SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM – 695011

PROJECT REPORT

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Programme: DM Cardiology

Month &Year of Submission: November 2005

Certificate

I, Dr. Bijulal .S, hereby declare that I have undertaken the work necessary for the project, under the guidance of the Faculty, Department of Cardiology.

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Place: Trivandrum

Date: 05/11/2005

Forwarded. He has carried out the minimum required procedures.

Signature 8/11/05

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LIST OF PROJECTS

1. ANGIOGRAPHIC COMPARISON BETWEEN STABLE ANGINA AND ACUTE CORONARY SYNDROME REGARDING NUMBER OF UNSTABLE PLAQUES

2. LONG TERM CLINICAL FOLLOW-UP OF PATIENTS WITH TWO VESSEL CORONARY ARTERY DISEASE NOT INVOLVING LEFT ANTERIOR DESCENDING ARTERY

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ANGIOGRAPHIC COMPARISON BETWEEN STABLE ANGINA AND ACUTE CORONARY SYNDROME REGARDING NUMBER OF UNSTABLE PLAQUES

Background and review of literature

Acute coronary syndromes (ACS) are the leading cause of cardiovascular deaths. Of persons with acute coronary syndromes, one fourth have ST elevation myocardial infarction and three fourth have unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI). STEMI is commonly associated with acute total thrombotic occlusion of a coronary artery and UA/NSTEMI is associated with severe coronary occlusion but not total block of culprit coronary artery. Among patients with UA/NSTEMI between 40 and 60 percent have elevated troponin levels

However chronic coronary artery disease is commonly due to obstruction of coronary arteries by atheromatous plaques and cause symptom of stable angina pectoris

The pathophysiology of ACS 24 involves the acute phase of UA, but the actual pathophysiology of atherosclerosis starts much earlier and then may last many years after the clinical event. The acute event involves thrombus formation at the site of an eroded plaque and is known as atherothrombosis. Thus the pathophysiology of ACS can be divided into three phases, vis, the development of unstable plaque, acute ischemic event and long-term risk of recurrence of coronary event.

Rupture of the fibrous capsule of plaque [24] reflects an imbalance between the forces that impinge on the plaque's cap and the mechanical strength of the cap. Interstitial collagen provide most of the resistance to plaque rupture and factors which reduce the synthesis of collagen by smooth muscle cells such as T

cell derived interferon gamma favor plaque disruption. Increased catabolism of collagen by matrix metalloproteinases and elastolytic cathepsins contribute significantly to plaque rupture. Another feature of vulnerable plaque is relative lack of smooth muscle cells. Inflammatory markers can favor programmed cell death of smooth muscle cells. This lead to reduced collagen synthesis and weakening of fibrous cap. Another characteristic feature of vulnerable plaque is accumulation of macrophages and large lipid pool. Large lipid pool can serve to concentrate biomechanical forces on the shoulder region of plaque and can favor plaque rupture. Activated macrophages produce cytokines and favor cap weakening and smooth muscle apoptosis.

Current evidence suggests [14,15,16] that high-risk plaques are numerous in a given coronary tree and inflammation is wide spread. Previous studies have demonstrated evidence for plaque ulceration or thrombosis in more than one lesion in many cases. Individuals with multiple unstable plaques tend to have worse outcomes during follow-up. Several lines of evidence support systemic and diffuse nature of inflammation in individuals with ACS. Studies have demonstrated increased levels of myeloperoxidases in great cardiac vein samples, elevation of C reactive protein[13] and other markers of inflammation. This is so even in the absence of biochemical evidence of myocardial injury that might elicit a secondary inflammatory response. Thus a combination of imaging studies and investigations using inflammatory markers support the systemic and diffuse nature of plaque vulnerability. This recognition has therapeutic

implications. In addition to revascularization such individuals require plaque passivation therapy.

Chronic coronary artery disease and the syndrome of stable angina is related to stable coronary plaques and the symptom is precipitated by increased demand or transient reduction in supply related to coronary vasoconstriction (dynamic stenosis and variable threshold angina)

Angiographic assessment of plaque vulnerability

Ambrose et al [2]classified coronary plaques according to their morphology into

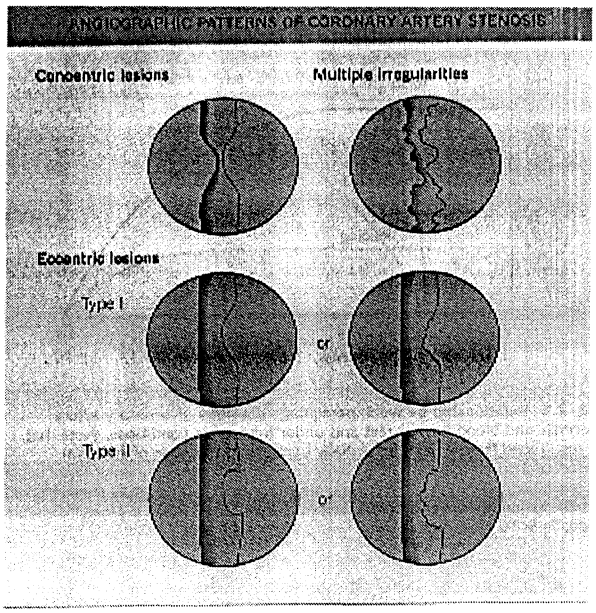
(a) Concentric stenosis – symmetric narrowing of coronary artery with symmetric stenosis

(b) Eccentric stenosis

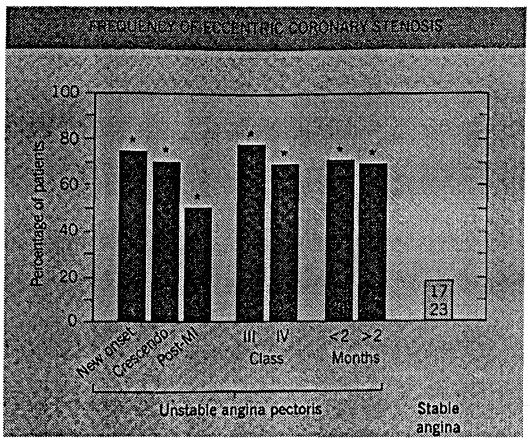
(i) Type I eccentric lesions – an asymmetric stenosis with smooth borders and broad neck

(ii) Type II eccentric lesions – asymmetric stenosis with narrow base, overhanging edges or very irregular borders

(c) Multiple irregularities



Goldstein et al [1] considered a lesion to be complex, if it demonstrated two of the four characters. These are presence of thrombus, plaque ulceration, plaque irregularity and impaired distal flow. They exclude chronic total occlusions by noting their tapering end and multiple fine collaterals. They noticed that 40 percent of patients with acute MI have another unstable plaque in coronary tree.



Ambrose et al –frequency of type II eccentric lesions in UA and stable angina

Kassi et al[19] noticed 2.6 vulnerable plaques per patient in a cohort of patients with unstable angina.

A number of morphologic characters are associated with increased risk of plaque instability. These are irregular contours, greater lesion length, steeper inflow and outflow angle, ulceration, thrombosis and symmetry index.

However the progression and instability have not been consistently demonstrated always and there is a significant overlap between behavior of smooth and complex lesions. But generally unstable plaques tend to clump together in a given patient.

However resolution of X ray angiography is 150 to 200 micrometers and there is significant variance between CAG and post mortem studies and significant inter operator difference in image interpretation.

