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ORIGINAL RESEARCH

Intravascular ultrasound-virtual histology (IVUS-VH)study in patients with ST elevation myocardial infarction

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Abstract

Introduction: The characterization of atherosclerotic burden of apparently healthy region in culprit coronary arteries in ST segment elevated myocardial infarction has not been yet fully established. It has been found that patients with acute coronary syndrome have more vulnerable plaque in the non-culprit segment than patients with stable angina.

Aims: This study is done in patients with ST elevation myocardial infarction to characterize the plaque burden adjacent to the culprit lesion, atherosclerotic plaque in that area and to establish the relationship, if any, between the vulnerable plaque and coronary risk factors.

Materials and methods: It is an observational study done in the department of Cardiology, Medical College and Hospital, Kolkata from February 2012 to March 2013.**50** Subjects who fulfilled the predetermined inclusion criteria was studied.Between the above-mentioned study period, we performed intravascular ultrasound- virtual histology (IVUS-VH)study among STEMIpatients who are undergoing non-emergent percutaneous coronary interventionat our catheterization laboratory.

Results: Majority of our study population was male (72%) and mostly in the 45-54 years age group.Mean age of the patients was 54.76 years. Majority of patients presented within the reperfusion window, mean duration of chest pain at presentation being 11.94 hoursAmong the IVUS parameters mean plaque volume was 57.58 mm3 and mean area stenosis at the non culprit segment was 40.52%. Presence of vulnerable plaque in the non-culprit segment was not found to be related to either type, number of coronary arteries involved or grade of TIMI flow.Occurrence of vulnerable plaque was not found to be associated with smoking status, family history of premature coronary artery disease, hypertension, diabetes, associated peripheral or coronary artery disease or wall involved. Although Killip class at presentation or shock was not associated with the vulnerable plaque, incidence of heart failure was.

Conclusions: Presence of vulnerable plaque has been found to be positively correlated with the high sensitive C- Reactive Protein, dyslipidemia status, specifically HDL-C, total cholesterol and total cholesterol: HDL-C ratio underscoring the possible role of inflammation and lipid derangement in the causation and precipitation of acute coronary event.

Keywords: C- Reactive Protein, Dyslipidemia status, Acute coronary segment**.**

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Introduction

Atherosclerosis remains the major cause of death and premature disability worldwide and current predictions estimate that, in near future, atherosclerosis will become the leading global cause of morbidity and mortality. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and has distinct clinical manifestations that depend on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction and angina pectoris. Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia. In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability. Involvement of the splanchnic circulation can cause mesenteric ischemia. Atherosclerosis can affect the kidneys either directly (e.g., renal artery stenosis) or as a common site of atheroembolic disease.

Even within a particular arterial bed, stenoses due to atherosclerosis tend to occur focally, typically in certain predisposed regions. In the coronary circulation, for example, the proximal left anterior descending coronary artery exhibits a particular predilection for developing atherosclerotic disease. Indeed, atherosclerotic lesions often form at branching points of arteries which are regions of disturbed blood flow. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ectasia and the development of aneurysmal disease, for example, frequently occur in the aorta. In addition to focal, flow-limiting stenoses, nonocclusive intimal atherosclerosis also occurs diffusely in affected arteries, as shown by intravascular ultrasound and post-mortem studies.

Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth, linear fashion but discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be chronic, as in the development of stable, effort-induced angina pectoris or predictable and reproducible intermittent claudication. Alternatively, a dramatic acute clinical event such as MI, stroke, or sudden cardiac death may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated post-mortem.

Plaques are very heterogeneous in size and composition, even plaques located next to each other and exposed for the same systemic risk factors. Hypocellular tissues (fibrosis, calcium, and necrosis) constitute by far the most voluminous plaque components. Most plaques remain asymptomatic (subclinical disease), some become obstructive (stable angina), and a few, if any, become vulnerable and lead to atherothrombotic events such as a fatal heart attack or a disabling stroke[2].

During percutaneous coronary intervention, the parts of the vessels adjacent to the culprit lesion, which appear angiographically normal, are conventionally considered as healthy. The characterization of atherosclerotic burden of this apparently healthy region has not been yet fully established. It has been found that patients with acute coronary syndrome have more vulnerable plaque in the non-culprit segment than patients with stable angina[8,10]. Intravascular ultrasound (IVUS) and virtual histology has emerged as an excellent modality for the assessment of plaque composition and identification of high-risk plaque. Subset of patients with ACS who have vulnerable plaque in the non-culprit segments are more likely to have worse outcome and thereby needs to be addressed more aggressively with systemic plaque stabilization therapy in addition to local therapy. The principal objective of this study is to identify this subgroup of patients who present with acute ST elevation myocardial infarction using IVUS.

