by altering preexisting coronary plaques, which causes intimal disruption and penetration of macrophages or aggregation of platelets. These processes -in turn -may lead to the

formation of foam cells and the proliferation of smooth-muscle cells.

Erosion of Coronary Plaque without Rupture[12]

An alternative mechanism of luminal narrowing may involve the rapid proliferation and migration of smooth-muscle cells in response to endothelial injury. Rapid conformational changes in the shape and size of a lesion due to the expansion of the smooth muscle may lead to the relatively abrupt onset of luminal narrowing and symptoms of ischemia. Current techniques cannot clearly distinguish between patients whose acute symptoms are due to conventional plaque rupture and those whose symptoms are due to minor erosions or conformational changes.

ATHEROSCLEROSIS IS AN INFLAMMATION;[13]

Inflammation has potential role in every stage of atherogenesis. Oxidative stress, modified lipoproteins and haemodynamic force cause insult to the vascular endothelium. Injured endothelium produces several responses like endothelial

dysfunction, characterized by upregulation of vascular adhesions molecule I (VCAM-1) and intercellular adhesion molecule (ICAM - 1), that along with chemokines increase the adhesion of mononuclear leukocytes, and subsequently it migrates into the subendothelial space. Simultaneously there is uptake of low density lipoproteins (LDL) by monocyte derived macrophage and it transforms into lipid-laden foam cells which are the key elements of fatty streaks.These fatty streaks are the first recognizable progenitors of atherosclerotic lesion. The mononuclear cells release cytokines, interlukin- 1 (IL-1) and interlukin-6 (IL-6) that promote oxidation/ uptake of LDL, cellular recruitment & release of CRP from hepatocyte, it also releases mitogens that stimulate smooth muscle cell proliferations & maturation of fatty streak. A fibrous cap forms over this developing mixture of inflammatory and smooth muscle cells, intracellular, and extra- cellular lipids which eventually become recognizable as an advance complex atherosclerotic plaque.

This cap composed of dense extra cellular matrix that is derived from type I and III collagen and elastin and forms a barrier between the procoagulant contents of atheroma core and circulating

blood. Erosion or rupture of this barrier causes exposure of atheroma core and promotion of thrombus formation. When the forming thrombus leads to rapid compromise of arterial flow, acute myocardial ischemia or infarction may result. The extent of coronary stenosis does not match with the progressive risk of acute coronary syndrome. This discordance between the involvement of angiographic stenosis of coronary arteries and the acute coronary syndrome has redirected the emphasis from the arterial lumen, visualized by angiography towards the characteristic of atherosclerotic lesion and the factors that influence it's vulnerability to rupture. Macrophage and T lymphocyte dominate at the site of plaque regardless of their lesion morphology. The exact mechanism by which these cells cause plaque disruption, still not well defined but several potential links have emerged. Inflammatory cytokines stimulate smooth muscle cells, and macrophage that produce collagenase and elastase which degrade protective extracellular matrix. Interferon (produced by T lymphocyte in atheroma core) decreases the collagen by smooth muscle cells. Inflammatory cells and mediators promote thrombus

formation and vessels occlusion by modulation of platelet activation, coagulation cascade and vasomotor functions[21,22].

C - REACTIVE PROTEIN[14,15,16]

CRP[14] is the most reliable marker of inflammation, now viewed as a prominent partaker in endothelial dysfunction and atherosclerosis. It is 1, 35,000 dalton non-immunoglobin protein, having five identical subunit (pentameric). C-reactive protein was first described by Tillet and Francis in 1930. They concluded that sera of patients suffering from acute infection precipitated with a non-proteic pneumococcus extracts called C polysaccharide in the presence of calcium ions. The protein that caused this reaction was therefore called C-reactive protein (CRP). CRP specifically recognizes phosphocholine, the hydrophilic part of phosphatidyl choline of the cell membranes, complexion of CRP to the cell wall activates compliment via classical pathway thus stimulate macrophages and other cells to undergo phagocytosis. Cytokines like interleukin-6 stimulate hepatocyte to preferentially produce positive acute phase protein. High concentration of CRP found in

the condition listed in recent studies have proved that, quantification of C reactive protein is superior than cytokine measurement (like interleukin-6, interleukin ß1, tumor necrosis factors) for detecting the presence of inflammation in intensive care patients. The advancement in the understanding of pathophysiology of atherosclerotic vascular disease have come new insights regarding potential indicators of underlying atherosclerosis and cardiovascular risk.

The role of inflammation to atherogenesis has attained increased recognition and attention has focused on several key mediators and novel markers of the inflammatory process, including acute phase reactant, C-reactive protein. High sensitive assay for CRP have now been developed and able to detect mild elevation of CRP even within normal range. Over the last decade various studies proved that mild elevation of CRP and cardiodiovascular risk among those without apparent clinical cardiovascular disease and those for whom the focus is on secondary prevention. The data have revealed that interaction between baseline concentration of CRP and the efficacy of common

pharmacological therapies in primary and secondary prevention, suggesting not only that it may modify the increased risk associated with elevated CRP but also that inflammatory markers may be useful in targeting preventive therapies.

FUNCTIONS OF CRP [18,19,20]

The function of CRP is felt to be related to its role in the innate immune system (Du Clos, Terry V 2000). Similar to immunoglobulin IgG, it activates complement, binds to Fc receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fc receptors leads to the generation of proinflammatory cytokines that enhance inflammatory response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Thus CRP is thought to act as a surveillance molecule for altered self and certain pathogens. This recognition provides an early defence and leads to a proinflammatory signal and activation of the humoral, adaptive immune system.

CRP binds to molecular groups found on a wide variety of bacteria and act as an opsonin. Thus a number of functions have been ascribed to CRP, including initiation of opsonization and

phagocytosis and activation of complements, neutrophils, and monocyte-macrophage. Collectively these properties imply an important role for CRP in the recognition of microbial organisms and as an immunomodulator in the host defence. CRP may also be important in the recognition of necrotic tissues. (Gershov D et al)

HIGH SENSITIVE C — REACTIVE PROTEIN: ***A Novel Biochemical***

Markers and Its Role in Coronary Artery Disease[23]

CRP concentration increases in the presence of inflammation, infection, and tissue injury. Depending on the severity of the inflammatory stimulus (infection, inflammation), CRP levels can increase up to levels 500 times normal. The 19-hour half-life makes CRP easy to detect in circulation. Although the sensitivity range of standard CRP assays (3–200 mg/L) is adequate to evaluate clinically significant inflammatory processes, the tests are not precise enough to sense small changes in CRP levels associated with Cardio Vascular risk in apparently healthy individuals. As a result, a high sensitivity assay has been developed and is currently in use as highly sensitive CRP (hs-CRP). The hs_CRP assays can

detect low-grade inflammatory activity (as low as 0.15 mg/dL) within the vascular system, which helps to predict the first or recurrent coronary events. Baseline levels of CRP are strong independent risk predictors of future MI, stroke, and peripheral vascular disease. CRP level helps to stratify risk among patients with acute coronary syndromes (>0.16 mg/dL confers a higher rate of death, acute MI, or need for revascularization). In apparently healthy adults, a high CRP level (>0.16 mg/dL) is predictive of unstable angina, MI, stroke, a higher risk of restenosis, an increase in the incidence of complications after percutaneous transluminal coronary angiography and after coronary artery bypass graft surgery for the subsequent 8 years[24].

Infection, hs_CRP, Coronary Risk

Various studies proved that certain pathogens notably cytomegalovirus virus (CMV), Chlamydia pneumoniae, helicobacter pylori are associated with atherogenesis and development of clinically relevant CAD, perhaps via inducement of vascular inflammation. Zhu and colleagues[25] demonstrated that a link between anti-CMV antibodies and high CRP level in patients with both an elevated CRP level and seropositivity to CMV versus

patients with CMV seropositivity alone. This finding suggests that CMV contributes to atherogenesis by provoking an inflammatory response. Further study has confirmed that risk of angiographically documented CAD and the magnitude of increase in CRP levels are associated with an increased pathogen burden (including CMV and C. pneumoniae). This association emphasizes the role of the inflammatory response and host defense mechanism in atherosclerosis.

Risk factors and markers of inflammation (Rosenson RS, Koenig W.[26])

Clinical Risk Factor	**Marker association**
Cigarette smoking	Twofold higher concentrations CRP than in nonsmokers
Obesity, overweigh	Significantly higher hs_CRP levels than in normal-weight persons
Insulin resistance	Correlates with hs_CRP and fibrinogen
Metabolic syndrome	Linear relation with CRP

Type II diabetes	hs_CRP predicts development

PREDICTIVE VALUE OF hs-_CRP AND ITS ADVANTAGE OVER THER BIOCHEMICAL MARKERS FOR CAD.

Data from Physician Health Study (PHS)[27] and Women's Health Study (WHS)[28] showed that predictive values of hs_CRP are significantly higher than other traditional biochemical cardiovascular risk markers like total cholesterol (TC), HDL-cholesterol (HDL-C), LDLcholesterol (LDL-C) and than others novel markers like lipoprotein-a [Lp(a)], homocystein, apolipoprotein A1 and B.

