Histopathological analysis of the coronary atheroma extracted during coronary artery bypass graft surgery

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Article Info

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Abstract

This study aims to evaluate the histopathological analysis as well as the effect of coronary endarterectomy with severe calcified coronary artery disease. During the year of 2015 to 2017, a total of 135 patients (56 patients of stable angina and 79 patients of unstable angina) underwent atherectomy in adjunct to off-pump coronary artery bypass graft surgery. Histopathological study of atheroma specimen demonstrates the presence of calcification, foam cell, cholesterol clefts, thrombus, smooth muscle cell, and also necrotic tissue using standard hematoxylin and eosin stain techniques. However, smooth muscle cells and foam cell were identified with plaque using the monoclonal antibodies. Thrombus was more common in unstable angina group of patients (64.4%) in comparison to the patients with stable angina (23.2%). An accelerated progression pattern of smooth muscle cell proliferation and calcification were observed which was also common and significantly higher in unstable angina group of patients. The presence of thrombus and accelerated progressive pattern of smooth muscle cell proliferation in unstable angina patients imply the episodic disruption of atheromatous plaque followed by sub-sequent healing and may play a vital role in the pathophysiology of underlying angina pectoris.

Introduction

A condition named unstable angina is differentiated by the symptoms severity and how it is progressed to infarction or may be sudden death, which has been into different clinical series.[1] In angiography, unstable angina shows that there is a plaque whose morphology shows an irregular eccentric stenosis, along with overhanging edges. In some percentage of cases in the culprit plaque, an intraluminal filling defect is found with a non-occlusive thrombus.[2, 3] From the pathological findings, it is identified that the plaque disruption occurs where the thrombus is projected into the lumen. However, ante-grade blood flow is kept in procession. Moreover, the activated platelet giving a layer cover the projecting thrombi, which then forms the emboli in the intra-myocardial vascular bed.[3-5] According to the clinical spectrum, the crescendo type of unstable angina is severe which is clear by the pathological process.[6] Though the necropsy material is solely taken in case of the severe end of disease, the atheroma plaque material is taken from the live patient along with the stable and unstable angina.[7] The common facts in the studies that the thrombus comes from the plaque which is responsible for unstable angina rather than from stable angina. Variable factors are chargeable for unstable angina pectoris, also the thrombus formation and coronary plaque rupture, abnormalities in the coagulation-fibrinolysis system and coronary spasm, where not always the thrombus is in unstable angina neither absent in all stable angina. Nevertheless, the thrombus formation and coronary plaque rupture are the direct causes.[5, 8, 9]

The existence of thrombus in the study population with unstable angina pectoris is proved in the studies which include intracoronary endoscopy, autopsy specimens, intravascular ultrasound imaging, coronary endarterectomy and coronary arteriography.[10] It is not properly investigated that the process of the acute deterioration of angina pectoris which results from the intimal proliferation, then the interventional therapy like percutaneous transluminal coronary angioplasty or coronary endarterectomy is connected to the development of acute coronary syndromes. The fact that thrombus is responsible for producing the angina is not even clear. For this reason, examining tissue specimens is collected at the time of endarterectomy during coronary artery bypass graft surgery.[11] Several studies have been done to determine several clinical classifications and

Table I

Demographic and morphological variables of atheroma specimen

Variables		Stable angina (n = 56)	Unstable angina (n = 79)
Age (years)		59.5 ± 5.5	58 ± 6.5
Sex	Male	85.7%	85.3%
	Female	14.3%	14.7%
Risk factors	Hypertension	92.9%	79.4%
	Diabetes mellitus	66.1%	55.9%
	Smoking	80.4%	61.8%
	Family history	30.4%	47.1%
Morphology	Smooth	60.7%	61.8%
	Complex	39.3%	38.2%
Histological characteristics	Thrombus	23.2%	64.6%
	Cholesterol	19.6%	26.5%
	Accelerated progression	30.4%	97.1%
	Macrophage	66.1%	61.8%
	Smooth muscle cell	41.1%	50.0%
	Calcification	30.4%	60.8%
Length of atheroma (cm)		7.5 ± 2.5	8.5 ± 5.5

severity of unstable angina. The aim of this study was to correlate the relationship among unstable angina and morphological features of atheroma extracted during off-pump coronary artery bypass graft surgery.