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Materials & methods

It is observational study done in the department of Cardiology, Medical College and Hospital, Kolkata from February 2012 to March 2013. Fiftysubjects who fulfilled the predetermined inclusion criteria was studied.Between the above-mentioned study period, we performed IVUS-VH study among STEMIpatients who are undergoing non-emergent percutaneous coronary interventionat our catheterization laboratory. Before catheterization,a protocol-based clinical examination was used to determinedemographic profile, cardiac history, atherogenic risk factors, features of extra coronary vasculardisease, co morbidities, indications for cardiac catheterization,indications for percutaneous coronary intervention.

Inclusion Criteria

Patients with ST elevation myocardial infarction (STEMI), who were undergoing angioplasty, were included in the study. Written informed consent was obtained from all patients.

Exclusion Criteria

Patients with STEMI requiring primary angioplasty, Elderly patients who were not candidates for revascularization, Patients with Non-ST elevation Myocardial infarction or Unstable angina, Known or suspected acute or chronic renal failure, History ofcontrast nephropathy, Electrolyte imbalance, Patients with bypass graft lesions, with heavily calcified lesions, ostial lesions or inability to obtain adequate IVUS image for analysis.

Data was obtained as age, sex distribution, major risk factors of atherosclerosis namely, smoking, hypertension, diabetes mellitus, dyslipidemia, family history of premature coronary artery disease.

Clinical examination with special reference to cardiovascular system.Routine blood examination like hemoglobin, ESR, total WBC count, differential WBC count, platelet count. Blood biochemistry like fasting and post prandial blood sugar, urea, creatinine, sodium, potassium, lipid profile, hs-CRP was done.

Electrocardiography, echocardiography (with special reference to systolic function, regional wall motion abnormality, left ventricular wall thickness, any mechanical complication, pulmonary hypertension, pericardium, diastolic dysfunction).Coronary angiography was done Intravascular ultrasound and virtual histology.

Study Techniques

Between the above-mentioned study period, we screened allpatients undergoing non-emergent coronary angiography at our hospital and evaluated them for study inclusionaccording to predetermined inclusion criteria. Before catheterization,a protocol-based clinical examination was performed to record information including demographic profile, cardiac history, indications for cardiac catheterization andatherogenic risk factors. Blood samples will be collected from all subjects in the supine position on admission. The culprit lesions were identified on the basis of the combination of the angiographic lesion appearance, electrocardiographic changes, and the wall motion abnormality on the echocardiography. The study segment was determined as an angiographically nonobstructive (<50%) segment with 5 mm length, located >5 mm proximal to the PCI target lesion (culprit lesion)[8]. A total of 5 IVUS images were captured at an interval of 1 mm for 5 mm length and the findings were averaged. A virtual histology-intravascular ultrasound (VH-IVUS) catheter was pulled back with a manual transducer pullback system. A single observer who was blinded to the clinical and angiographic findings analyzed the IVUS images of the non-culprit segment. Quantitative measurements were performed according to the American College of Cardiology Clinical Expert Consensus Document on IVUS[9]. The raw radiofrequency data

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was captured at the top of the R-wave and reconstructed the color-coded map that classified coronary plaque into different components (IVUS Lab Software, Volcano Therapeutics, USA). Fibrous component was shown in green, fibro-fatty plaque in greenish-yellow, dense calcium in white, and necrotic core in red, based on mathematical autoregressive spectral analysis of IVUS backscatter. VH-IVUS-derived thin-cap fibroatheroma (VH-TCFA), the so-called vulnerable plaque, was defined as a segment fulfilling the following criteria in at least 3 consecutive frames: (1) necrotic core >10% without evident overlying of fibrous tissue; and (2) percent plaque volume >40% [6].

Statistical Analyses

Statistical analysis was done by using SPSS version 17. Continuous and categorical variables were expressed as mean ± standard deviation and proportions. The mean values of continuous variables were compared between vulnerable and nonvulnerable plaques by use of unpaired Student's t-test. Chi-squared tests and Fisher's exact tests were used for analyzing the association between categorical variables with vulnerable plaque.A P-value <0.05 was considered as statistically significant.