Other methods of assessing plaque vulnerability

(a) High frequency intra vascular ultrasound[10] – characteristically unstable plaque is soft, echo lucent and eccentric. Overall ability of IVUS to predict plaque vulnerability is limited at present. However IVUS radio frequency signal analysis and elastography appear promising.

(b) Angioscopy[11]– by revealing color, contour and configuration angioscopy convey information about plaque stability. Yellow plaques are consistent with lipid rich atheroma while white gray plaques are fibrous plaques. Yellow plaques and thrombus are more prevalent in unstable angina. Thrombus is five times more likely to be seen over a yellow plaque than a white plaque. Angioscopy is much more sensitive than angiography and IVUS for detection of unstable plaque.

(c) Optical coherence tomography—OCT obtain micrometer level tomographic images analogous to IVUS, but measure back scattered light instead\ad of sound. Intensity of reflected infra red light is measured with interferometer. Image resolution is of order of 10 microns

(d) Thermography -- Region with superficial inflammation and endothelial denudation have higher plaque temperature and it correlates with plaque vulnerability.

(e) Raman spectroscopy [12]—Elucidate chemical composition and structure of a biologic tissue. Raman spectra are highly specific for individual molecules and can provide information about tissue of interest. Can classify coronary arteries as non-atherosclerotic, non-calcified plaques and calcified plaques and can accurately determine cholesterol content and can predict vulnerability.

Aim of study

To compare coronary angiogram of patients with acute coronary syndrome with that of patients with stable angina regarding presence of multiple unstable plaques and to correlate with recurrent ischemic events on follow-up

Materials and methods

Inclusion criteria

One hundred and two consecutive patients whose indication for coronary angiogram was acute coronary syndrome and ninety-eight consecutive patients whose indication for angiogram was stable angina pectoris were studied, over a time period extending for a 3-month period starting from first of November 2004.They were followed up for 6 months regarding recurrent ischemic events

Exclusion criteria

Patients with unclear history and patients without obstructive coronary artery disease

Study details

Careful clinical history was obtained prior to procedure and clinical diagnosis of chronic stable angina or recent ACS was made. Severity of stable angina was

graded using Canadian cardiovascular society classification. Unstable angina was graded according to Braunwald's classification. In patients with STEMI, location of MI was noted. Levels of cardiac enzymes, if available, were noticed. Diagnosis of myocardial infarction was made on grounds of history, pathological Q waves and regional wall motion abnormality by echocardiography. Clinical history was obtained regarding presence and duration of major atherosclerotic risk factors such as cigarette smoking, systemic hypertension, diabetes mellitus and family history of premature coronary artery disease. Left ventricular function was assessed by echocardiography prior to procedure in all patients.

Coronary angiogram was carefully studied regarding the number and morphology of obstructive lesions. Morphology was assessed according to classification given by Ambrose et al. Lesions were also assessed regarding presence of thrombus, fissure and flow distal to the stenosis was graded according to thrombolysis in myocardial infarction (TIMI) flow grade. Quantitative coronary angiogram was done for lesions of indeterminate severity.

A lesion was considered to be unstable if it showed at least two of the following characteristics which are presence thrombus, presence of fissured plaque, plaque irregularity and impaired distal flow (<TIMI 3 flow). Thrombus is defined as abrupt vessel cut off with persistence of contrast or intra luminal filling defect in a patent vessel within a stenotic region with surrounding homogenous contrast opacification. Plaque fissuring or ulceration is defined as presence of contrast beyond vessel lumen and hazy contours. Chronic total occlusions were differentiated from unstable plaque by noting their tapering end and multiple fine

collaterals. An anatomically remote plaque was defined as plaque in a different artery or different branch or in the same branch when the lesions are separated by an intervening disease free segment of vessel. The number of stable and unstable plaques in a given patient and the location of plaques were assessed. Depending on clinical and angiographic assessment patients were either subjected to revascularization (by PCI or CABG) or were given medical therapy. These patients were followed up and were asked to report for clinical follow up after 6 months. Recurrent events during this period were noticed. Recurrent event was defined as episode of ACS or cardiac death in the follow up period.

Statistical analysis

Baseline demographic variables, clinical variables, angiographic variables and outcome were compared between the two groups. Numerical variables were expressed as mean +/- SD. Frequencies and percentages are given for categorical variables. Univariate and multivariate analysis were performed regarding correlation between conventional coronary risk factors and presence of multiple unstable plaques. Categorical variables were assessed by chi-square test. Continuous variables were assessed by student's T test. P value less than 0.05 was considered as significant.

Results

Demographic variables

Age

Mean age of the study population was 53.60 years (range 26-76 years)

Mean age of patients with stable angina pectoris was 54.65 years and mean age of patients with ACS was 52.59 years

Sex

181 patients were males and 19 patients were females in the cohort. In patients with ACS 12 patients were females and in patients with stable angina 7 patients were females

Clinical presentation in ACS

ST elevation myocardial infarction

Of 102 patients with ACS, 53 patients had recent myocardial infarction and 44 of them had post MI angina. 32 patients had anterior wall infarction, 19 patients had inferior wall infarction and 2 patients had lateral wall infarction.

Unstable angina / Non ST elevation myocardial infarction

49 patients had unstable angina or non-ST elevation myocardial infarction. By Braunwald's classification 14 patients had class I unstable angina, 24 patients had class II unstable angina and 11 had class III unstable angina. 10 patients had recent worsening of stable angina amounting to unstable angina.

Stable angina pectoris

Of 98 patients with stable angina, 70 patients had CCS class 2 angina, 28 had class 3 angina and none had class 4 angina. Duration of angina ranged from 5 months to 9 years with mean duration of 1.37 years.

54 patients in this group had sustained previous myocardial infarction - anterior wall infarction in 21 patients, inferior wall infarction in 30 patients and lateral wall infarction in 3 patients. Of these, 34 patients were in the stable angina group and 20 in the ACS group

In the total cohort 19 patients had left ventricular systolic dysfunction, 13 in the ACS group and 6 in the stable angina group. Presence of LV dysfunction correlated with previous anterior wall myocardial infarction, but not with recent ACS or revascularization

Atherosclerotic risk factors

48.5% patients have diabetes mellitus. Mean duration of diabetes mellitus was 83 months in this cohort. Mean duration of diabetes is 77.31 months in patients with ACS and 88.3 months in patients with stable angina.

58% of patients had systemic hypertension. Mean duration of systemic hypertension was 67.4 months. Duration of hypertension was 72.27 months in patients with ACS and 62.6 months in patients with stable angina

43.6 % patients have an abnormal lipid profile.

116 patients were smokers, 61 patients in stable angina group and 55 patients in ACS group

UNSTABLE PLAQUE

Total of 197 angiographic unstable plaques were present in this cohort of patients.

Unstable plaque and ACS

Frequency of unstable plaques

159 unstable plaques were observed in 102 patients with ACS. 6 patients with history of ACS did not have angiographically demonstrable unstable plaque.