Materials and Methods

This study involved a total 135 patients with diffuse coronary artery disease with stable angina pectoris (56 patients), as well as unstable angina (79 patients) in whom coronary endarterectomy was performed in the year of 2015 to 2017 (Table I). Informed written consent was taken from all the study patients and data was collected in a data collection sheet. Following coronary endarterectomy, all patients prescribed aggressive medical management inclu-ding anti-coagulation therapy with nitrates, double anti-platelet agent, beta blocker for lifelong and also warfarin for 6 months. Immediately after coronary artery bypass graft surgery, patients were treated with injection heparin subcutaneously (5,000 units/day) up to 3rd postoperative day bridging to oral warfarin therapy. The anticoagulation dose was adjusted according to INR level, and targeted INR was 1.5-2.5. NYHA functional class was utilized to diagnosed unstable angina, and degree of coronary artery stenosis measured by both intervention cardiologist as well as cardiac surgeon in both pre-operative and postoperative conditions who were unknown about patient's clinical status. After end-arterectomy, the length of atheroma was measured, and collected specimens were processed for histo-pathological analysis after being fixed in 10% buffered formalin; stained with hematoxylin and eosin, and examined under the light microscopy. Histopathological analysis was also performed by a pathologist who was blinded about the clinical scenario, and in case any doubt histopathology slide reviewed with another pathologist.

Histopathological technique

Initially, the atheromatous plaque was labeled and grossly examined to categorize as it was predominantly either fibrous, lipid-laden, calcified, thrombotic or intermediate. The length was measured with a 30 cm ruler, and a section of atheroma for histopathology was taken and remaining part was stored in normal saline for biochemical analysis. Then, two or three tissue blocks obtained by the cross-section of the specimen and stored in a labeled butter paper blotted by hematoxylin and eosin stain inside a cassette which was dipped overnight into a formalin container. Furthermore, these specimens were sent for automated tissue processing, and the slides were observed under a microscope and photomicrographs were taken from a multi-head (40x magnification; Olympus, Japan) camera. The categorization of atheroma was completed based on both the previous and current findings from the slide. The presence of fibro-cartilaginous tissue, smooth muscle elements, inflammatory cells, cholesterol cleft, calcifications and thrombus were noted from the microscopic examination.

Results

A total of 135 atheroma specimen was analyzed and the majority population was male. About two-thirds patients were suffered from hypertension and smoking. The morphological analysis demonstrates smooth rather than complex features; with most common histopathological findings like the presence of calcification, thrombus, foam cell, cholesterol, smooth muscle cell, and accelerated progression pattern (Figure 1). Nonetheless, all above features were observed more common in unstable angina rather than stable angina, except macrophage which was similar in both study group. However, the accelerated pattern was significantly higher in the unstable angina group. The average length of the collected atheroma specimen was 7.5 ± 2.5 and 8.5 ± 5.5 cm in stable angina and unstable angina respectively (Table I).

One-year survival rate following the coronary endarterectomy was about 99 and 97% in stable angina and unstable angina respectively. However, according to the NYHA (New York Heart Association) functional classification, a great improvement regarding myocardial revascularization was documented as about 98% in stable angina, and 97% in