Ridker et all[27,28] studies demonstrates that hs_CRP, is the single strongest predictor of risk in comparison with LDL-C which is a lesser predictor of future risk .Furthermore, in multivariate analysis that accounted for CAD risk factors (obesity, hypertension diabetes, and family history), only hs_CRP and the ratio of TC to HDL-C[29] had independent predictive value. In the same study of postmenopausal women, hs_CRP was shown to be predicting risk

among those with LDLC value < 130mg/l, a concentration deemed "desirable" by the current National Cholesterol Education Program Guidelines for primary prevention and the study demonstrated that hs_CRP can identify individuals at increased risk of developing future coronary events who otherwise would be missed if only lipid measurements were used. hs_CRP: Prognostic Indicator in Acute Coronary Syndrome.

Erythrocyte sedimentation rate (ESR) is more commonly used as a non-specific marker of disease activity. The ESR, which is an indirect parameter of acute phase protein changes, can be influenced by concentrations of fibrinogen, monoclonal proteins and red cell morphology, whereas CRP has no cross-interfaces. CRP is useful for its negative predictive value as a negative CRP rules out the possibility of an inflammatory or necrotic course. The serum CRP concentrations increase faster than that of the ESR and when the condition subsides, CRP falls very quickly, reaching normal levels several days before the ESR normalises .These several disadvantages prevent it from being an ideal laboratory test to monitor acute inflammation or tissue injury.

Several studies showed that measurement of hs_CRP either at admission or at discharge in patients of acute coronary syndrome have prognostic value. Liuzzo et al showed that patients with severe unstable angina in absence of myocardial necrosis (proved by absence of cTnT, cTnI), hs_CRP concentration >3mg/L) at admission were associated with increased incidence of recurrent angina, coronary revascularization, MI, and cardiovascular death (CVD).Some groups later demonstrated that hs_CRP >3mg/L at discharge in 53 patients of unstable angina (UA) was associated with increased readmission for recurrent ischemia and MI.

Thrombolysis in Myocardial Infarction (TIMI 11A) study demonstrated that in UA & Non ST elevation MI (NSTEMI) patients markedly increased hs_CRP at presentation in 437 patients was a good predictor of 14 days mortality. Furthermore, hs-CRP helps to identify those patients with negative cTnT (qualitative rapid bed test with cut-off <0.2μgm/L) who were at increased risk of mortality. Recent study by De Winter et al showed that hs_CRP > 5mg/L at admission in 150 patients with acute coronary syndrome were associated with an increased incidence of major cardiac events within 6 month regardless of cTnI values.CRP is an

appropriate marker because it has long half life, remain stable over time without any circadian rhythm and fasting blood samples is not required.

hs- CRP: Angina Pectoris[30]:

CRP level correlates with clinical severity of CAD and coronary events in both acute and sub acute phases of myocardial ischemia. UA patients who are hospitalized, whose hs_CRP > 0.3mg/L have more ischemic events in hospital than patients with lower CRP levels.CRP levels are significantly lower in patients with stable angina than in those with UA or MI. In patients with UA, elevated hs_CRP is strong predictor of plaque instability.

Bazzino[31] et al compared the prognostic value of stress test and CRP after medical stabilization of UA and it showed that elevated CRP levels were associated with adverse events, when compared with stress testing. CRP levels have high sensitivity and specificity. Moreover an elevated hs_CRP level at the time of hospital

discharge appears to be a more sensitive and specific test marker for increased risk than a positive stress test. Higher hs_CRP levels are strong predictor of recurrent cardiac events whereas low CRP levels suggest a good out- come.

hs- CRP: Predictor of Future Cardiovascular Events[32]

Several prospective studies have demonstrated that hs_CRP is a predictor of future cardiovascular morbidity and mortality among individuals with known cardiovascular disease. Data from the European Concerted Action on Thrombosis and Disabilities (ECAT)[33] Angina Pectoris Study Group, a study of 2121 men and women with stable and unstable angina, demonstrated that each standard deviation increase in hs_CRP was associated with a 45% increase in the relative risk (RR) of nonfatal MI or sudden cardiac death.

The Cholesterol and Recurrent Events (CARE)[34] trial, hs_CRP was a predictor of recurrent coronary events in men and women who had already suffered a MI. Those with hs_CRP

concentrations in the highest quintile had an 80% higher chance of developing another coronary event within the 5-year study period. Therefore, hs- CRP has the potential to be used in the stratification of patients into high- and low-risk groups. Perhaps of greater clinical importance is the demonstration that hs_CRP concentrations predict first MI and stroke. To date, 10 prospective studies, 6 in the US and 4 in Europe, have consistently shown that hs- CRP is a powerful predictor of future first coronary event in apparently healthy men and women.

Multiple Risk Factors Intervention Trial (MRFIT) [35]demonstrated a direct positive association between hs- CRP and CHD mortality in men followed over a 17-yearPeriod. This relationship, however, was evident only among smokers. A similar association between hs_CRP and future coronary events was noted in the Cardiovascular Health Study and Rural Health Promotion Project, which included men and women over 65 years of age with sub clinical cardiovascular disease[36].

The Physicians' Health Study (PHS) demonstrated similar positive association between hs_CRP and future coronary events in

apparently healthy men[37]. Unlike the observation in MRFIT, however, this association was evident in both smokers and nonsmokers. This study showed that those in the highest quartile of hs_CRP had a twofold higher risk of future stroke, threefold higher risk of future MI and fourfold higher risk of future peripheral vascular disease The European MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg study showed that an increase of one standard deviation in the log-transformed value of hs_CRP was associated with a 50% increase in coronary risk and that subjects with hs_CRP concentrations in the highest quintile had a 2.6-fold higher risk of developing future coronary events[38].

The Women's Health Study (WHS) showed that hs_CRP is a strong predictor of future cardiovascular events in women[39]. In stratified analyses, hs_CRP continued to be a strong predictor of future cardiovascular events even among subgroups of women with no history of hyperlipidemia, hypertension, smoking, diabetes, or family history of CHD[40]. The hs- CRP concentrations seen in these postmenopausal women were somewhat higher than those reported previously in men.

EFFECT OF ASPIRIN AND STATIN ON hs_CRP LEVEL

Although "Statins" lower levels of atherogenic lipids and induce regression of atherosclerotic lesion, other actions beside of lipid metabolism may account for some beneficial effects like:

* It suppresses the expression of adhesion molecule on endothelium.

* Decreases production of metalloproteinases by macrophage that allows plaque rapture.

* Alter macrophage content within the plaque.

So it is believed that "Statins" have anti-inflammatory effects on blood vessel walls.Statins also reduce CRP levels. Pravastatin Inflammation / CRP Evaluation Trial[41] showed that Pravastatin reduced CRP levels at 12 and 24 weeks independent of LDL-C. Five year randomized trial of lovastatin for primary prevention of coronary events showed that[42], lovastatin therapy reduced CRP by 14.8% and decreased cardiac events in patients with CAD.

Aspirin has cardioprotective effects in patients with CAD. Recent study suggested that beside antithrombotic effect it has some immunological effects that modulate vascular inflammation. Ridker and colleagues first reported that aspirin reduces vascular risk (MI, ischemic events) in apparently healthy men in those with highest level of hs_CRP. Ikonomidis et al[44] also demonstrated that aspirin reduces circulating levels of CRP and atherogenic cytokines macrophage colony stimulating factors and IL-6 in CAD patients. Kennon et al[45] also showed that aspirin lowered hs_CRP level in patients who are hospitalized with acute coronary syndrome. These data suggest that novel approaches to modulating atherosclerosis may be provided by cyclooxygenase-2 inhibitors and statin as well as by other evolving and novel therapy that target inflammatory cascade.

The conclusion of the AHA/CDC report is that high-sensitivity CRP is probably the best supported inflammatory marker. Results less than 1.0 mg per dL represent low risk; 1.0 to 3.0 mg per L average risk; and greater than 3.0 mg per L, high risk. Results greater than 10 mg per L may represent a chronic

inflammatory or infectious process. Measurements of hs_CRP may be useful to identify patients without known cardiovascular disease who may be at higher risk than is estimated by major risk factors and patients at intermediate risk who require further evaluation or therapy, and to motivate moderator high-risk patients to improve their lifestyles

The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial demonstrated that combination therapy with aspirin (75 to 325 mg/day) and clopidogrel was more effective than aspirin alone in preventing cardiovascular events, combination therapy, especially may be considered in the patients with CAD and elevated hs_CRP levels.

MATERIALS AND METHODS

STUDY DESIGN

This study is a single centre prospective analytical study carried out in the Institute Of Internal Medicine, Madras Medical College during the period of January 2006 to August 2007. Total numbers of patients were 75. All the patients in this study were hospitalized, no out patients were included .Patients were admitted in Medical Wards and Intensive Medical Care Unit .A detailed informed consent was obtained from the patients. Our institution`s ethical

committee clearance was obtained. Standard approved protocol was used for treating all the patients.

INCLUSION AND EXCLUSION CRITERIA

Patients of both younger and older age groups were included. Inclusion Criteria on admission were patients admitted with angina pectoris or equivalent type of ischemic Discomfort with at least one of the features

1) Rest pain lasting for more than 20 minutes (if not interrupted by Treatment)

2) Severe chest pain of new onset

3) Chest pain occurring in crescendo pattern (more severe, prolonged and more than previously) with ST/T segment changes suggestive of ischemia.