Results

Table 1: Baseline characteristics of study population

	Mean	Std deviation
Age (years)	54.76	9.122
Chest Pain duration (hrs)	11.94	6.753
BMI	24.004	2.907
Hemoglobin	12.656	2.353
LV Ejection fraction (%)	45.44	8.384
Systolic BP	146.84	35.964
Diastolic BP	85.96	14.326
Random Blood sugar	159.78	65.617
Creatinine	1.35	0.55
LDL-C	130.30	31.628
HDL-C	43.50	6.683
Total Cholesterol	204.28	36.599
TG	150.80	50.053
hs CRP	4.034	2.167

Majority of our study population was male (72%) and mostly in the 45-54 years age group.Mean age of the patients was 54.76 years. Majority of patients presented within the reperfusion window, mean duration of chest pain at presentation being 11.94 hours. Obesity was not very common among the study population with mean BMI of 24. Majority of patient had mild LV systolic dysfunction, mean LVEF being 45.44%. Mean systolic blood pressure, unlike diastolic, was in the hypertensive range (146 mm Hg). Mean creatinine was on the higher side (1.35) and so also blood sugar (159 mg/dl). Mean hs CRP was pretty high (4.034). Among the lipid parameters, mean serum LDL-C and total cholesterol were on the higher side, 130.30 mg/dl and 204.28 mg/dl respectively. Only 4% patient had positive family history of premature coronay artery disease. Forty eight percent patients were smokers. Diabetes and hypertension were present in 54% cases and 58% cases, respectively. Forty two percent patients were dyslipidemic.

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Table 2: IVUS – VH baseline characteristics

	Mean	Standard deviation
EEM Volume (mm^3)	114.42	15.575
Lumen Volume (mm^3)	57.50	15.231
Plaque Volume (mm^3)	57.58	6.240
Area Stenosis (%)	40.52	3.919
Fibrous plaque volume (mm^3)	22.82	1.112
% Fibrous plaque	67.1	1.657
Fibrofatty plaque volume (mm^3)	3.834	0.758
% Fibrofatty plaque volume	13.6	1.82
Necrotic plaque volume (mm^3)	3.856	0.497
% Necrotic plaque	10.500	2.402
Dense calcium plaque volume (mm^3)	2.398	0.267
% dense calcium	6.690	0.476

Among the IVUS parameters mean plaque volume was 57.58 mm3 and mean area stenosis at the non culprit segment was 40.52%. Major contribution in plaque volume was from fibrous tissue and necrotic core was very much prevalent in the non culprit area with a mean of 10.5%. Using the definition of vulnerable plaque which consisted of necrotic core > 10% and plaque volume >40%, it was found that its occurrence was quite common, present in 46% of study population.

Table-3: Relationship between vulnerable plaque and variables

Relationship between vulnerable plaque and sex			
	Vulnerable plaque	**Non vulnerable plaque**	**Total**
Male	15 (41.7%)	21(58.3%)	36 (100%)
Female	8 (57.1%)	6 (42.9%)	14(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value = 0.324			
Relationship between vulnerable plaque and type of coronary artery involvement			
LAD	13	17	30
LCx	3	4	7
RCA	6	7	13
Total	23	27	
p value = 0.98			
Relationship between vulnerable plaque and number of coronary artery involvement			
SVD	13	16	29
DVD	7	8	15
TVD	3	3	5
Total	23	27	
p value =0.97			
Relationship between vulnerable plaque and TIMI flow			
TIMI grade	**Vulnerable plaque**	**Non Vulnerable plaque**	**Total**
0	4	2	6
1	3	5	8
2	2	3	5
3	14	17	31
Total	23	27	
p value =0.718			