53 patients had a single unstable plaque, 27 patients had 2 unstable plaques, 12 patients had 3 unstable plaques and 4 patients had 4 unstable plaques (1.56 plaques per patient)

49 patients with unstable angina or non-ST elevation MI had 82 unstable plaques with 20 patients having 1 unstable plaque, 16 having two unstable plaques, 6 patients having 2unstable plaques and 3 having 4 unstable plaques (1.67 plaques per patient)

53 patients with myocardial infarction had 77 angiographic unstable plaques (1.45 plaques per patient). 33 patients had single unstable plaque, 11 patients had two unstable plaques, 6 patients had 3 unstable plaques and a single person had 4 unstable plaques

42.2% patients with ACS had multiple unstable plaques

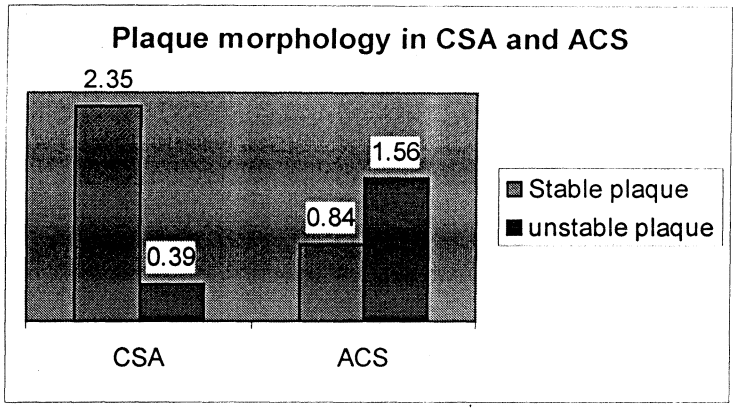


Table 1-demographic variables and plaque morphology in ACS and stable angina

	CSA	ACS	P
Age	54.65	52.59	NS
Sex females	7	12	NS
Sex males	91(92.9%)	90(88.2%)	NS
DM	54	43	NS
HTN	58	58	NS
S. Cholesterol (Mg%)	206	172	NS
Unstable plaque per patient	0.39	1.56	0.0001
Stable plaque per patient	2.35	0.84	0.0001

Location of unstable plaques

Majority of unstable plaques were located in left anterior descending artery. 104 unstable plaques were located in left anterior descending artery, 39 in circumflex artery and 54 in right coronary artery. Majority of unstable plaques were located in the proximal coronaries. In LAD artery 88% of unstable plaques were present in proximal or mid LAD or major diagonal branch. In circumflex artery 78% of unstable plaques were located in proximal circumflex artery or major obtuse marginal branch. In right coronary artery 76% of unstable plaques were located in proximal of mid part of the vessel.

Table 2- unstable plaques in ACS and stable angina

Number of unstable plaques	Patients with ACS	Patients with CSA
0	6	67
1	53	24
2	27	7
3	12	0
4	4	0
Total	159	38

Correlations of unstable plaque

The presence of unstable plaque correlated with ACS, ST elevation myocardial infarction, post MI angina and revascularisation

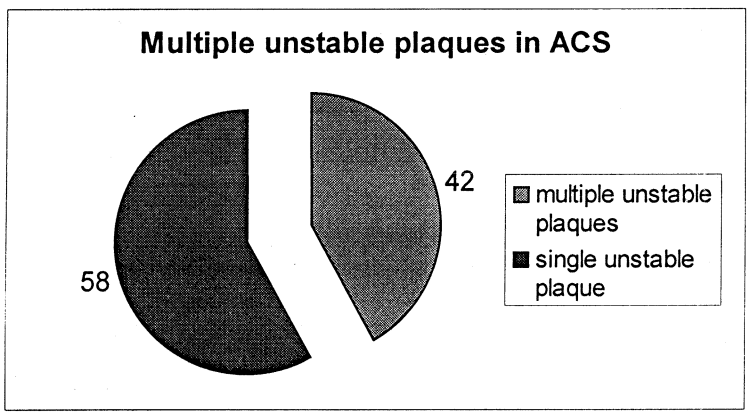
No correlation was observed between the number of unstable plaques and presence of atherosclerotic risk factors such as diabetes mellitus, systemic hypertension,dyslipidemia, smoking habit and LV dysfunction

Unstable plaque in stable angina

In the cohort of 98 patients with stable angina 38 angiographically unstable plaques were observed, without history suggestive of ACS. No association between coronary risk factors and unstable plaques were observed in this group also.

Multiple unstable plaques

50 patients had more than one unstable plaque, 43 patients in ACS group and 7 in stable angina group.



Correlates of multiple unstable plaques

Presence of multiple unstable plaques correlated with diabetes mellitus (p= 0.02), ACS and revascularisation

Table 4 – correlates of unstable plaque

	P value
Diabetes mellitus	0.058
Systemic hypertension	0.657
Smoking habit	0.054
Dyslipidemia	0.168
ACS	0.0001
Myocardial infarction	0.0001
Post MI angina	0.0001
LV dysfunction	0.324
Revascularisation	0.0001

Stable plaques

230 stable plaques were observed in 98 patients with stable angina. Presence of stable plaque correlated with diabetes mellitus, but not with systemic hypertension, smoking habit or lipid levels.

86 stable plaques were observed in the cohort of patients with ACS (0.84 plaques/patient). The correlation between ACS and presence of stable plaque was statistically significant because stable plaques coexisted with unstable plaque. Presence of stable plaque did not correlate with revascularization

Table 3 –stable plaques in stable angina and ACS

Number of stable plaques	Patients with ACS	Patients with CSA
0	44	2
1	38	19
2	15	37
3	3	27
4	1	10
5	1	2
6	0	1
Total	86	230

Total number of atheromatous plaques was more in the stable angina group, compared with ACS group (2.73 plaques/patient versus 2.40 plaques/patient, p=NS). The difference between the two groups was regarding the morphology of the plaque, with multiple unstable plaques in the ACS group and multiple stable plaques in the stable angina group and different clinical correlates associated with each types of plaques.

Table 5 – correlates of stable plaque

	P value
Diabetes mellitus	0.05
Systemic hypertension	0.657
Smoking habit	0.448
Dyslipidemia	0.238
Revascularization	0.215
LV dysfunction	0.346
Stable angina	0.0001

REVASCULARIZATION

153 patients underwent revscularisation.47 patients were considered for medical treatment after CAG. 88 patients underwent coronary artery bypass grafting and

65 patients underwent percutaneous coronary intervention. Revascularization correlated with presence of multiple unstable plaque, ACS, stable angina, and presence of unstable plaque in left anterior descending artery and circumflex artery but not with presence of coronary risk factors

Recurrent events

Follow-up data is available for 110 patients, 60 patients in the ACS group and 50 patients in the stable angina group

28 patients had recurrent events during follow-up period of 6 months.23 patients developed recurrent ACS. 2 patients had hospitalization with worsening heart failure and 3 patients died during this period.

One patient died of intractable ventricular tachycardia after coronary angiogram and PCI. 1 patient died of progressive heart failure after CABG. One patient sustained sudden cardiac death while waiting for CABG. All patients who died had multiple unstable plaques.

23 patients had recurrent ACS over the period of observation, 19 in the ACS group and 4 from the stable angina group.7 of them had undergone revascularization previously, 3 had PCI and 4 had CABG. 8 patients had elevated troponin levels during subsequent ACS. 2 patients developed ST elevation myocardial infarction, one related to sub acute stent thrombosis. Of these, 20 patients were documented to have at least one unstable plaque and 11 of them had more than one unstable plaque ($p=0.104$). 3 patients without documented unstable plaque developed ACS on follow-up.

On univariate analysis no statistically significant correlation was observed between recurrent events and coronary risk factors, clinical presentation, presence of stable plaque, unstable plaque and multiple unstable plaque.