Patients were excluded if

- Interval of more than 24 hours of occurrence of pain before hospitalization,
- Presence of ST segment elevation at the time of admission ,

- H/O documented myocardial infarction within pervious 2 months ,
- Elevated CPK MB isoform on admission ,
- Intercurrent inflammatory or neoplastic conditions likely to be associated, with acute phase response by clinical examination and history,
- Surgery or major trauma in previous month,
- Having known thrombotic or bleeding disorder,
- Presence of acute rheumatic fever , collagen vascular disorder,degnarative disease .,
- Patient already taking drugs like statins etc which decreases the level of hs_CRP

STUDY PROTOCOL AND LABORATORY INVESTIGATIONS

Preliminary history with detail questioning regarding

1. Chest pain and angina equivalent, its character ,duration ,severity and frequency of angina,
2. Symptoms suggestive of heart failure like breathing difficulty ,dyspnea on exertion, PND, orthopnea etc.,
3. Risk factors like h/o smoking and alcoholism for considerable period of time, type II DM ,systemic hypertension and women in post menopausal group(PML) and
4. Past history and Previous treatment details were taken followed by physical examination

A sample of 3cc blood was drawn by venipuncture and transferred to dry plain bottle and sent for the analysis of the inflammatory marker of our study highly sensitive CRP (hs_CRP). The method used for analysis is fully automated Nephlometry called BN 100- Nephlometry.

The principal of BN 100- Nephlometry[46]

This ultra-sensitive immunoturbidimetric assay uses the method called particle- enhanced immunonephlometry to quantitate hs_CRP in serum .Polystyrene particles coated with monoclonal antibodies against CRP become agglutinated when mixed wit samples containing CRP.The intensities of light scattering by agglutination is measured by nephlometry and is directly related to CRP. The assay has sensitivity of 0.1 mg/litre. The ready-to-use liquid reagents can be placed directly on a chemistry analyser and will yield precise results in minutes (Cortlandt Manor, NY, USA).

Other Routine blood investigations such as

1. Complete blood count which includes Hb,TC,DC,ESR,Platelet count,
2. Blood sugar, urea,
3. Serum creatinine, electrolyte, serum creatinine kinase –MB isoform, and
4. Fasting lipid profile were obtained.

The standard 12 leads conventional Electrocardiograph (ECG) was taken at the time of admission and analysed for the ST Depression (STD) which is suggestive of ischemia.

FOLLOWUP:

All the patients were followed up for the period of 7 days. Everyday details about the severity of angina and its equivalent, duration, number of episodes, were noted.

Routine physical examination and ECG was taken both in the morning and in the evening and additional investigations were taken if needed.

TWO DIMENSIONAL TRASNSTHORACIC ECHOCARDIOGRAPHY was taken for the all the patient at the time of discharge and their cardiac function and ejection fraction was accessed.

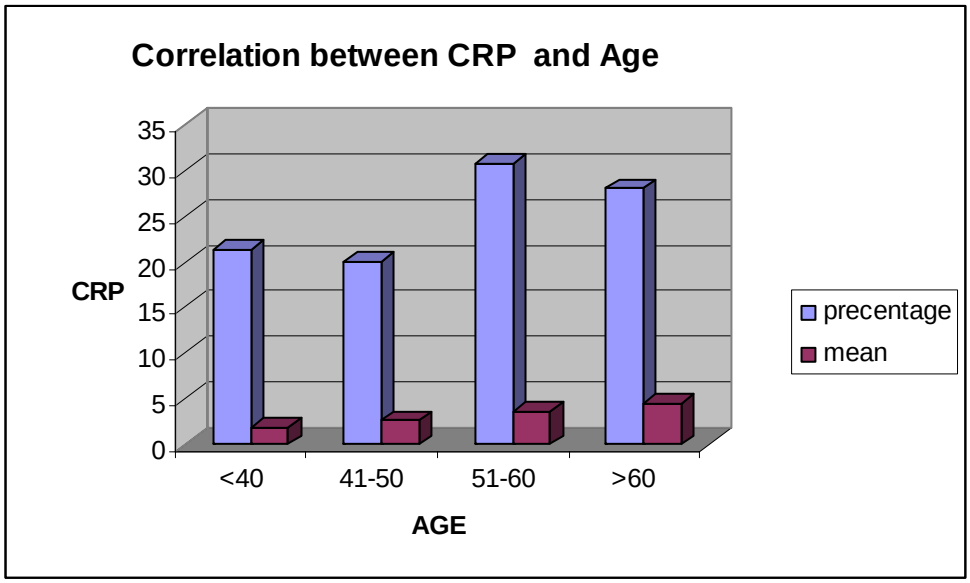
Patients were discharged on 8th day if they were stable without any additional ischemic episodes or complication otherwise their hospitalization were prolonged.

Standard guidelines for the treatment of unstable angina by American heart association were followed. The treatment modified according to the complications during the hospital stay.

OBSERVATIONS

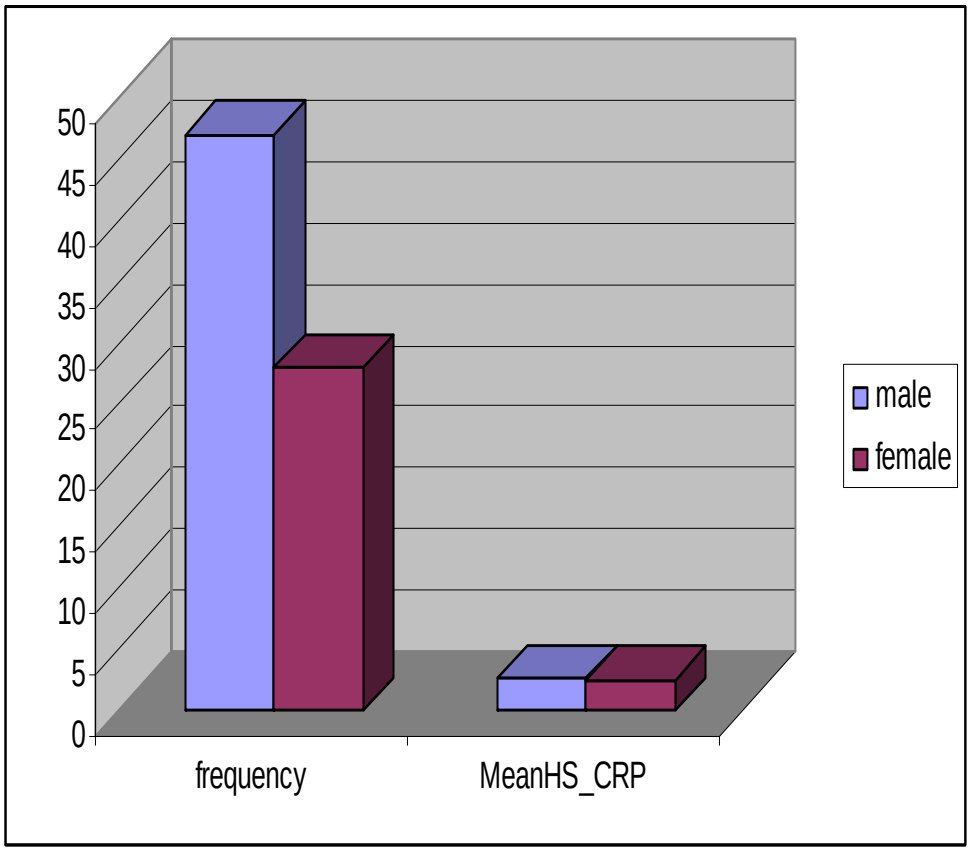
AGE AND hs-CRP

Age	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
<40	16	21.33	1.84	2.01
41-50	15	20	2.62	2.02
51-60	23	30.67	3.67	2.38
>60	21	28	4.5	1.72



SEX AND hs-CRP

Sex	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
Male	47	62.7	2.65	2.25
Female	28	37.33	2.54	2.46



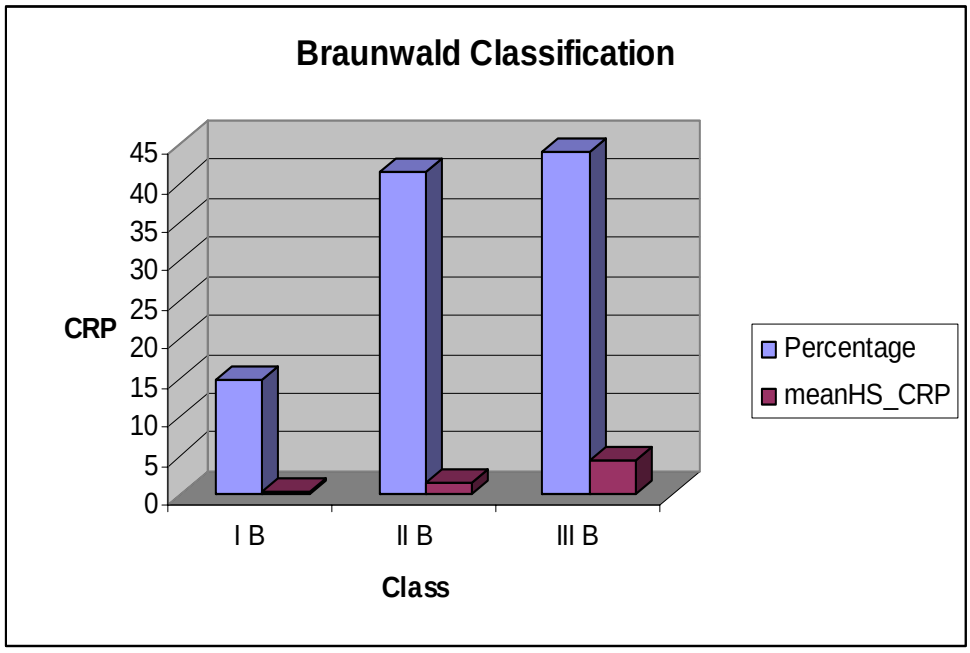
SEX

Braunwald Class and hs-CRP

Braunwald class.	Frequency	Percentage	Mean hs-CRP(mg/dl)
I B	11	14.67	0.42
II B	31	41.33	1.51