LAD: Left anterior descending, LCx: left circumflex, RCA: right coronary artery

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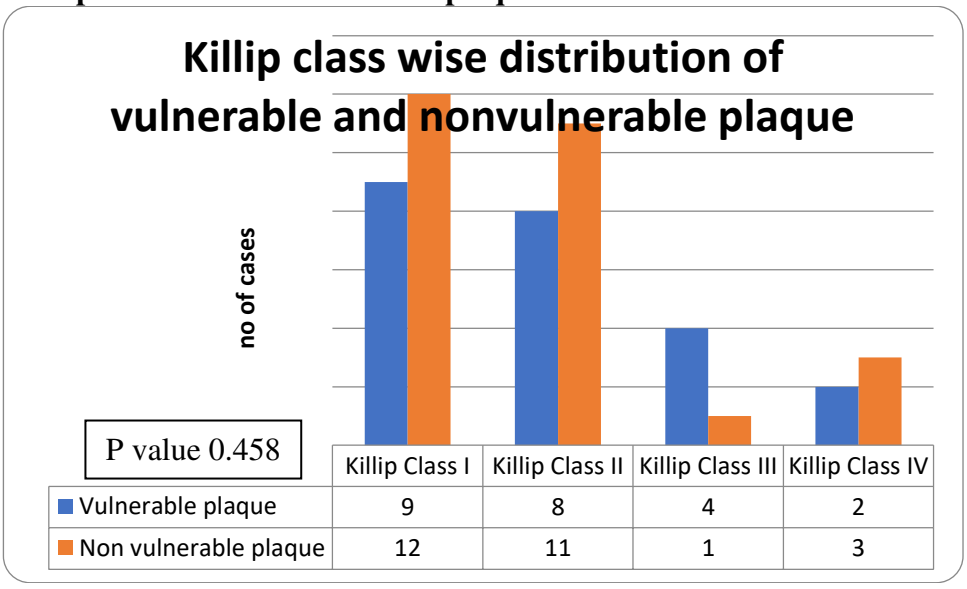
SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease
Presence of vulnerable plaque in the non-culprit segment was not found to be related to either type, number of coronary arteries involved or grade of TIMI flow.

Table-4: Relationship between vulnerable plaque and risk factor

Relationship between vulnerable plaque and smoking status			
Smoker	9(37.5%)	15(62.5%)	24(100%)
Non smoker	14(53.8%)	12 (46.2%)	26(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value =0.247			
Relationship between vulnerable plaque and family history of premature CAD			
Positive	0(0%)	4(100%)	4(100%)
Negative	23(50%)	23(50%)	46(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value =0.115 (Fisher's Exact Test)			
Relationship between vulnerable plaque and diabetic status			
Diabetic	13(48.1%)	14(51.9%)	27(100%)
Non Diabetic	10(43.5%)	13(56.5%)	23(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value =0.741			
Relationship between vulnerable plaque and hypertension status			
Hypertensive	15(51.7%)	14(48.3%)	29(100%)
Non Hypertensive	8(38.1%)	13(61.9%)	21(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value = 0.34			
Relationship between vulnerable plaque and dyslipidemic status			
Yes	14(66.7%)	7(33.3%)	21(100%)
No	9(31%)	20 (69%)	29(100%)
Total	23 (46%)	27(54%)	50 (100%)
P value = 0.013			

Occurrence of vulnerable plaque was not found to be associated with smoking status, family history of premature coronary artery disease, hypertension, diabetes, associated peripheral or coronary artery disease or wall involved.

Figure 1: Killip class wise distribution of plaque



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Although Killip class at presentation or shock was not associated with the vulnerable plaque, incidence of heart failure was

Table-5: Relationship between vulnerable plaque and continuous variables

	Vulnerable plaque Mean (SD)	Non vulnerable plaque Mean (SD)	P value
Age (years)	54.96(9.366)	54.52(9.030)	0.867
Body Mass Index	24.656(3.20)	23.23(2.35)	0.086
Pulse rate/ min	84.61(21.6)	92.44(23.68)	0.231
LVEF (%)	46.3(7.50)	44.7(9.14)	0.507
Hemoglobin gm%	12.22(2.40)	13.02(2.29)	0.232
Random BS	168.09(76.992)	152.7(54.63)	0.414
Creatinine (mg/dl)	1.24(0.41)	1.448(0.632)	0.193
LDL-C (mg/dl)	141.78(32.48)	120.52(27.86)	0.116
HDL-C (mg/dl)	40.70(4.87)	45.89(7.15)	0.005
Total cholesterol (mg/dl)	219.04(36.78)	191.7 (31.98)	0.007
Triglyceride (mg/dl)	169.91(47.56)	158.52(46.99)	0.122
Total Cholesterol/ HDL-C	7.90(1.02))	5.01(0.93)	0.03
hs CRP (mg/dl)	5.33 (2.21)	2.93 (1.39)	<0.0001

Among the other variables neither of age, BMI, pulse rate, LV ejection fraction, hemoglobin, blood sugar, serum creatinine and LDL-C level were associated with vulnerable plaque. However, it was found to be associated with HDL-C, total cholesterol and the ratio of total cholesterol and HDL-C.