DISCUSSION

The presence of coronary plaques with complex morphologic feature is the hallmark of acute coronary syndrome and it correlates with plaque rupture and thrombosis. The results of this study demonstrate that a sizable number of patients with ACS harbor multiple unstable plaques, which is true for both ST elevation myocardial infarction and unstable angina/ non-ST elevation MI. These observations support the hypothesis that plaque instability is not merely a local vascular accident, but probably reflects a systemic process with multifocal destabilization of atheroma. No association was demonstrated between presence of multiple unstable plaques and major atherosclerotic risk factors except diabetes mellitus, suggesting a factor beyond the major risk factors being responsible for plaque destabilization. This factor is likely to be systemic inflammation, which is responsible for multifocal plaque instability. Presence of multiple unstable plaques also correlated with revascularization. Previous studies also have demonstrated presence of multiple unstable plaques in patients with ACS. In one autopsy series of patients dying of myocardial infarction 115 separate thrombi were identified in 74 patients. Angiographic natural history studies in patients with acute myocardial infarction have demonstrated rapid progression of both culprit and non-culprit lesions over a period of one month supporting concept of multifocal plaque instability. Previous studies have shown association between presence of multiple unstable plaques and recurrent clinical event, need for surgical revascularization, and unfavorable outcome. However in this study no correlation was noticed between the presence of multiple unstable

plaques and recurrent events. This may be related to the incomplete follow-up or related to aggressive plaque passivation therapy.

Clinical observation support the concept that systemic process influence plaque instability. Patients with acute myocardial infarction have evidence of systemic inflammation as evidenced by elevated levels of C-reactive protein and amyloid associated protein. Elevation of serologic markers of macrophage activity (neopterin levels) has been correlated with presence of multiple complex plaques in patients with unstable angina. The cardio protective effects of aspirin may be partly mediated by its systemic anti-inflammatory activity. The reduction in recurrent myocardial infarction produced by statins which stabilize the plaque gives support to the notion that unstable coronary artery disease is a multifocal process influenced by systemic factors.

Good correlation was observed between the diagnosis of ACS and presence of unstable plaque. This correlation indicate that angiographic assessment of plaque instability is indeed valid and the criteria put forward by Ambroise et al hold good in assessing a vulnerable plaque. This is very important in the Indian scenario, where access to sophisticated investigations such as IVUS is limited. Moreover in clinical setting, where immediate decision-making is very important regarding treatment options, angiographic assessment of plaque vulnerability may alone be feasible. Hence data obtained in this study regarding concordance between angiographic unstable plaque and ACS is very important

Limitations of the study

Angiographic differentiation of chronic total occlusion from thrombus-loaded vessel is difficult. The criteria used (fine tapering lesion with collaterals and history of ACS beyond preceding 3 months) may not always differentiate chronic total block from thrombus-loaded vessel. It may be possible that some plaques classified as unstable can be chronic total blocks and vice versa.

Follow-up data is available for 110 patients only limiting assessment of correlations between recurrent events and baseline data

CONCLUSION

Sizeable numbers of patients with acute coronary syndrome have multiple unstable plaques demonstrable by coronary angiography implying multifocal nature of acute coronary syndrome and importance of systemic factors in plaque vulnerability

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Abbreviations used

ACS -Acute coronary syndrome

CSA -Chronic stable angina

CABG - Coronary artery bypass grafting

IVUS - Intra vascular ultrasound

LV -Left ventricle

NSTEMI - Non ST elevation myocardial infarction

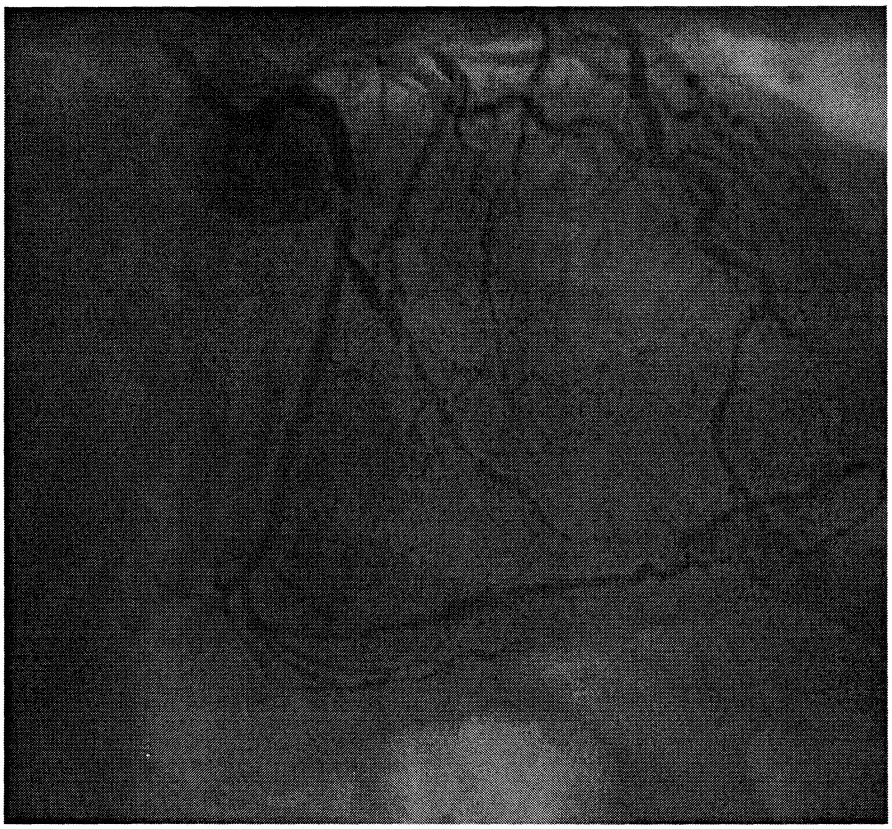
PCI - Percutaneous coronary intervention

STEMI – ST elevation myocardial infarction

TIMI -Thrombolysis in myocardial infarction

UA -Unstable angina

LONG TERM CLINICAL FOLLOW-UP OF PATIENTS WITH TWO VESSEL CORONARY ARTERY DISEASE NOT INVOLVING LEFT ANTERIOR DESCENDING ARTERY



Background

Atherosclerotic coronary artery disease constitute a spectrum of disease ranging from non obstructive coronary atheroma going through the phases of asymptomatic CAD, silent ischaemia, stable angina pectoris, unstable angina, ST elevation myocardial infarction (STEMI) and sudden cardiac death. Stable angina and silent ischaemia are manifestations of chronic coronary artery disease with reduced myocardial oxygen supply related to atheroma, producing the syndrome of angina of demand. Unstable angina and STEMI are manifestations of a vulnerable plaque, with atherothrombosis, producing subtotal or total occlusion of epicardial coronary artery and usually is associated with myocyte necrosis. The conversion of a stable atheromatous plaque into a vulnerable plaque depends upon various factors such as inflammation, lipid content of the plaque and the strength of fibrous capsule of the plaque.

The clinical presentation and long term prognosis varies markedly in the cohort of CAD. At one extreme are patients with chronic stable angina and preserved LV function and at the other extreme are patients who suffered myocardial infarction and having LV dysfunction. The single most important prognostic variant is LV function.