III B	33	44	4.37

'p' value of <0.001

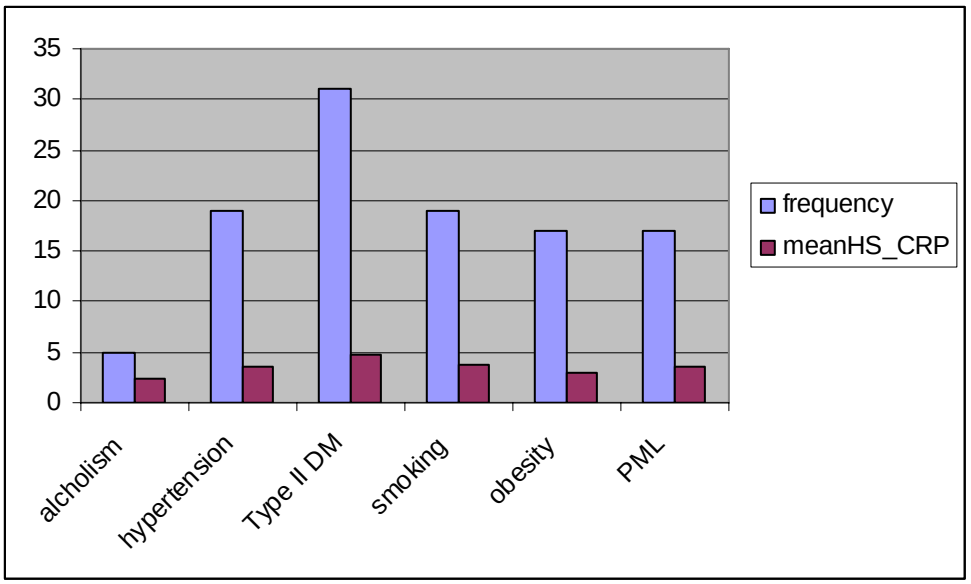


Risk Factors and hs-CRP

RISK FACTORS	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD	P VALUE
Alcoholism	5	6.67	2.36	2.84	*0.807*
Hypertension	19	25.33	3.6	2.48	0.030
Type II DM	31	41.33	4.76	2.31	<0.001
Smoking	19	25.33	3.78	2.72	***0.020***

Obesity	17	22.67	3.05	2.51	0.030
PML	17	22.67	3.48	2.64	*0.079*

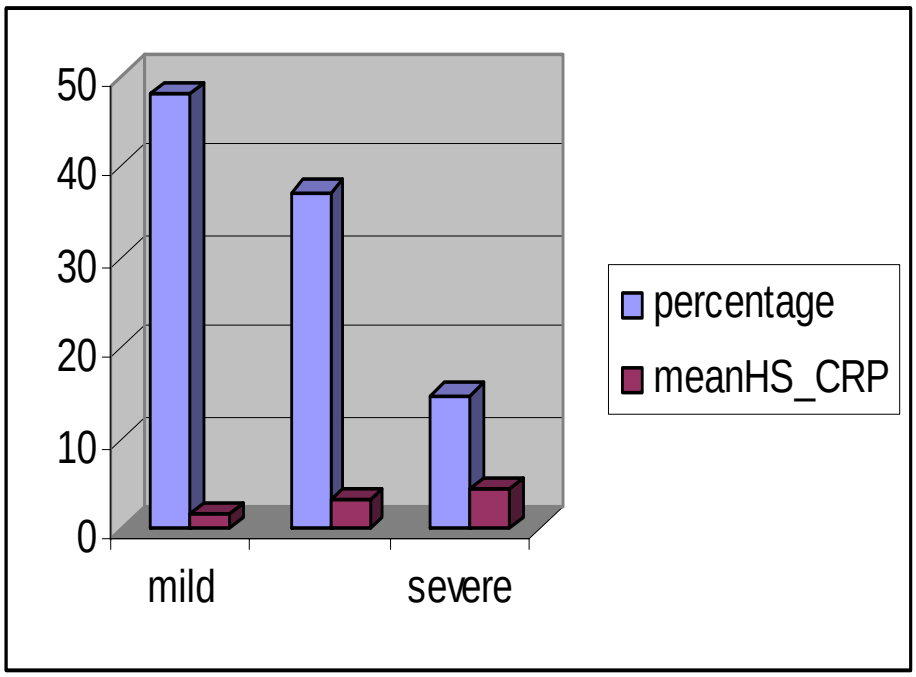
RISK FACTORS



Severity of Pain and hs-CRP

Severity of pain	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
Mild	36	48	1.62	1.92
Moderate	**28**	**37.33**	**3.18**	**2.36**
Severe	11	14.67	4.38	1.96

'P' value of <0.001

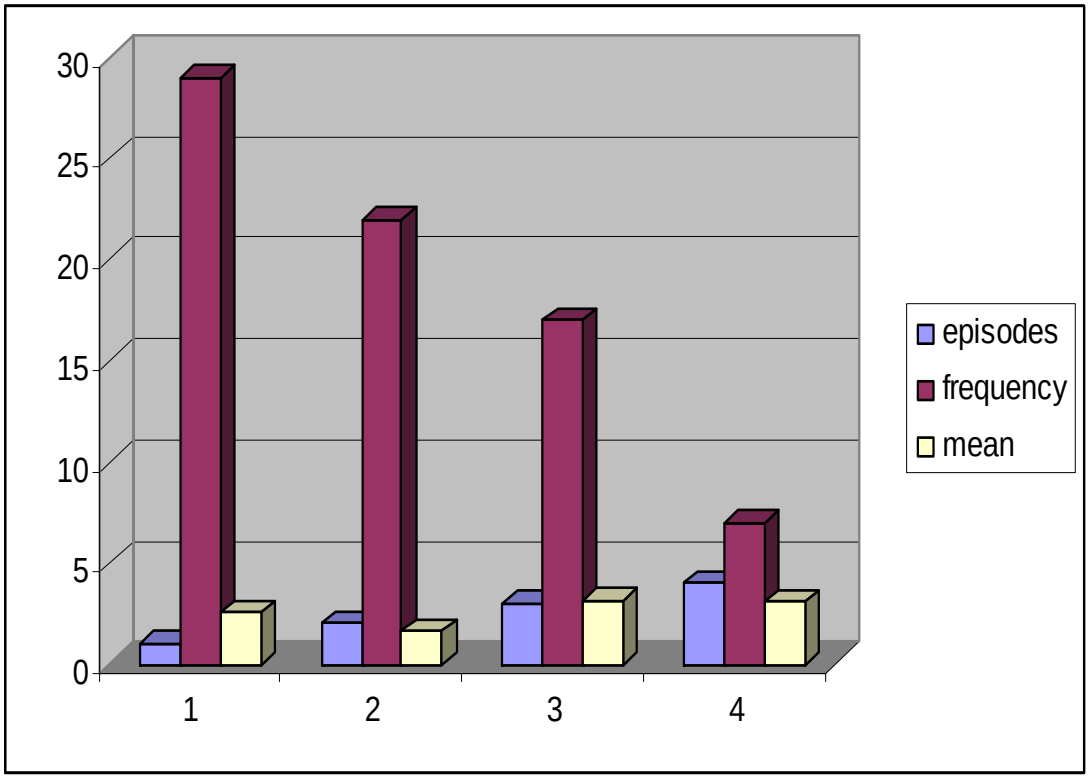


SEVERITY OF PAIN

No of Episodes of Chest Pain and hs-CRP

Episodes	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
1	29	38.67	2.54	2.06
2	22	29.33	1.62	1.92
3	17	22.67	3.18	3.06
4	7	9.33	3.08	3.02

'P' value of 0.02

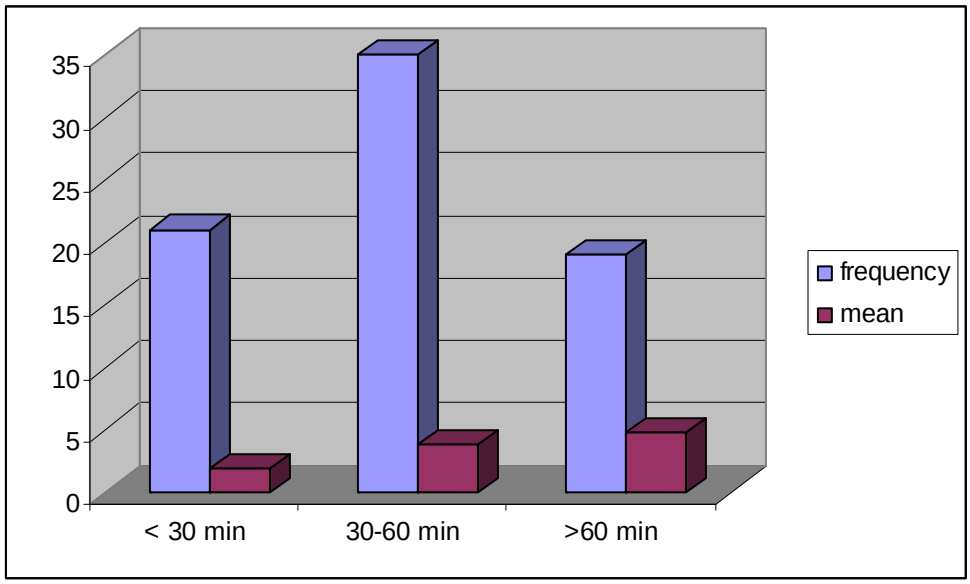


NO. OF EPISODE OF CHEST PAIN

Duration of Chest Pain and hs-CRP

Duration of chest pain	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
< 30 min	21	28	1.9	2.07
30-60 min	35	46.7	3.83	2.38
>60 min	19	25.3	4.8	1.72