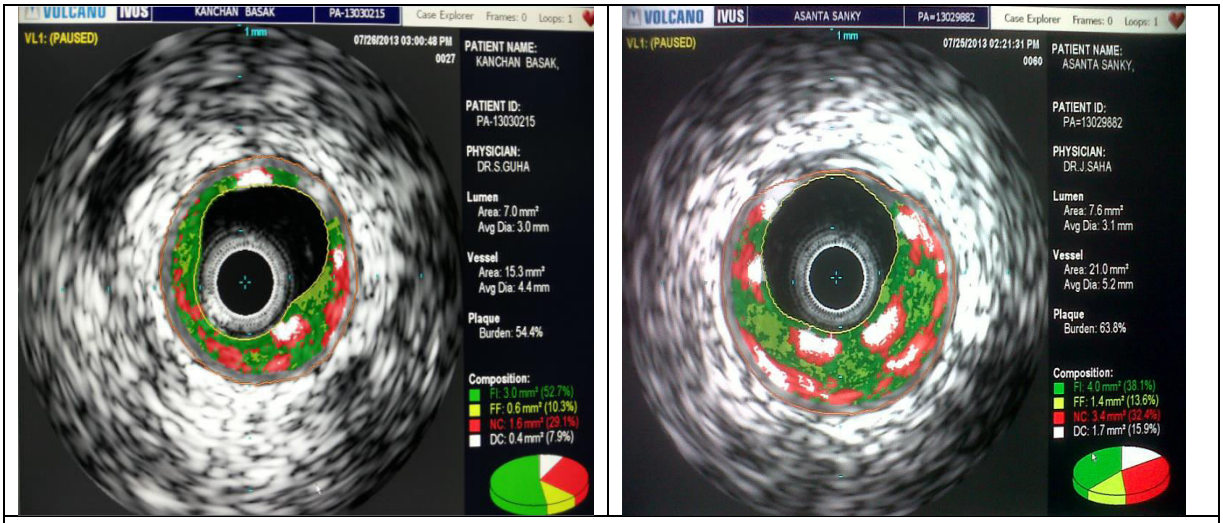

Figure-2. Example of commonly performed direct and derived IVUS measurements.Panels A and B illustrate the reference segment, whereas **panels C and D** represent the stenosis. In **Panel B**, the EEM and lumen areas are traced. In **panel D**, the minimum and maximum lumen diameters are illustrated using a double headed arrow (**open and solid arrowheads**, respectively). In **panel D**, the minimum and maximum atheroma thickness is also illustrated using **double headed arrows** (**white** for minimum and **black** for maximum). Also in **panel D**, the EEM and lumen areas are traced and the arc of calcification **(dotted line)** is shown. EEM : external elastic membrane.

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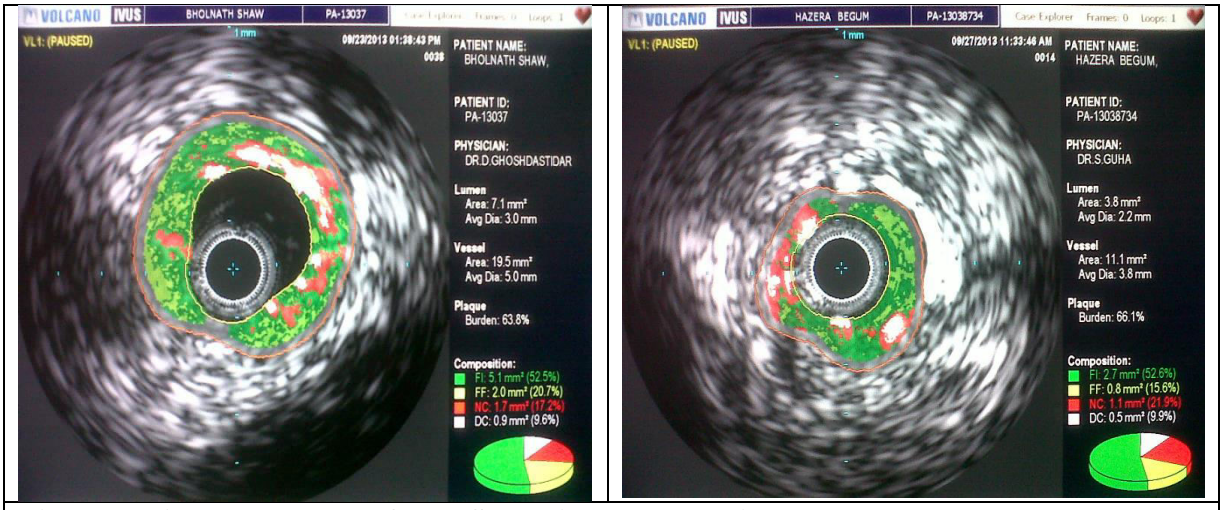