LV function after myocardial infarction depends on the amount of myocardial necrosis, which occurred during infarction. Patients with 15% LV myocardial loss develop reduced ejection fraction and elevated LV end diastolic pressure and volume. Patients with 25% myocardial losses have clinical heart

failure and patients with more than 40% myocardial loss develop cardiogenic shock.

There are two other factors, which contribute to LV dysfunction after myocardial infarction, which are infarct expansion and LV remodeling. Infarct expansion is defined as acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis. This is caused by slippage between the muscle bundles, disruption of normal myocardial cells and tissue loss within the necrotic zone. There is disproportionate thinning and dilation of infarct zone prior to development of a healthy scar. Apex, being the thinnest region of LV, is most prone for infarct expansion. Infarct expansion plays an important role in LV remodeling, but remodeling also involves dilation of viable portion of LV and continues fro months or even years after MI. This dilation can be considered as a compensatory mechanism whereby stroked volume is maintained in the short term at the expense of elevated end diastolic volume, end diastolic pressure, and increased wall stress. However on long course, this adaptation is detrimental. This leads on to neurohormonal activation, further LV dilatation, apoptosis and irreversible LV dysfunction and heart failure.

Left anterior descending artery provides the major share of perfusion to left ventricle. However, circumflex artery and right coronary artery also provides important share of blood supply to left ventricle, supplying the inferoposterolateral area. Atherosclerosis involving these vessels and infarction associated with these vessels are also important in the short term and long term outcome. With large infarctions involving these vessels, such as those associated with dominant

circumflex artery, depending on the amount of myocardial necrosis patients can develop LV dysfunction and heart failure [13,15]. These patients are prone for infarct expansion and LV remodeling and heart failure on follow up. However the prognosis associated with a small area of infarction such as isolated inferior wall infarction is generally favorable other than the risk of arrhythmic death. The 30-day mortality associated with small inferior wall MI and moderate to large inferior wall MI is 4.5% and 6.4% respectively and the one-year mortality is 6.7% and 8.4%. These figures are comparable to that associated with distal LAD or diagonal infarct. The 30-day mortality associated with mid LAD and proximal LAD infarctions are 9.2% and 19.6% respectively.

Right ventricular MI is associated with right coronary artery infarction and is usually associated with inferior wall MI. 50% of patients with inferior wall MI have some evidence of involvement of right ventricle and usually has infarction of inferoposterior wall and inferior septum. 3-5% of autopsy proven myocardial infarction has isolated RVMI. However RVMI is less common than anticipated because of lesser oxygen requirement of thin walled right ventricle and its perfusion from cavity blood. Collateral circulation of right ventricle is richer than that of left. So right ventricle can sustain longer periods of ischaemia and still can show good recovery of contraction after revascularisation. RVMI can rarely cause cardiogenic shock and constitute 2% of cases of cardiogenic shock.

Other problem associated with non LAD infarction is acute mitral regurgitation [14,15] which could be due to

(a) Papillary muscle and LV dysfunctions with annular dilation and incomplete coaptation of mitral leaflet.

(b) Rupture of tip or trunk of papillary muscle

(c) Rupture of chordae tendinae

Majority of acute mitral regurgitation is due to papillary muscle rupture. Papillary muscle has disadvantaged blood supply because they are at the terminus of cardiac arterial circulation. In addition papillary muscles are subjected to high degree of tension development during systole. Coexistent LV dilation result in abnormal axis of contraction of papillary muscle and resultant increased stretch and propensity for rupture. Anterolateral papillary muscle has dual blood supply from left anterior descending artery and circumflex coronary artery. Postero medial papillary muscle has single source of blood supply from posterior descending artery. So posteromedial papillary muscle ischaemia, infarction and rupture are five times more common than anterolateral papillary muscle. In patients with papillary muscle rupture right coronary artery is the culprit vessel in 70% cases and circumflex in 30% cases. In patients with non-rupture related mitral regurgitation also there is preponderance of involvement of non-LAD vessels – culprit artery is RCA in 27% cases, circumflex artery in 33% cases, RCA and circumflex in 33% cases and LAD in 6% cases. Papillary muscle rupture can occur even in small MI and usually occur within 2- 9 days of MI, but can occur as early as 24 hours.

Other problem associated with infarction involving RCA and circumflex artery is AV nodal block, which is related to AV nodal ischaemia, necrosis and

increased parasympathetic activity. Usually these patients have associated atherosclerotic disease involving LAD and larger infarctions. These patients may require temporary pacemaker implantation. However complete heart block is usually reversible and permanent pacemaker implantation is rarely required.

Chronic coronary artery disease involving circumflex and RCA is generally associated with favorable outcome. However the myocardium at jeopardy associated with disease of these two vessels is similar to that associated with LAD artery and infarction associated with these vessels can be associated with bad prognosis. This happens especially in patients with left dominant circulation and in patients with collateralization of one of these vessels by the other, without collaterals from LAD.

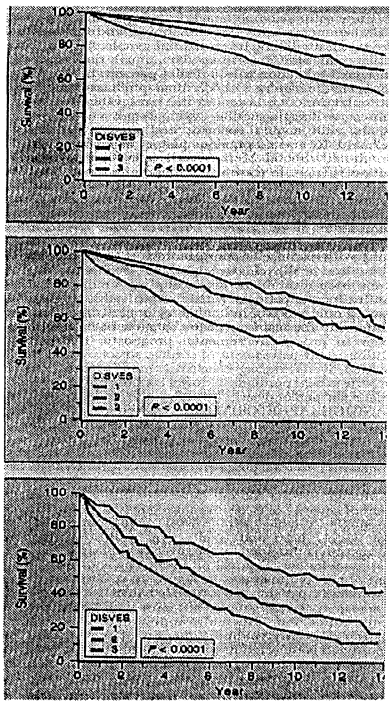
In the CASS registry, in medically treated patients, the 4-year survival was 92% for single vessel disease, 84% in two-vessel disease, and 68% with three-vessel disease. The presence of left main disease, shortened survival significantly. The 4-year survival was 92% for patients with ejection fraction more than 50%, 83% for patients with EF of 35-49%, and 58% for patients with EF less than 35%. Patients with good LV function have 4-year survival of 94% with single vessel disease, 91% with two-vessel disease and 79% with three-vessel disease. Patients with poor LV function have 4-year survival of 67% with single vessel disease, 61% with two-vessel disease, and 42% with three-vessel disease. These data indicate that LV function is a better predictor of survivor than number of diseased vessels and also stress the importance of LAD in natural history of chronic coronary artery disease. European coronary artery

surgery study evaluated only patients with at least two-vessel disease and 4-year survival in the medically treated group was 93% for two-vessel disease and 84 % for three-vessel disease, again stressing importance of LAD. In CASS study[1], mortality benefit following CABG was observed in patients with left main disease, proximal LAD disease, and LV dysfunction, again citing the importance of proximal LAD involvement in prognosis.

However importance of non-LAD vessels in the natural history of chronic coronary artery disease[2,3,5] and acute coronary syndrome cannot be neglected. The 4-year survival of 84% associated with 2-vessel disease is considerably less than expected survival of general population. Moreover the morbidity associated with chronic CAD and risk of mortality from ACS is also important in this population. Non-LAD disease constitute considerably to the number of PCI being done. ACC/AHA guidelines for revascularization in stable angina states CABG as class I indication in patients with two-vessel disease without significant proximal LAD lesion, when a large area of viable myocardium with high-risk criteria on non-invasive evaluation is identified. This also stresses the importance of non-LAD vessels in outcome of chronic coronary artery disease.