P’ value of <0.001

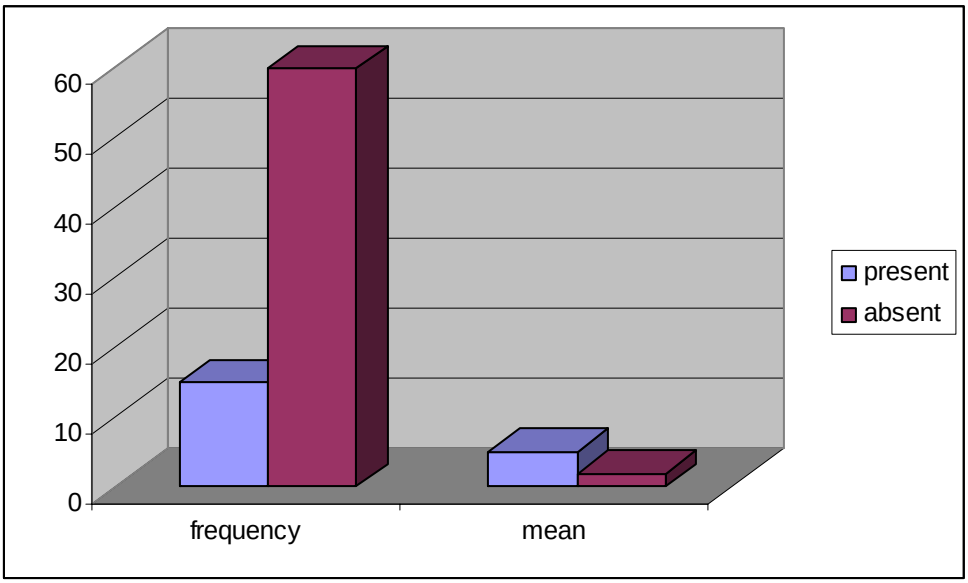


DURATION OF CHEST PAIN

Heart Failure and hs-CRP

Heart failure	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
Present	15	20	5.07	1.88
Absent	60	80	1.99	1.99

‘*p’ value* of <0.001

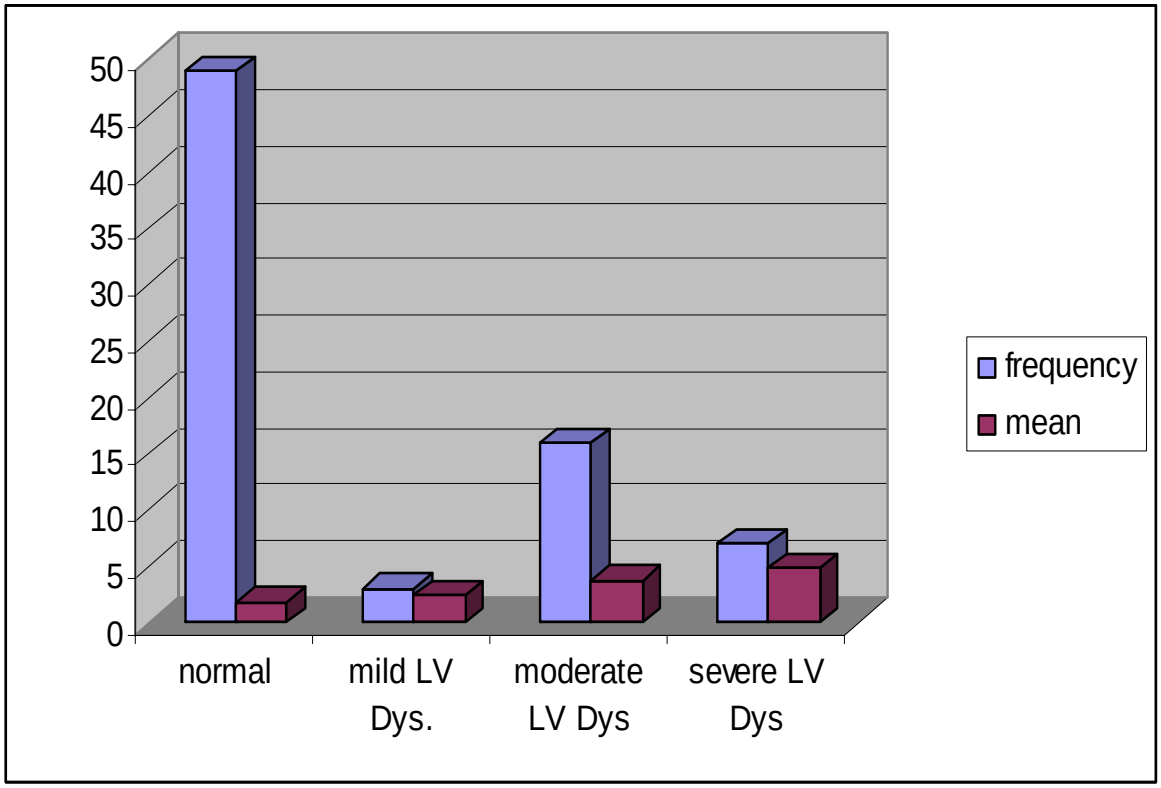


HEART FAILURE

ECHOCARDIOGRAPHY and hs-CRP

Echo	Frequency	Percentage	Mean hs-CRP(mg/dl)	SD
Normal	49	65.33	1.9	2.07
Mild LV Dys.	3	4.6	2.5	2
Moderate LV Dys	16	21.33	3.83	2.38
Severe LV Dys	7	9.33	4.8	1.72

P value < 0.001



ECHOCARDIOGRAPH

hs-crp	Frequency	Percentage
<1	32	42.67
1-4	20	26.67
>4	23	30.67

DEVELOPMENT OF ARRTHYMIAS

	RBBB	VPC	LAHB	LBBB	II BLOCK	SINUS BRADY	SVT
TYPES	8	10	4	3	1	1	1

ARRTHYMIAS AND hs-CRP

ARRTYMIAS	FREQUENCY	Mean hs-CRP(mg/dl)	SD
Present	28	5.07	1.88
Absent	47	1.99	1.99

ECG CHANGES AND hs_CRP

ECG	PERCENTAGE	Mean hs-CRP(mg/dl)
LWI	*13.33*	*3.14*
ILI	*16*	*2.55*
ASI	*21.33*	*3.04*
IWI	*24*	*2.02*
AII	*13.33*	*1.87*
AWI	*12*	*3.31*

LWI- LATERAL WALL ISCHAEMIA

ILI – INFEROLATERAL WALL ISCHAEMIA

ASI – ANTERO SEPTAL ISCHAEMIA

IWI – INFERIOR WALL ISCHAEMIA

AII –ANTEROINFERIOR WALL ISCHAEMIA

AWI –ANTERIOR WALL ISCHAEMIA

DISCUSSION

Total number of patients included in this study were 75. Variables that were analysed in this study were age, sex, and severity of angina, no. of episodes of angina per day, duration of each anginal episode, development of heart failure, arrhythmias and

risk factors of cardiovascular disease. This study compares these variables with the level of hs_CRP in the serum. In this study, mean value of hs_CRP were found to be 2.61 mg/dl.

AGE

Of the 75 patients, 16 patients were in age group less than 40 years, 15 patients were between 41-50 years, 23 patients were between 51-60 years, and 21 patients were more than 60 years. The mean hs_CRP level in each group were 1.84, 2.62, 3.67and 4.50 mg/dl respectively . Thus there is gradual increase in hs_CRP levels with increasing age.

This correlate with previous study by M.A. Mendell et al, Praful patel et al, that there is an elevation of hs_CRP level with increasing age. Another study by Seishi Yamada et al in Japanese population also confirms this observation. In the study by Naomi et al that in elderly patient there is increase in hs_CRP level which in turn increases the production of tissue factors by monocytes. The monocytes titer factor production is increased by several folds in elderly patients. This titer factor is responsible for activation of

extensive coagulation cascade leading to thrombus formation and acute coronary events in elderly population. These elevations of hs_CRP in postmenopausal women were more than that of men in the similar age group.

SEX

In this study, number of male patients were 47 (62.67%) while no number of female patients were 28 (37.23), and their average hs_CRP were 2.65 and 2.54 mg/dl respectively.

In previous study Nakagomi et al showed that CRP level were more in men comparing with women in younger age group (<50 yrs) but as the age advances the CRP level gradually rises and at post menopausal age that CRP level were significant greater than the CRP values in men of similar age group. Also there is gross increase in CRP levels in younger women (<50 yrs) comparing to post menopausal women also noted in this study. The same observations were also seen in other studies conducted by M.A. Mendall et al and Yamada et al. But in women Health Study (WHS) states that although no difference in hs_CRP values was

noted between premenopausal women and age-matched males, recent reports showed that hormone replacement therapy (estrogen alone or estrogen and progestin) is associated with increased hs_CRP concentrations. These findings suggest that the increased hs_CRP seen in the WHS subjects may reflect the influence of hormone replacement therapy rather than the effect of gender. *In our study no significant difference is noted between two sexes.*

Braunwald classification:

This classification was proposed to assess the severity and risk stratification in unstable Angina. In this study out of total number cases, 11 patients were classified under class IB, 31 patients under class IIB and 33 patients were under class IIIB and their mean hs_CRP value were 0.42, 1.51, and 4.37 mg/dl respectively with '*p' value of <0.001* which denotes significant at 1% level which implies there is significant increase in the level of hs-CRP over progressing Braunwald classes from IB to IIIB.