Figure-3. A-E Examples of IVUS VH image analysis. FI: fibrous tissue, FF: fibrofatty tissue, NC: necrotic core, DC: dense calcium

Discussion

It is well established that prevention of adverse cardiac events such as myocardial infarction and sudden cardiac death is of paramount importance in any patient with established coronary artery disease. Although all patients with documented coronary artery disease or a coronary artery disease equivalent are now considered candidates for systemic therapies such as antiplatelets, beta blockers, statins and angiotensin converting enzyme inhibitors, adverse events still do occur in spite of aggressive management. Several recent large randomized clinical trials have shown that in patients treated with high-dose statins, even optimal low-density lipoprotein cholesterol levels do not eliminate all events on follow-up.[3,4]

Thus, in addition to systemic therapy, investigators have been looking at the potential role for local or regional therapy for the vulnerable plaque.[5] If one can identify a vulnerable plaque and therapeutically reduce its vulnerability before symptoms arise, this might prevent subsequent infarctions and related complications. On the basis of the aforementioned trial data of residual cardiovascular events in patients receiving maximum therapy and the known histopathology of lesions responsible for myocardial infarction or sudden coronary death, the concept of identifying and treating vulnerable plaque with local or regional therapy has become a potential goal for future management. There have been several publications concerning vulnerable plaque pathophysiology, diagnosis, and potential management[6,7,8], and over years, several national and international symposia continuously highlight new information on vulnerable plaque and the prospects for local or regional therapy. However, until now there have been no objective criteria developed for the use of such local or regional therapy.

Plaque rupture is the most common substrate for coronary thrombosis in humans. However, 30% to 40% of coronary thrombosis occurs at sites at which plaque rupture cannot be identified. Hunt for the predisposing factor for plaque rupture has been an evolving area of research. In a landmark publication, Farb et al[9] described 50 consecutive cases of sudden cardiac death attributable to coronary thrombosis, in which 22 had superficial erosion of a proteoglycan-smooth muscle cell–rich plaque. No site of cap rupture could be identified. To establish clinical and histologic characteristics, the remaining 28 cases of plaque rupture served as controls. Eroded plaques were more frequently seen in pre-menopausal women. Of note, eroded plaques were less stenotic, had lower macrophage infiltration, and had a much lower incidence of calcification.

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Therefore, two different mechanisms, plaque rupture and erosion, can give rise to arterial thrombosis. The terms "high-risk" or "vulnerable" can be used as synonyms to describe plaques with an increased risk of thrombosis[6]. In addition to these terms, other terms, including culprit lesion, inflamed thin-cap fibroatheroma (TCFA), calcific nodule, thrombosed plaque, and vulnerable patient, have been used. This multiple terminology has created confusion and, therefore, has required standardization. To properly define adequate terminology and avoid confusion, a written consensus from a group of experts properly standardized these terms, providing definitions for proper implementation.[10]In addition, we also found it to be significantly associated with dyslipidemic status, especially low HDL, high total cholesterol and total cholesterol: HDL-C ratio. Whether these abnormalities are precipitating factor of acute coronary event or a result of it, is yet to be established.
However, our study is limited to small sample size. Our observations need to be substantiated by large randomized studies before any definite conclusion is made.

Conclusion

Prevalence of vulnerable plaque is quite high even in the apparently normal angiographic segments adjacent to the culprit lesion in patients with ST elevation myocardial infarction. Its presence has been found to be positively correlated with the high sensitive C- Reactive Protein, dyslipidemic status, specifically HDL-C, total cholesterol and total cholesterol: HDL-C ratio underscoring the possible role of inflammation and lipid derangement in the causation and precipitation of acute coronary event. Its association with occurrence of heart failure probably indicates more widespread disease process in this subgroup of patients. The subset of patients with acute coronary segment who have vulnerable plaque in the non-culprit segments are more likely to have worse outcome and probably needs to be addressed more aggressively.

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