However ACC/AHA Guidelines for revascularisation in UA/NSTEMI and chronic stable angina has placed PCI as Class II b indication in patients with proximal LAD disease, LV dysfunction and treated diabetes mellitus. This recommendation indirectly stresses the importance of proximal LAD lesion over non-LAD disease in natural history of coronary artery disease.

Reviewing literature regarding natural history of patients with chronic coronary artery disease could identify no dedicated studies regarding outcome of patients with two-vessel disease not involving LAD. Hence this study was undertaken to understand the natural history of patients with two vessel CAD not involving LAD artery



Graph showing survival of medically treated patients in CASS registry. Top-patient with single, double or triple vessel disease with EF>50%. Middle- EF 35-50%. Bottom EF <35%

AIM OF STUDY

Long term clinical follow-up of patients with two vessel disease not involving left anterior descending artery regarding their long term prognosis and outcome

MATERIALS AND METHODS

Cardiac catheterization records of all patients performed between 1999 and 2002 were reviewed. Patients with two-vessel disease not involving left anterior descending artery were identified. The following clinical data were obtained--presence and duration of atherosclerotic risk factors, initial clinical presentation, symptom status, details regarding location of myocardial infarction, LV function at time of first evaluation, degree of mitral regurgitation, electrocardiographic abnormalities and the mode of therapy suggested after initial coronary angiography. Their coronary angiograms were reviewed and the diagnosis of two-vessel disease was confirmed. The location of the atheromatous plaque in coronary artery was noticed. For this, circumflex artery before major obtuse marginal branch (OM) was considered proximal segment, circumflex after major OM was considered distal and major OM was considered the third segment of circumflex artery. Right coronary artery before first right ventricular branch is considered as proximal part, after first RV branch up to acute marginal is considered as mid RCA and after acute marginal is considered as distal RCA and posterior descending artery is considered as the fourth segment of RCA.

Follow up data of these patients up to 2005 were obtained from medical records and clinical events and repeat procedures in this period were noticed. These patients were called for clinical assessment and the following information were obtained. These include history regarding cardiac events between first visit and last review, present symptom status, LV function, degree of mitral regurgitation, new ECG changes, and exercise test for inducible ischemia in symptomatic patients. Event is defined as death, ACS, hospitalization for heart failure and significant arrhythmia. LV systolic function was assessed by echocardiography. Ejection fraction was estimated using Simpson's formula. LV systolic dysfunction was defined as ejection fraction less than 45%. LV dysfunction was classified into mild, moderate or severe based on ejection fraction. (Mild LV dysfunction EF 35-45%, moderate LV dysfunction EF 25-35 %, severe LV dysfunction EF <25%) Regional wall motion abnormality, if any, were noticed and classified into areas of hypokinesia, akinesia and dyskinesia. Mitral regurgitation was quantified according to the area of regurgitant jet compared with left atrial area and graded into mild (jet area< 20%of left atrial area), moderate (jet area 20-40%) and severe (jet area >40%) [16]. From these data the conclusion regarding the prognosis in this group of patients were obtained

Statistical methods

Continuous variables were assessed by students T test. Categorical variables were assessed by chi-square test. P value <0.05 was considered as significant. All values were expressed as mean+/-standard deviation

RESULTS

Review of catheterization reports identified 98 patients with two vessel disease not involving left anterior descending artery

Demographic variables

Age at presentation ranged from 35 to 76 years with median age of 55 years

86 patients were males and 12 were females

Coronary Risk factors

35.7 % of patients have diabetes mellitus

59.2% of patients have systemic hypertension

65.3% of patients were smokers

40.2% patients had abnormal lipid profile

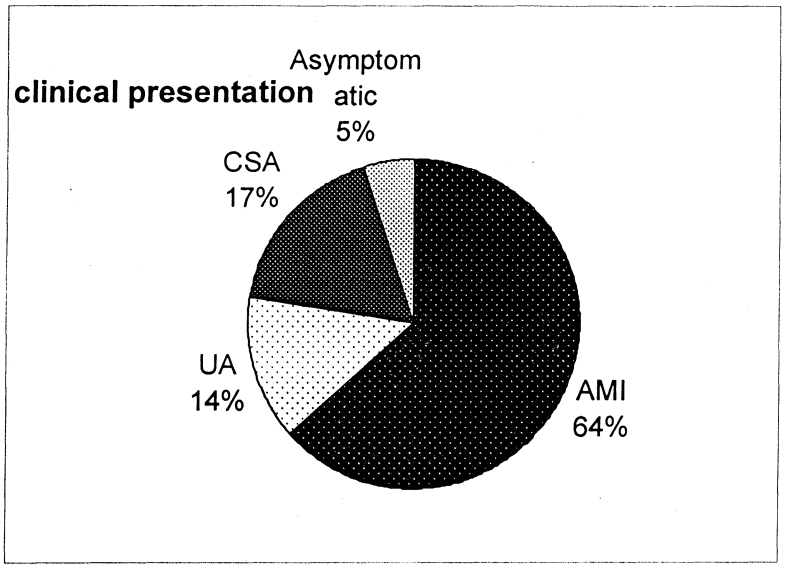
Clinical presentation

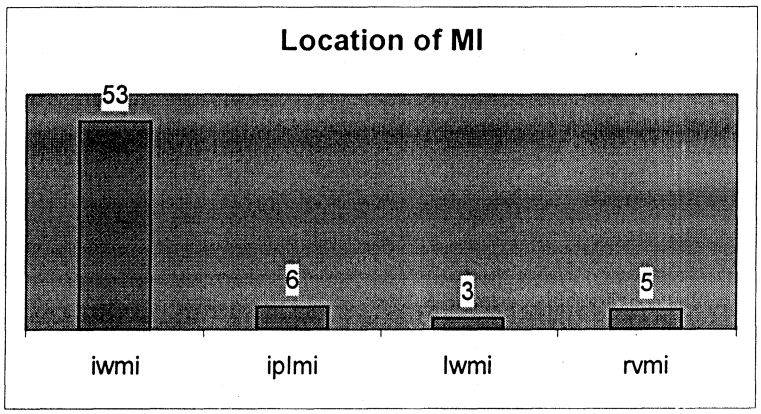
5 patients were asymptomatic at first evaluation. Indication for coronary angiogram was either for evaluation of a positive exercise stress test or pre operative evaluation for non cardiac surgery

17 patients had chronic stable angina

14 patients had unstable angina/Non ST elevation MI

62 patients sustained myocardial infarction previously. 53 patients had previous inferior wall myocardial infarction, 3 had isolated lateral wall infarction, 6 patients had infero lateral wall infarction and 5 patients had right ventricular infarction. Isolated right ventricular infarction was not present in this cohort.





ECG and exercise ECG

49 patients were evaluated with exercise stress test prior to CAG using Bruce protocol and was positive for inducible ischemia in 46 patients

Basal ECG showed pathological Q waves in inferior or lateral leads in 61 patients. T wave inversion in leads other than that showing pathological Q waves and leads AVR, V1 and V2 were present in 33 patients.