In a study by Ferreiros, Boissonet CP et al where 194 patients were studiedand found to have elevation of hs-CRP levels

which increased over progressing Braunwald classes from IB to IIIB and in this study Braunwald class C patients were not included because in post infarction angina of less than 2 weeks duration there may be a confounding factor in CRP elevation due to myocardial necrosis and it takes for minimum of 4 weeks for CRP values to come to normal after an acute myocardial infarction. In our study also Braunwald Class C patients were not included for same reason.

Coronary Risk factors:

Risk factors that were present in the study group were smoking, alcohol, hypertension, diabetes, post menopausal age group and obesity. Several CHD risk factors appear to modulate the inflammatory response and affect hs_CRP concentration.

Of the total number of patients, 19 patients had history of smoking for considerable period of time. Of these patients, the mean hs_CRP was 3.76 mg/dl when compared to those without the history of smoking was 2.06 mg/dl with '*p' value 0.020* which denotes significant at 5% level.

Cigarette smoking has also been shown to increase the concentration of several inflammatory markers, including hs_CRP,

interleukin-6, and soluble intercellular adhesion molecule-1. Increases of both interleukin-6 (Ridker PM et al) and soluble intracellular adhesion molecule-1 were shown to be associated with increased risk of future first coronary events in both men and women. Smoking cessation decreases these markers.

Of the total number of patients,the history of alcohol intake for significant period of time were found in 5 patients and their mean hs_CRP value was 2.84 mg/dl when compared to those who were not in the habit of taking alcohol is 2.30 mg/dl with '*p' value 0.807 which* indicates statistically not significant. These were no previous study that assessed the level of hs-CRP and alcohol intake.

Of the total number of patients, 17 patients were found to be obese by means of BMI and their mean hs_CRP value was 3.65 mg/dl when compared to those who were not obese with their mean hs_CRP value was 2.08 ,with 'P' value of 0.030 which denotes significant at 5% levels.

Obesity, for example, is directly associated with increased hs_CRP concentrations, an intriguing observation considering that interleukin-6, the primary stimulant of the de novo hepatic synthesis of CRP, is secreted by adipose tissue (Visser M, Bouter

LM, McQuillan GM, Wener MH, Harris TB et al). Therefore, the attenuation of the inflammatory response may represent a mechanism by which diet and weight loss reduces cardiovascular risk.

Of the total no. of patients, 19 patients had h/0 hypertension on treatment, and their mean hs_CRP value were 3.60 mg/dl when compared to those without hypertension was 2.27mg/dl, with 'P' value of 0.030 which denotes significant at 5% levels. This value significantly correlates with other studies.

Laurie G. Futterman *et al :* Hypertension may be linked to inflammation by angiotensin II. In addition to its vaso-constricting properties, angiotensin II can trigger intimal inflammation which leads to raise of hs-hs_CRP and the patient admitted with hypertension and unstable angina with high level of hs-hs_CRP were at high risk.

In this study group, 31 patients had Type 2 diabetes mellitus with their mean hs_CRP was 4.76 mg/dl when compared to 1.50mg/dl in non-diabetic patients group with 'P' value is <0.001 which denotes significant at 1% level.

Diabetic patients are reported to have increased hs_CRP values (Ford ES et al); In this regard, links between hs_CRP and the insulin resistance syndrome have also been reported (Yudkein et al). In addition, experimental findings suggest that increased blood pressure promotes endothelial expression of cytokines and inflammatory activation. These observations suggest that perhaps better control of diabetes and hypertension may attenuate the contribution of the inflammatory response to overall cardiovascular risk. Taken together, the available evidence thus supports the hypothesis that hs_CRP concentrations correlate with endothelial dysfunction

Analysis of Anginal Episodes:

Regarding the average number of angina episodes per day in the study group, single episode was present in 29 patients with their mean hs_CRP 2.54 mg/dl, two episodes were present in 17 patients with their mean hs_CRP 3.18 mg/dl, and 4 episodes were present in 7 patients with their mean hs_CRP 3.08 mg/dl. Thus there is a progressive increase in hs-CRP levels with increase in number of anginal episodes with '*P' value of 0.02* which denotes significant at 5% levels.

Liuzzo et al. showed that in 31 patients with severe unstable angina and no evidence of myocardial necrosis, as documented by the absence of increased cardiac troponin T, hs_CRP concentrations >3 mg/L at admission were associated with an increased incidence of recurrent angina, coronary revascularization, MI, and cardiovascular death. The same group later demonstrated that hs_CRP >3 mg/L at discharge in 53 unstable angina patients was associated with increased readmission for recurrent instability and MI. In a similar study of unstable angina, Ferreiros et al. concluded that the prognostic value of hs_CRP measured at discharge was better than that determined at admission in predicting adverse outcome at 90 days.

Furthermore, hs_CRP was the strongest independent predictor of adverse events in multivariate analysis. Data from the Thrombolysis In Myocardial Infarction 11A (TIMI 11A), a study of unstable angina and non-Q-wave MI, showed that markedly increased hs_CRP (15.5 mg/L) at presentation in 437 patients was a good predictor of 14-day mortality in that population. Furthermore, hs_CRP helped to identify those patients with negative cardiac troponin T (qualitative rapid bedside method with cutoff of <0.2

μg/L) who were at increased risk of mortality .A recent report by de Winter et al showed that hs_CRP concentrations >5 mg/L at admission in 150 patients with non-ST-elevation acute coronary syndromes were associated with an increased incidence of major cardiac events within 6 months, regardless of cardiac troponin I values.

Duration and severity of angina

Regarding average duration of Anginal episodes, 21 patients had chest pain for < ½ hr with their mean hs_CRP 1.90mg/dl, 35 patients had for ½ -1 hr with their mean hs_CRP 3.83 mg/dl ,19 patients had for >1 hr with their mean hs_CRP 4.80 mg/dl. This shows that there is an increase in hs_CRP value with increase in duration of each episode with *'P' value of <0.001*, which denotes significant at 1% level.

Regarding of severity of Angina which is a subjective variable 36 patients had mild anginal episodes with their mean hs_CRP was 1.62 mg/dl, 28 patients with moderate anginal episodes with their mean hs_CRP 3.18 mg/dl, 11 patients with severe anginal episodes with their mean 4.38 mg/dl. Thus in this study there was steady increase in hs-CRP levels with increase in

severity of Anginal episodes with the *'P' value of <0.001* which indicates significant at 1% level.

In the study by Giovanna Liuzzo et al where prognostic value of CRP was studied. The patient with low hs_CRP elevation was discharged sooner from hospital had only few anginal episodes and most of which were silent and duration was minimal. In patients with high hs_CRP value has more number of ischemic episodes and signs of ischemic were significantly longer and they may need coronary intervention. Similar study by MP Holay et al states that high hs-CRP was associated with increased severity, duration, and number of episodes. This elevated hs-CRP values may be used for risk stratification of patients with unstable angina who need urgent coronary revascularization procedure. In a study by Biasucci et al who showed elevated CRP at discharge may associated with recurrent instability of Angina.

In another study by Liuzzo CRP levels a raised in patients who were undergoing coronary Angioplasty and severe unstable Angina. The elevation of CRP values in proportion to increase in frequency of Anginal episodes, severity of anginal episodes and

duration of each anginal episodes may reflect the severity of inflammation that is taking place is eroded or ruptured plaque on the vessel wall loading to thrombus formation and progression. The elevation of CRP may not be due to myocardial necrosis because the Troponin values in this study were within normal range.

ECG CHANGES

Out of 75 patients, the type of the regional wall ischemia and their frequency are narrated in the tabular column and there is no considerable remarks to the level hs_CRP and the area of ischemia.

Liao Y, Liu K, Dyer A, et al assesses the combined high-sensitivity CRP and ECG STD (ST Depression) criteria**.** Because CRP and STD criteria provided independent prognostic information**, t**he ability of the combination of these variables to improve prediction of mortality was assessed. In Cox analyses

stratified by study center, the combined CRP and ECG STD variable improved risk stratification compared to either CRP or STD alone for both CVD and all-cause mortality, with the presence of both ECG STD and an elevated CRP associated with the greatest risks

Arrhythmias:

Out of 75 patients, 28 patients developed some form of arrhythmias as indicated in tabular column with ECG changes.

Winter et al showed those patient admitted with high level of serum hs_CRP were prone to develop some form of Arrhythmias and more prone for sudden cardiac death.

Heart Failure and Echocardiography abnormality

Of the total number of patients, 15 patients developed heart failure during the hospital stay with their mean hs_CRP was 5.0 mg/dl when compared to those without heart failure of hs_CRP 1.99 mg/dl with '*p' value* of <0.001 which denotes significant as 1% level .