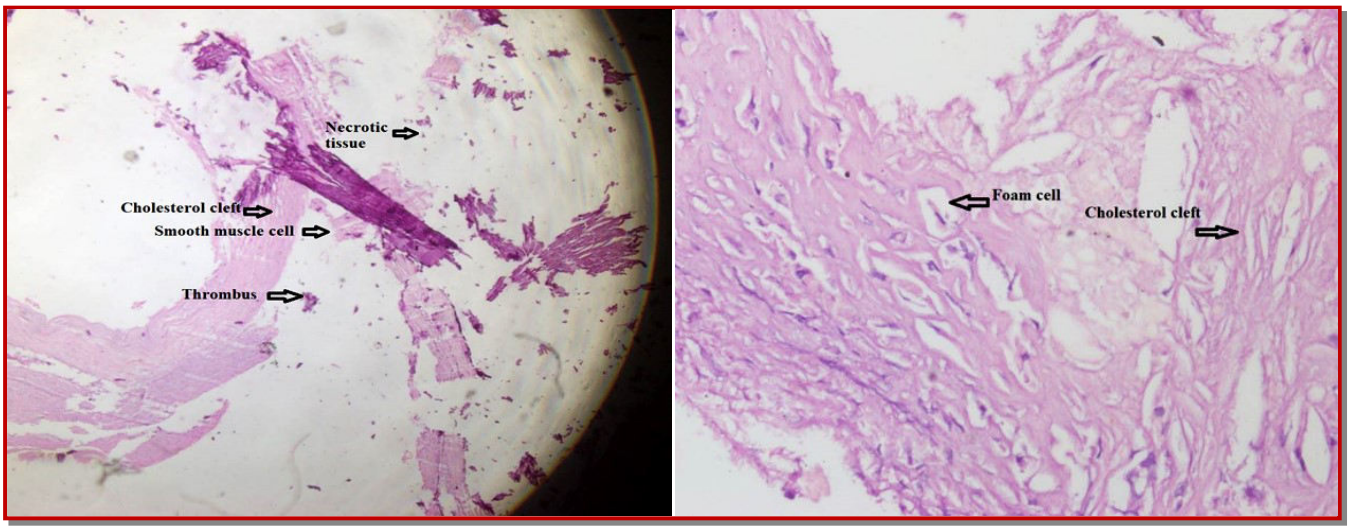

Figure 1: (A) Atheroma specimen illustrates smooth muscle cell, thrombus, cholesterol cleft with fragments of necrotic tissue (purple dot). (4x magnification); (B) Histological analysis (40x magnification) of atheroma observed accelerated progression pattern demonstrate foam cell with copious, well defined smooth muscle cells in a connective tissue matrix background (Hematoxylin and eosin stain)

unstable angina patients observed having NYHA functional class 1-2. Furthermore, in stable angina, the degree of stenosis was 76.5 ± 8.5 and 28.2 ± 12.5% before and after coronary endarterectomy respectively. However, the degree of stenosis was 89.5 ± 10.5 and 32 ± 11.5% before and after coronary endarterectomy in unstable angina group respectively (Table II).

Discussion

In this study, most common histopathological findings like presence of calcification, thrombus, foam cell, cholesterol, smooth muscle cell, and accelerated progression pattern of smooth muscle proliferation were more common in unstable angina group rather than in stable angina group. Moreover, NYHA functional class, and one-year survival rate following endarterectomy was similar between two study groups; and also angiographic evaluation demonstrates similar graft patency rate in both stable and unstable angina study group.

In a study, Fuster et al. (1992) observed small thrombi in only 11% when atherectomy for severe stenotic lesions was executed along with a histological study of derived fragments, though it was not focused either patient had unstable angina or any clinical features.[11] Several published articles observed that there are no past documents about the presence of thrombus in unstable angina patients.[5-9, 12] Restenosis after coronary endarterectomy has been associated to prompt arterial remodeling, mural thrombus formation and elastic recoil tendency of the arterial wall. However, advancement of coronary artery disease is not defined or anticipated.[13] In a study, Villadsen et al. (2017) found that coronary artery disease is a typical phenomenon in the unstable angina patients who became stabilized by rapid treatment procedure.[14] Moreover, chronic stable angina pectoris awaiting for coronary revascularization was also found in a state of progression of coronary stenosis which is also similar to other published articles.[3-5, 9, 15] Transfer of the smooth muscle cells from tunica media to the intima; along with propagation of the smooth muscle cells induced by the fragmentation of the internal elastic lamina plays a role in unstable angina.[16] In the study by Ahmed et al. (2003) found a common phenomenon that, greater percentage of smooth muscle cells in the remnant of re-stenotic lesions achieved by endarterectomy.[17] However, Marso et al. (2012) found that patient underwent percutaneous transluminal coronary angioplasty may develop total occlusion due to restenosis, and may also have only angina pectoris due to collateral circulation formation.[18] All these come to a conclu-