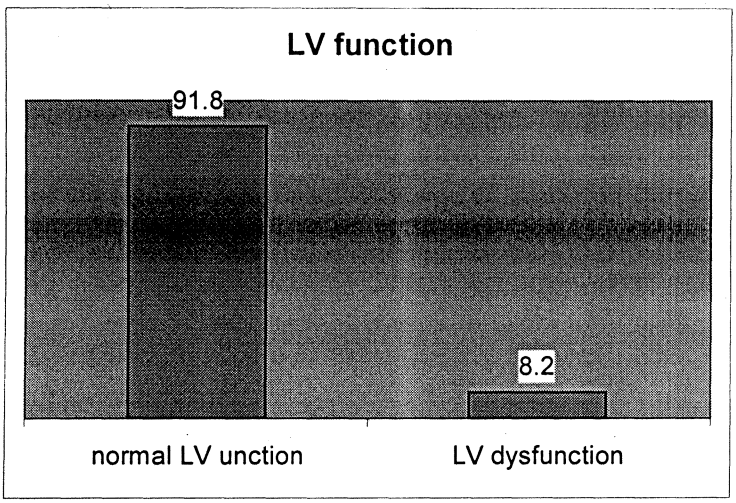
LOCATION OF CORONARY STENOSIS

Circumflex artery – 40.8% patients has disease of proximal circumflex artery, 37.8% has disease of distal circumflex artery and 46.9 % has disease of major obtuse marginal branch and 5.1% has disease of ramus internus branch

Right coronary artery – 4.9 % has disease involving proximal RCA, 37.8% has mid RCA disease and 46.9% has disease of distal RCA.

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

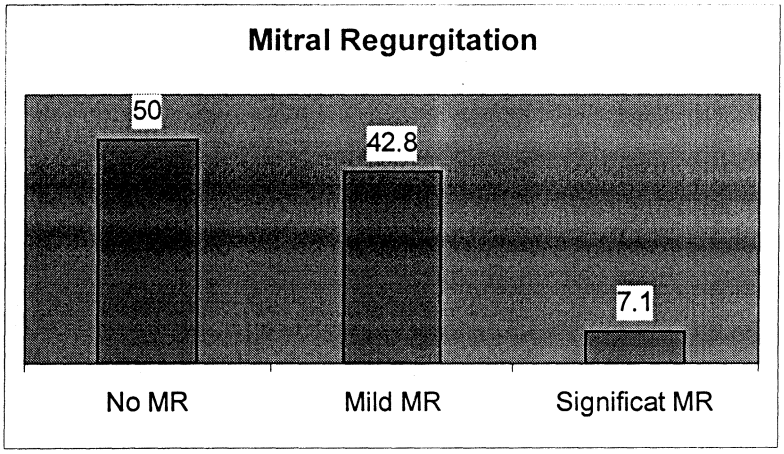
LV dysfunction at initial presentation was present in 8 patients. 6 of them had mild LV systolic dysfunction and two had moderate LV dysfunction. 5 of them had proximal circumflex lesion and 3 had distal circumflex lesion. RCA lesion was in proximal segment in 4 patients and in mid segment in 4 patients. However no statistically significant correlation was observed between lesion location, coronary risk factors and LV dysfunction. No association was observed between significant mitral regurgitation and LV dysfunction. LV dysfunction correlated with inferior wall MI and inferoposterolateral MI, but not with lateral wall MI.



Two of these patients underwent revascularization by PCI. One patient did not undergo revascularization because of non-viable myocardium. Others were considered for medical therapy in the absence of significant symptoms.

MITRAL REGURGITATION

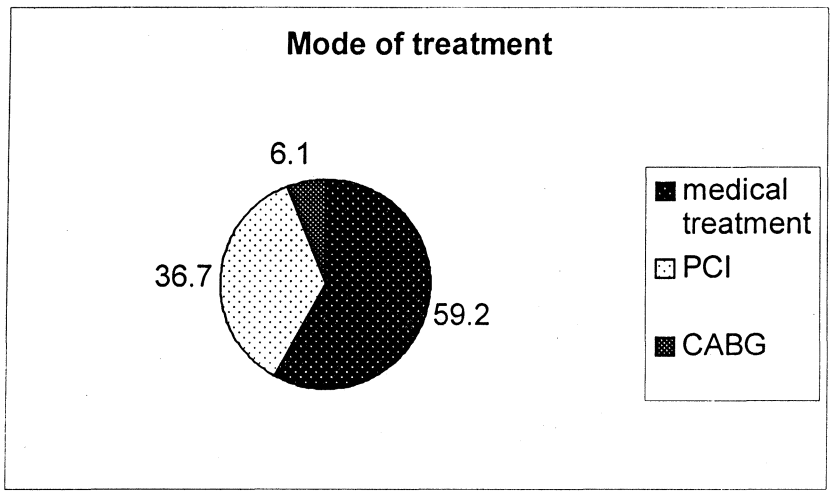
Some degree of mitral regurgitation was present in 49 patients (50% of patients). Mitral regurgitation was significant (defined as moderate or severe mitral regurgitation) in 5 patients. 4 patients had moderate mitral regurgitation and one had severe regurgitation. Mitral regurgitation was related to mitral valve prolapse in one patient. In other patients mitral regurgitation was ischaemic .No patient had papillary muscle or chordal rupture.



Presence of significant mitral regurgitation correlate with inferoposterolateral infarction (p=0.01), but not with inferior wall infarction and coronary lesion location. Statistically significant correlation was observed between presence of significant MR and decision regarding revascularization with PCI. Two patients had infero postero lateral infarction and two had inferior wall infarction. Two patients developed mitral regurgitation on follow up. In one patient it was related to in stent restenosis of right coronary stent and it regressed after repeat PCI. In the other patient mitral regurgitation was related to development of LV dysfunction. 4 patients had proximal circumflex disease and one had disease of major obtuse marginal branch (statistically not significant) and two had distal circumflex disease. RCA lesion location was in proximal RCA in 3 patients, mid RCA in 3 patients and distal RCA in one patient. 5 of them underwent percutaneous revascularization to right coronary artery. Circumflex artery was not revascularized in any of them. No patient underwent mitral valve replacement or bypass grafting.

TREATMENT

59.2% patients underwent medical therapy. 36.7% underwent PCI. 6.1% underwent CABG. PCI was attempted unsuccessfully in 6 patients (they were included in medical therapy group). 8 patients who where advised to undergo CABG and 3 who where advised PCI did not undergo the same due to personnel and social reasons. They were included in the medical therapy group. Patients who had minimal symptoms were predominantly subjected to medical therapy and who were symptomatic underwent revascularization by PCI.



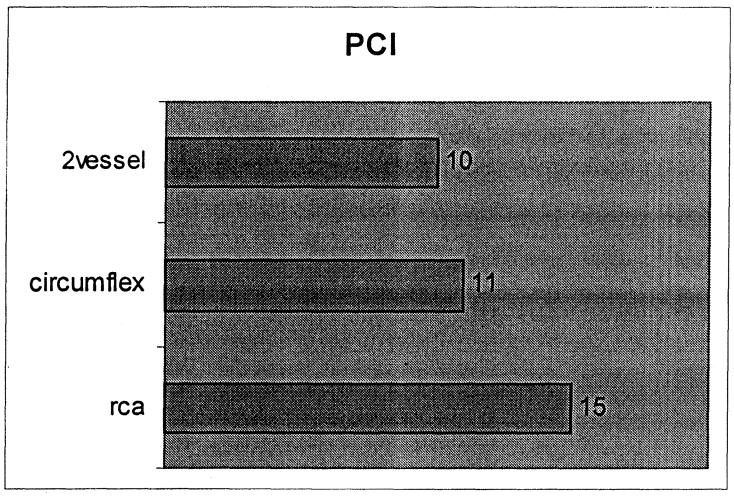
CABG

Out of 6 patients who underwent CABG, in only two patients CABG was considered after first evaluation, indication being symptomatic status and ostial location of stenosis. Two patients who were initially advised medical therapy, developed ACS on follow-up and were found to have three vessel disease on coronary angiography and underwent CABG. Another lady developed in stent

restenosis with significant symptoms and underwent CABG. The fourth patient underwent CABG along with excision of left atrial myxoma.