Of the total number of cases, 49 patients had normal LV function with their mean hs-CRP 1.90 mg/dl, 3 patients had mild LV dysfunction with their mean hs_CRP 2.50 mg/dl, 10 patients had moderate LV dysfunction with their mean hs_CRP 3.83 mg/dl, 7 patients had severe LV dysfunction with their mean hs_CRP 4.80 mg/dl. Thus there is steady increased hs_CRP value as severities of LV dysfunction increased with *'P' value <0.001* which denotes significant at 1% level.

Suleiman *et al* showed that plasma hs_CRP level is an independent marker of development of heart failure in patients with acute coronary syndrome .CRP levels may be related to inflammatory process associated with ischemic expansion and ventricular remodeling. Berton *et al* the first day hs_CRP level is the strongest predictor of both heart failure and depressed LV function.

This study carried out in 75 patients with unstable angina predicting the role of the elevated hs-CRP in the occurrence of minor and major coronary events during the hospital (average 7 days) and also the occurrence of complication in those patrients.The results of this study strongly correlates with hs-CRP elevation and the occurrence of minor and major coronary events and also the occurrence of complications .These findings correlates with results of other studies.

The hs- CRP level not only predicts the patient outcome in the hospital stay (short term) but also prognostic outcome and mortality in 1 month,3 months and 2 years in various studies carried out.

The hs- CRP level if combined with Trop-T, fibrinogen levels additionally predicts the prognostic outcome with greater sensitivity and specificity . The levels should be determined as early as possible after admission.

Should we include hs- CRP in the risk profile?

Based on solid and consistent evidence, the Centre for Disease Control and Prevention and the American Heart Association issued a recommendation for the screening of hs-CRP as a routine part of global cardiovascular risk assement and the determination of hs-CRP should be done at least done at baseline.

hs-CRP ,a modifiable risk factor?

There are increasing evidence that decrease in hs- CRP were associated with decreasing coronary events and progression of atherosclerosis. The addition of Aspirin and Statins to the therapy modifies the inflammation and decrease the hs- CRP levels. Also evidenced that Statins possess the properties beyond the lipid lowering effects , include anti-inflammatory effects which seems to be independent of their antilipaemic effect.

SUMMARY:

hs_CRP estimation was done for 75 patients of Unstable Angina admitted in the medical ward of Institute Of Internal Medicine ,Madras Medical College Hospital following observation was made.

- hs_CRP level in unstable Angina patients strongly correlates with number, duration and severity of Anginal episodes.
- hs-CRP level strongly correlates with development of other complications such as development of heart failure, arrhythmias, left ventricular dysfunction.
- hs_CRP level is increased in smoker, obesity, diabetes, hypertension, family history, post meno pausal women comparing to those without these risk factors.
- hs_CRP level also increasing with advancing age
- hs_CRP level progressively increased in patients from IB to IIIB in Braunwald classification.

CONCLUSION

Our understanding of atherosclerosis has evolved beyond the view that these lesions consist of a lifeless collection of lipid debris. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process. Substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease. Clinical studies affirm correlation of hs_CRP is the novel and evolving biomarker of inflammation with propensity to develop ischemic events and with prognosis after ACS. Intralesional or extralesional inflammation may hasten atheroma evolution and precipitate acute events. Hs_CRP elicited by inflammation may not only mark increased risk for vascular events, but in some cases may contribute to their pathogenesis. This new insight into the role of inflammation in the pathobiology of atherosclerosis has initiated important new areas of direct clinical relevance. We can use hs_CRP today for risk stratification.

Based on various studies, increased hs_CRP levels inpatients with high risk cardiovascular disease without documented CAD

warrant treatment with statin even if LDL-C levels are within target range. Patients with documented CAD and high hs-hs_CRP levels should be followed, and there risk factors should be managed aggressively..

Finally, the quest to identify proximal stimuli for inflammation, as one pathogenic process in atherogenesis or trigger to lesion complication, may yield novel therapeutic targets in years to come.

Sl. NO.	Age	Braunwald classification	Angina equivalent	Risk factors	Previous H/O CAD	Angina episodes / day	Duration of each episode	Severity of Angina	Arrythmias	Heart failure	MI	E
1.	45/F	II B	Angina	DM / SHT	Nil	One	240 min	Moderate	NO	NO	NO	L
2.	40/M	III B	Angina	Smoker	CSA 2 Yrs.	Three	240 min	Severe	RBBB	NO	NO	
3.	50/F	I B	Angina	Nil	Nil	One	30 min	Mild	NO	NO	NO	
4.	40/F	II B	Angina	DM	Nil	One	60 min	Mild	NO	NO	NO	A
5.	48/M	II B	Angina	DM	CSA 2 yrs	Three	60 min	Moderate	NO	NO	NO	I
6.	35/F	II B	Angina	Obese	Nil	Four	120 min	Moderate	NO	NO	NO	A
7.	54/M	III B	Angina /Syncope	DM /SHT	ASMI 5 yrs before	Three	120 min	Severe	VPC	YES	NO	AS
8.	58/M	III B	Angina/ Palpitation	Smoker/ Alcoholic	CSA 1 Yr	Two	240 min	Severe	NO	NO	NO	A
9.	40/M	II B	Angina	SHT	Nil	Single	60 min	Mild	NO	NO	NO	A
10.	54/M	III B	Angina	SHT/obese	CSA 2 yrs	Four	240 min	Severe	NO	NO	NO	I
11.	55/M	II B	Angina/ Epigastric pain	Alcoholic / DM	Nil	Four	30 min	Moderate	NO	NO	NO	I
12.	50/M	I B	Angina		NO	One	30 min	Mild	NO	NO	NO	A
13.	50/F	II B	Angina	DM	ASMI 5 yrs	One	60 min	Mild	NO	YES	NO	I
14.	55/M	I B	Angina	Smoker/DM	CSA	Two	60 min	Mild	NO	NO	NO	A
15.	75/M	II B	Angina Dys. IV	SHT	CSA TMT YESve	One	20 min	Moderate	NO	NO	NO	A
16.	55/M	III B	Angina Dyspnea C IV	Smoker	AWMI 2 yrs	Three	30 min	Moderate	LBBB	YES	NO	A
17.	40/F	I B	Angina	DM	NO	Two	20 min	Mild	NO	NO	NO	A
18.	65/M	III B	Angina/ Syncope	DM /SHT	AWMI 2 yrs	Three	60 min	Moderate	VPC	NO	NO	I
19.	70/M	III B	Angina Dysp. C IV	DM /SHT	HA	Two	20 min	Moderate	LAHB	YES	NO	I

Sl. NO.	Age	Braunwald classification	Angina equivalent	Risk factors	Previous H/O CAD	Angina episodes / day	Duration of each episode	Severity of Angina	Arrythmias	Heart failure	MI	E
20.	60/M	II B	Angina Syncope	Smoker/ Alcoholic	NO	Three	30 min	Mild	NO	NO	NO	
21.	50/F	II B	Angina Syncope	DM	NO	Two	120 min	Mild	NO	NO	NO	I
22.	40/F	I B	Angina	DM	CSA TMT YESve	Two	120 min	Mild	NO	NO	NO	A
23.	48/F	III B	Angina Syncope	SHT/DM	NO	Four	60 min	Moderate	RBBB	NO	NO	I
24.	60/M	III B	Angina	Smoker	Nil	Four	60 min	Mild	NO	NO	NO	A
25.	48/M	II B	Angina	NO	NO	One	60 min	Mild	NO	NO	NO	I
26.	61/F	III B	Angina/ Dys. C IV	DM	Old MI	Three	30 min	Moderate	LBBB	YES	NO	A
27.	40/M	III B	Angina	Obese	NO	Three	20 min	Moderate	LAHB	NO	NO	I
28.	63/F	III B	Angina Syncope	PML	NO	One	20 min	Severe	NO	NO	NO	A
29.	65/M	II B	Angina / Palpitation	Smoker / Alcoholic	NO	One	60 min	Mild	NO	NO	NO	A
30.	30/M	I B	Angina / Palpitation	Smoker	NO	One	60 min	Mild	WPW Syndrome	NO	NO	A
31.	65/M	II B	Angina / Palpitation	NO	NO	Two	120 min	Moderate	First degree AV block	NO	NO	
32.	30/M	III B	Angina	DM/SHT	CSA TMT YES	Three	120 min	Severe	VPC	NO	NO	
33.	45/M	I B	Angina	NO	NO	Oe	20 Min	Mild		NO	NO	A
34.	25/M	III B	Angina	Smoker / Alcoholic	CSA TMT YES	Two	60 min	Severe	NO	NO	NO	
35.	40/F	II B	Angina	NO	NO	Two	30 min	Moderate	NO	NO	NO	A
36.	45/F	II B	Angina	DM	NO	Three	40 min	Moderate	NO	NO	NO	
37.	59/F	III B	Angina Dys C IV	DM / SHT/ obese	Old MI AWMI	Four	60 min	Severe	LBBB	YES	NO	A
38.	64/M	II B	Angina	DM	NO	Three	40 min	Moderate	NO	NO	NO	
39.	60/M	II B	Angina / Palpitation	DM / Obese	NO	Two	20 min	Moderate	Sinus Brady	NO	NO	I