Table II

Early outcome following endarterectomy at 1 year follow-up

Variables		Stable angina (n=56)	Unstable angina (n=79)
Survival rate (%)		98.9	97.2
Angina free survival rate (%)		97.6	95.8
NYHA functional class (%)	Class 1-2	98.2	96.5
	Class 3-4	1.8	3.5
Follow-up evaluation with angiogram			
Degree of stenosis (%)	Preoperative	76.5 ± 8.5	89.5 ± 10.5
	Post-endarterectomy	28.2 ± 12.5	32 ± 11.5

sion that there is a remarkable difference among the cases who develop unstable angina, and probable causes may due to re-stenotic lesions after coronary endarterectomy and those due to the formation of new arteriosclerotic lesions which is also similar to other published articles.[7-10, 15-19]

Following pathologic reports of atheroma material, there is an intimate relation between acute ischemic events like unstable angina and myocardial infarction and intracoronary thrombosis.[20]

Lansky et al. (2012) observed in a study that more than sixty percent of specimens were found with fresh occluding thrombi.[21] Along with this dissolving of plaque rupture and intimal collagen fibers was found. It was concluded by saying that thrombus formation and coronary plaque rupture play an important role in the advancement of myocardial infarction. However, there are many clues found that are the cause of no thrombus in atherectomy samples which are of unstable angina patients. Among them one is pure coronary spasm detected reason of angina, another one is specimens of plaque found from atherectomy may laps the thrombus.[8-13, 19, 22] From angiographic studies of unstable angina, a greater frequency of thrombus was detected. The most important justification is the period between the endarterectomy procedure and the onset of symptoms. The thrombus in plaque that is within or on the surface with lysed immediately or commence proliferation of smooth muscle cells, where connective tissue replaced by thrombus.[23] In a study, Bild et al. (2005) observed that about one-third cases of unstable angina known to have thrombus, and the rest of the cases was caused due to smooth muscle proliferation.[24] It is known that plaques are at the uncertainty of rupture when it has a thin and soft fibrous cap with a large lipid core comprising of cholesterol, foam cell, macrophages, and few smooth muscle cells. Furthermore, the vulnerability of plaque is measured by 4 main factors- the size and constituents of the lipid core, the smooth muscle cell content of the cap, the thickness of the cap covering the core and the extent of macrophage infiltration into the cap.[5-10, 15-24]

Conclusion

In presence of thick fibrous cap, the thrombus burden and plaque rupture are rare, but the accelerated pattern of smooth muscle cell proliferation is also observed in apparently stable plaques. Thus, in comparison to unstable angina, the circumstances of acute coronary artery occlusion are less, and prognosis is supportive in stable angina patients. Moreover, it can be summarized that silent plaque progression can be formed by occult thrombosis; that's why aggressive medical management including proper anticoagulation therapy and surgical skill to remove adequate distal atheroma plaque remains the key strategy to achieve good myocardial revascularization.

References

1. Braunwald E. Unstable angina: A classification. Circulation 1989; 80: 410-14.
2. Ranjan R, Adhikary D, Mandal S, Seedher A, Adhikary AB. Outcome of coronary endarterectomy with coronary artery bypass grafting in patients with diffuse coronary artery disease in Bangladesh: A retrospective cohort study. JRSM Cardiovasc Dis. 2017; 6: 1-7.
3. Alfredsson J, Lindbäck J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: From the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Eur Heart J. 2011; 32: 3128-36.
4. Feyter PJ, Ozaki Y, Baptista J, Escaned J, Mario CD, Jaegere PPT, Serruys PW, Roelandt JR. Ischemia-related lesion characteristics in patients with stable or unstable angina: A study with intracoronary angioscopy and ultrasound. Circulation 1995; 92: 1408-13.
5. Adhikary AB, Ranjan R, Saha H, Saha SK, Adhikary D, Mandal S. A systemic review on coronary endarterectomy in ischemic heart disease. Chest Heart J. 2017; 41: 66-72.
6. Baber U, Stone GW, Weisz G, Moreno P, Dangas G, Maehara A, Mintz GS, Cristea E, Fahy M, Xu K, Lansky AJ, Wennerblom B, Mathey DG, Templin B, Zhang Z, Serruys PW, Mehran R. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. J Am Coll Cardiol Img. 2012; 5: 53-61.
7. Ranjan R, Adhikary AB. Outcome of coronary endarterectomy with off-pump coronary artery bypass grafting: A retrospective study. Bangabandhu Sheikh Mujib Med Univ J. 2017; 10: 189-94.
8. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, Wilson DJ, Zuckerman A, Wenger NK. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: The TNT (Treating to New Targets) study. J Am Coll Cardiol. 2008; 51: 1448-54.
9. Ranjan R, Adhikary D, Saha H, Mandal S, Saha SK, Adhikary AB. Outcome of CABG with or without coronary endarterectomy in Bangladesh: A retrospective cohort study. Bangladesh Heart J. 2017; 32: 77-84.
10. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM. Diabetes and mortality following acute coronary syndromes. JAMA. 2007; 298: 765-75.

11. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med. 1992; 326: 310-18.

12. MacLeod DC, Strauss BH, deJong M, Escaned J, Umans VA, van Suylen RJ, Verkerk A, de Feyter PJ, Serruys PW. Proliferation and extracellular matrix synthesis of smooth muscle cells cultured from human coronary atherosclerotic and restenotic lesions. J Am Coll Cardiol. 1994; 23: 59-65.

13. Rosenschein U, Ellis SG, Haudenschild CC, Yakubov SJ, Muller DWM, Dick RJ, Topol EJ. Comparison of histopathologic coronary lesions obtained from directional atherectomy in stable angina versus acute coronary syndromes. Am J Cardiol. 1994; 73: 508-10.

14. Villadsen PR, Petersen SE, Dey D, Zou L, Patel S, Naderi H, Gruszczynska K, Baron J, Davies LC, Wragg A, Bøtker HE, Pugliese F. Coronary Atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain. Eur Heart J Cardiovasc Imaging. 2017; 18: 556-67.

15. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, Marre M, Steg PG, Gowda N, Gore JM. GRACE investigators. Implications of diabetes in patients with acute coronary syndromes. The global registry of acute coronary events. Arch Intern Med. 2004; 164: 1457-63.

16. Nicholls SJ, Murat ET, Kalidindi S, Wolski K, Moon KW, Sipahi I, Schoenhagen P, Nissen SE. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling. J Am Coll Cardiol. 2008; 52: 255-62.

17. Ahmed S, Cannon CP, Giugliano RP, Murphy SA, Morrow DA, Antman EM, Braunwald E, Gibson CM. The independent and combined risk of diabetes and non-end stage renal impairment in non-ST-segment elevation acute coronary syndromes. J Natl Med Assoc. 2003; 95: 1042-47.

18. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, Lansky A, Templin B, Zhang Z, de Bruyne B, Serruys PW, Stone GW. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. J Am Coll Cardiol Img. 2012; 5: 42–52.

19. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008; 358: 580-59.

20. Kestenbaum BR, Adeney KL, de Boer IH, Ix JH, Shlipak MG, Siscovick DS. Incidence and progression of coronary calcification in chronic kidney disease: The Multi-Ethnic Study of Atherosclerosis. Kidney Int. 2009; 76: 991-98.

21. Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, De Bruyne B, Farhat N, Niess G, Jankovic I, Lazar D, Xu K, Fahy M, Serruys PW, Stone GW. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. J Am Coll Cardiol Img. 2012; 5: 62-72.

22. Ranjan R, Adhikary D, Saha H, Saha SK, Hasan K, Adhikary AB. Coronary atheroma [14 cm] extracted from the right coronary artery during off-pump coronary artery bypass grafting. Bangabandhu Sheikh Mujib Med Univ J. 2017; 10: 97-100.

23. Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, Bakhai A, Cohen DJ, Kuntz RE, Ho KK. Beyond restenosis: Five-year clinical outcomes from second-generation coronary stent trials. Circulation 2004; 110: 1226-30.

24. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005; 111: 1313-20.