PCI

36 patients underwent PCI. 15 patients underwent PCI to RCA. 11 patients underwent PCI to circumflex artery and 10 patients underwent double vessel PCI. Stents were used in 28 patients.



FOLLOW-UP

Follow up data is available for 80 out of 98 patients. 61 patients came personally for follow-up. 19 patients informed their present symptomatic status via letter or phone call.

Mean follow up period is 2.96 years (range 2 - 10 years).

44 patients are in NYHA functional class 1, 32 patients are in functional class 2 and 2 patients have class 3 symptoms.

MORTALITY

Two patients died during follow up period. One patient had sudden cardiac death and the second patient with severe aortic valve stenosis, who declined surgery, died of heart failure.

LV Function and mitral regurgitation on follow-up

One patient with normal LV function to begin with, developed mild LV systolic dysfunction after follow-up period of 28 months. One patient with LV systolic dysfunction had good improvement in LV function after PCI. For other patients no change in LV function was observed.

2 patients developed mitral regurgitation during follow up. In one patient it was related to in stent restenosis and it improved after repeat PCI. In the other patient, it was related to development of LV dysfunction. Only in one patient, a reduction in severity of mitral regurgitation was noticed over follow-up period, which was attributable to PCI. In one patient moderate MR worsened to severe MR in 3 years follow-up.

RECURRENT CARDIAC EVENTS

17 patients developed clinical cardiac event during follow-up. 15 patients developed acute coronary syndrome (including four patients with instent restenosis), 1 patient developed complete heart block, 1 patient had recurrence left atrial myxoma after surgery and one patient developed worsening of LV function and developed mitral regurgitation. Of 15 patients with ACS, 1 patient developed ST elevation MI (IWMI) and others had UA/NSTEMI. By Cox regression analysis significant mitral regurgitation was found to be associated with recurrent events (p=0.002). Association was noticed between PCI and recurrent events related to in stent restenosis, which was nearing statistical significance (p=0.054).

4 patients developed angiographic in stent restenosis. One patient underwent repeat PCI, another underwent CABG. Other two patients are on medical therapy owing personnel preference.

Repeat CAG

15 patients underwent repeat CAG in a time span ranging between 1 to 7 years after first CAG (mean 2.73 years), indication being recurrent events

5 patients were noticed to have disease of LAD artery, 4 developed in stent restenosis and in patient lesion in circumflex artery has worsened to total occlusion. In 5 others CAG was similar to initial study.3 patients with new LAD lesion underwent revascularization (2 persons underwent CABG and one

underwent PCI). Other two patients with new LAD lesion preferred medical treatment.

Complete heart block

5 patients had transient complete heart block during episode myocardial infarction as per available history. It was reversible in all patients except one, who required permanent pacemaker implantation. CHB was seen in two patients without recent myocardial infarction and was the indication for coronary angiogram in one patient. One patient with documented two-vessel disease developed CHB on follow-up. Both required permanent pacemaker implantation

Other observations

9 patients were noticed to have atherosclerotic disease involving abdominal aorta and lower limb vessels. 3 patients had infra renal aortic aneurysm and two of them underwent surgery with good result. Third person was not subjected to surgery in view of high risk involved. 6 patients have occlusive arterial disease of lower limb vessels and 3 patients underwent femoro popliteal bypass grafting

DISCUSSION

This study identified that a significant number of patients with two-vessel disease not involving LAD has two adverse prognostic factors regarding long term outcome. These are the presence of LV systolic dysfunction and significant mitral regurgitation. LV dysfunction and mitral regurgitation was noticed to exist independent of each other. 14 patients (14.3%) have either LV dysfunction or significant mitral regurgitation, thus placing a significant number of populations at risk of developing future heart failure. So this study identifies a high-risk population in whom development of heart failure is to be watched for and optimal therapy is to be instituted to prevent or retard progression of LV dysfunction. However clinical heart failure was not manifested in this study group probably due to short-term follow-up.

Study also demonstrate that at least in a minority of patients LV function can improve and mitral regurgitation can regress after revascularisation and such therapy should be given for patients with LV dysfunction or significant mitral regurgitation

Paucity of CABG was another noted observation. Only 6 patients underwent CABG .In none of them CABG was the automatically chosen method for revascularization. Two patients underwent CABG after developing LAD disease. Two patients underwent CABG because of unsuitable anatomy for PCI. One lady underwent CABG for stent restenosis and one patient underwent CABG along

with other cardiac surgery. This reflects the reluctance on part of cardiologists to offer surgical revascularization for patients without significant LAD disease, stressing the importance of proximal LAD involvement in survival benefit after CABG and probably only symptomatic benefit with revascularizing non LAD artery. However this may not be always true as reflected in this study with 14.3% incidence of LV dysfunction or significant mitral regurgitation

Significant number of patients had recurrent ACS, thus identifying a cohort of population where recurrent events may be anticipated. Recurrent events related to angiographic in stent restenosis are comparable to general incidence of instent restenosis with non-drug eluting stents.

Survival of these patients over the mean follow-up period of 2.96 years is 97.4%, which is higher compared with previously available data regarding survival of patients with two-vessel disease. However CASS demonstrated 5-year mortality of only 8% in medically treated and 5% in surgically treated patients with mild angina. Majority of patients in this study was mildly symptomatic at time of CAG and this along with uninvolved LAD artery may be responsible for the favorable outcome regarding mortality in this group. Other factors are unavailability of follow-up data of 18 patients and improvement in medical therapy over the years.

Another important observation is the association of myocardial infarction involving infero postero lateral wall with significant mitral regurgitation and LV dysfunction. Patients with infero postero lateral infarct have larger amount of myocardial loss leading to systolic dysfunction. However mitral regurgitation was

not associated with LV dysfunction, suggesting the importance of ischaemia in etiology of mitral regurgitation

Importance of repeat coronary angiogram in patients with recurrent events was noticed in this study, with 5 patients developing significant lesion in LAD artery leading to surgical revascularisation. Non-invasive assessment of these patients may be difficult because of presence of pre existing stenosis. These patients constitute a high-risk cohort because of large area of myocardium at jeopardy and evaluation with coronary angiogram should be considered in all patients with recurrent clinical events. The observation of development of new plaques also calls for aggressive risk factor modification in this group of patients.

Limitations of the study

Lack of follow up of 19 patients prevented complete assessment of natural history of this cohort.

CONCLUSION

Combined involvement of circumflex artery and right coronary artery constitute an important subgroup of patients with chronic coronary artery disease where left ventricular systolic dysfunction and significant mitral regurgitation should be anticipated.

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Abbreviations used

CABG	-Coronary artery bypass grafting
CAD	-Coronary artery disease
CASS	-Coronary artery surgery study
EF	- Ejection fraction
LAD	-Left anterior descending artery
LV	-Left ventricle
MR	-Mitral regurgitation
PCI	- Percutaneous coronary intervention
RCA	– Right coronary artery