Sl. NO.	Age	Braunwald classification	Angina equivalent	Risk factors	Previous H/O CAD	Angina episodes / day	Duration of each episode	Severity of Angina	Arrythmias	Heart failure	MI	E
40.	64/M	III B	Angina	Smoker / SHT	CSA TMT YES	Four	60 min	Moderte	NO	NO	NO	A
41.	40/F	II B	Angina	SHT	NO	One	20 min	Mild	NO	NO	NO	I
42.	82/F	I B	Angina	NO	NO	One	10 min	Mild	NO	NO	NO	I
43.	56/F	II B	Angina	DM	NO	Three	30 min	Mild	NO	NO	NO	A
44.	40/M	III B	Angina / Dys C IV	DM / SHT	NO	Two	40 min	Moderate	VPC	YES	NO	A
45.	35/M	II B	Angina	Smoker	NO	Two	30 min	Moderate	NO	NO	NO	I
46.	70/F	III B	Angina / Dys IV	DM / SHT	CSA	Three	20 min	Mild	LBBB	YES	NO	A
47.	65/M	II B	Angina	DM	NO	One	30 min	Mild	NO	NO	NO	L
48.	65/M	III B	Angina	DM / Obese	NO	One	20 min	Mild	NO	NO	NO	
49.	54/F	I B	Angina	DM / Obese	NO	One	20 min	Mild	NO	NO	NO	
50.	48/M	I B	Palpitation / Angina	Smoker / DM	NO	One	30 min	Mild	SVT	NO	NO	
51.	42/M	II B	Angina	Obese	NO	One	60 min.	Mild	NO	NO	NO	A
52.	58/M	III B	Angina / Dys C. IV	Smoker	NO	Two	20 min	Moderate	LBBB	YES	NO	A
53.	60/M	II B	Angina	Obese	NO	One	20 min	Mild	NO	NO	NO	L
54.	64/M	II B	Angina / Dys C. IV	Obsese /PML	CS A^{YES}	Three	10 min	Moderate	RBBB	YES	AIMI	A
55.	58/F	II B	Angina / Palpitation	PML	NO	Two	30 min	Mild	NO	NO	NO	I
56.	58/M	II B	Angina / Syncope	Nil	NO	Three	60 min.	Moderate	NO	NO	NO	I
57.	40/M	III B	Palpitation / Angina	Smoker	NO	One	20 min	Mild	SVT	NO	NO	L
58.	70/F	III B	Angina / Dys IV	PML	AWMI 2 Yrs.	Two	20 min	Mild	VPC	YES	NO	L
59.	70/M	III B	Angina / Dys IV	DM/SHT	IWMI 5 Yrs.	Two	20 min	Mild	VPC	YES	NO	I
60.	80/M	II B	Angina	Smoker	NO	One	30 min	Mild	NO	NO	NO	I

Sl. NO.	Age	Braunwald classification	Angina equivalent	Risk factors	Previous H/O CAD	Angina episodes / day	Duration of each episode	Severity of Angina	Arrythmias	Heart failure	MI	E
61.	64/M	I B	Angina	NO	TMT YES	Two	20 min	Mild	NO	NO	NO	L
62.	52/F	II B	Angina	DM	NO	One	20 min	Mil	NO	NO	NO	A
63.	49/F	III B	Angina /Palpitation	Obese / PML	NO	Three	40 min	Moderate	Sinus Brady	NO	NO	L
64.	54/M	II B	Angina	DM / SHT	NO	One	120 min	Mild	NO	NO	NO	A
65.	55/F	III B	Angina	PML	NO	Two	120 min	Severe	LBBB	YES	NO	
66.	56/M	III B	Angina / Dys C IV	Smoker / SHT	NO	Two	30 min	Moderate	VPL	NO	NO	L
67.	70/M	III B	Angina /Palpitation	NO	CSA	One	20 min	Moderate	NO	NO	NO	A
68.	56/F	II B	Angina Syncope	Obese / DM	NO	One	20 min	Moderate	BI Fascicular Block	NO	NO	A
69.	60/F	II B	Angina / Palpitattion	PML / Obese	CSA	Two	20 min	Mild	NO	NO	NO	
70.	45/M	III B	Angina / Dys C IV	Smoker	ASMI 2 Yrs.	One	30 min	Severe	VPC LAHB	YES	NO	A
71.	40/M	III B	Angina	Smoker	NO	One	30 min	Moderate	SVT	NO	NO	A
72.	64/M	III B	Angina	DM / SHT	CSA	Two	40 min	Mild	NO	NO	NO	A
73.	42/M	III B	Angina / Palpitation	Smoker	NO	Two	40 min	Moderate	VPC	NO	AWMI	I
74.	60/F	III B	Angina	NO	NO	One	40 min	Mild	NO	NO	NO	
75.	58/F	III B	Angina Dys. C IV	DM/ SHT/ Obese	AWMI 6 Yrs.	Three	120 min	Severe	LBBB	YES	NO	A

SHT- systemic hypertension DM-Diabetes mellitus Obe-Obesity
SM-Smokers

LWI- lateral wall ischemia VPC-Ventricular premature complex
PML-Postmenopausal ASI – antero septal ischemia

ILI – inferolateral wall ischemia SVT-Supraventricular tachycardia
LBBB-left bundle branch block C IV-Class IV

. IWI – inferior wall ischemia LAHB-Left anterior hemi block AII –anteroinferior wall ischemia

RBBB-Right bundle branch block
LV Dysfn.-LV Dysfunction.

AWI –anterior wall ischemia

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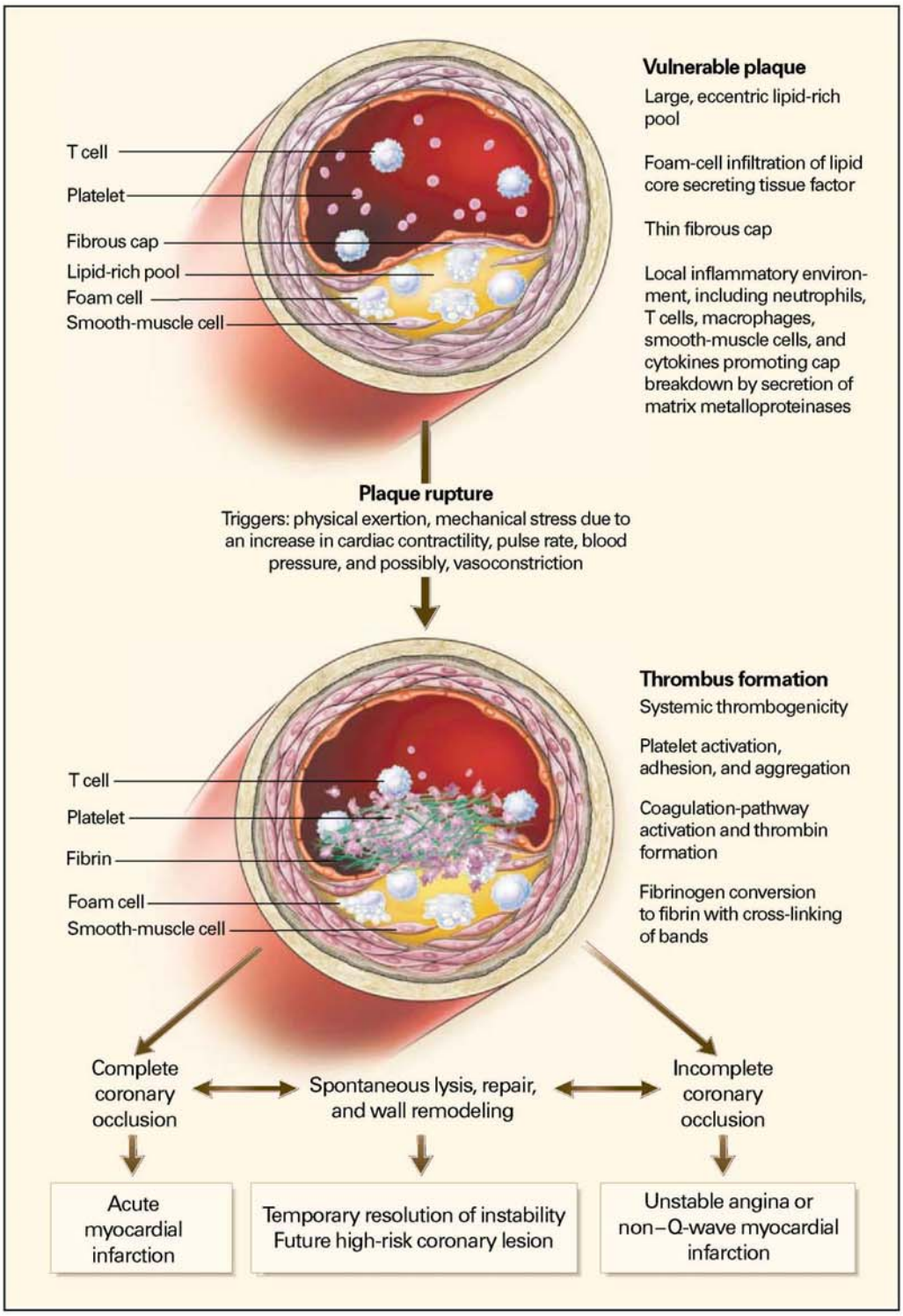

Pathophysiologic Events Culminating in the Clinical Syndrome of Unstable Angina.

Numerous physiologic triggers probably initiate the rupture of a vulnerable plaque. Rupture leads to the activation, adhesion, and aggregation of platelets and the activation of the clotting cascade, resulting in the formation of an occlusive thrombus. If this process leads to complete occlusion of the artery, then acute myocardial infarction with ST-segment elevation occurs. Alternatively, if the process leads to severe stenosis but the artery nonetheless remains patent, then unstable angina occurs.