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Atherosclerosis and plaque rupture: An update

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Atherosclerosis and Plaque Rupture: An Update

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Atherosclerosis complicated by plaque rupture and superimposed thrombosis is primarily responsible for acute coronary syndromes. Plaques most vulnerable to rupture contain a large extrac~ellular lipid-rich core, thin afibrous cap with reduced collagen content and smooth muscle density and increased numbers of activated macrophages. Macrophages have the ability to secrete proteolytic enzymes and often infiltrate the region of imminent plaque rupture. Plaque disruption tends to occur at points where a plaque surface is the weakest and coincides with points where biochemical and haemodynamic stresses act on plaques. Reduced matrix synthesis as well as increased matrix degradation may predispose fibrous caps to rupture spontaneously or in response to extrinsic mechanical or hemodynamic stresses. Control of cholesterol levels and factors that produce endothelial injury may result in plaque stabilization, prevent plaque rupture and ultimately lead to reduction in the frequency of acute coronary syndromes. The concept of plaque stabilization seems plausible. Indirect data from clinical trials involving hypocholestremic drugs and avoidance of risk factors provide strong support for this new paradigm. Thus, plaque stabilization may prove to be an important modality for reduction of lethal consequences of coronary atherosclerosis.

Introduction

Atherosclerosis, global in distribution has reached epidemic proportions in the Western societies[1-4]. Although clinically it may not be evident until middle age or later, atherosclerosis is considered to be a slowly progressing and complex disease that begins in childhood[5]. It remains a leading cause of death, carries serious morbidity and accounts for about one-third of all deaths ‘and two-thirds of deaths due to cardiovascular complications[6]. Progression of this disease from a relatively benign state to a life-threatening acute coronary syndrome depends on the type of plaque. The treatment of plaque disruption with superimposed thrombosis requires an understanding of the pathophysiology of plaque rupture. Recent advances in molecular pathology, coronary diagnostic techniques including pharmacotherapy of cardiovascular disorders have opened up new windows to study the factors lead ing to plaque rupture. This paper deals with the basic concept of atherosclerosis, its complications and pharmacological interventions to reduce the consequences of atheromatous plaque rupture.

Epidemiology and risk factors

Atherosclerosis is most prevalent among the populations of North America, Europe, Australia, New Zealand and Soviet Union. In contrast, it is much less common in central and South America, Africa, Asia and the Orient. Epidemiological studies are indicative that advancing age, male gender and certain genetic factors increase the risk of atherosclerosis (Table I).

Table I. Risk factors for developing atherosclerosis.

Major risk factors	Other risk factors
Hypertension	Obesity
Diabetes mellitus	Advanced age
Hyperlipidemia	Male sex
Cigarette smoking	Physical inactivity
Family history	Homocystinuria
Low levels of HDL	Emotional stress

HDL: High-density lipoproteins.

This familial predisposition is most likely polygenic, in particular, the disorders like hyperlipidemia, hypertension and diabetes mellitus. The risk factors that predispose to atherosclerosis and the resultant ischaemic heart disease have been identified by a number of prospective studies, most notably, the Framingham Study and the Multiple risk factor intervention trial[7,8] as summarized in Table II.

Table II. Risk factors for spontaneous plaque rupture.

Atheroma with a thin fibrous cap.
Soft plaque with a necrotic core
Clusters of foam cells within the fibrous cap
Intimal clusters of leukocytes
Adventitial bands of mononuclear leukocytes

The most important of these are hyperlipidaemia[9,10], hypertension[11] cigarette smoking[12] and diabetes[13]. Less pronounced and difficult to assess risk factors include, insufficient regular physical activity, stress, obesity, use of oral contraceptives, hyperuricaemia, high carbohydrate intake and hyperhomocysteinemia[14]. Demonstration of an epidemiologic association does not necessarily prove a pathogenetic relationship, so the cause and pathogenesis of atherosclerosis remain subject of lively

speculation and controversy.

Pathogenesis

Atherosclerosis with plaque disruption or fissuring with superimposed thrombosis frequently complicates its course. The importance of atherosclerosis has stimulated enormous efforts to investigate its causes and a number of hypotheses for its pathogenesis have been proposed.

I. Response-to-injury hypothesis

Originally, traced back to von Rokitansky and Virchow[15,16] and formally proposed in its current form by Ross[17,18], the lesions of atherosclerosis represent a chronic form of inflammatory fibro-proliferative response of the arteial wall to various injuries stimuli[19]. This may be defensive response which becomes the disease process itself. The hypothesis postulates that the initiating event in the atherogenic process is some form of overt injury (oxidized cholesterol, cigarette smoke, homocystinemia, catecholam ines, hyperglycaemia or hypertension) to the vascular intima which results in morphologically detectable endothelial damage. Further investigation of this fibromuscular proliferative phenomenon has revealed an abundance of cytokines, growth factors and other vasoactive substances that cause vascular smooth muscle migration, proliferation and extracellular matrix secretion. This process is considered to be mediated by platelet--derived growth factor, angiotensin, thrombin, interleukin-l and tumour necrosis factor and a number of other factors[15,16,19].

2. Endothelial injury and dysfunction

Although experimental denudation of the intimal lining is sufficient to elicit a complex response to injury phenomenon, this form of mechanical damage is not relevant to natural atherosclerosis. Indeed, early lesions of atherosclerosis in diet-induced animal models typically fail to reveal any overt endothelial injury[20]. Endothelial dysfucntion, a phenotypic modulation to a non adaptive functional state, might result in an imbalance between endothelial-dependent procoagulation and anticoagulation mechanisms and may result in an acute, localized thrombotic event or a chronic thrombotic tendency of the vessel wall. Endothelial dysfunction may also involve decreased production of endothelium-derived relaxing factor (EDRF), resulting jn vasospastic tendency (vasoconstricti on, platelet aggregation, vasospasm and thrombosis) as observed in early atherosclerosis[21,22].

3. Endothelium-dependent mechanisms of leukocyte recruitment in atherosclerosis

During development of atherosclerosis, an important change in the endothelium is its modulation to a proinflammatory state, with upregulation of cell surface adhesion molecules and chemo-attractant factors that promote leukocyte recruitment and activation[23]. In fact, adherence of circulating blood monocytes to the intact intimal surface of large arteries is the earliest morphologically detectable cellular event in atherogenesis[24]. These cells migrate across the endothelium, tend to replicate and become transformed into lipid-laden foam cells. In addition to accumulating cholesterol esters[19], this differentiating monocyte-macrophage population of cells can cause progression of lesions through local generation of cytokines, growth factors, procoagulant and fibrinolytic components, eicosanoids and toxic oxygen products. Leukocyte-selective nature of this mononuclear recruitment is suggestive of endothelium-dependent adhesion mechanisms which are analogous to those recently described in acute and chronic inflammation[25]. These observations have led to the hypothesis that these localized mononuclear leukocyte-endothelial interactions reflect specific molecular changes in the adhesive properties of the endothelial surface. This in turn may involve inducible endothelial-leukocyte adhesion molecules (ELAMS) Expressed in atherosclerotic lesions[26].

Immunohistochernical studies have localized the expression of these molecules at various stages of atherosclerotic lesion development in experimental animals and in some instances in humans[27]. The relative contributions of these mechanisms of leukocyte recruitment to the atherogenic process is an area of ongoing study that has important pathogenetic as well as therapeutic opportunities.

Morphology

Fatty streaks: Fatty streaks, the earliest lesion of atherosclerosis, are not significantly raised and do not cause any disturbance in blood flow. However, they may be the precursors of the more ominous atheromatous plaques[28]. Fatty streaks begin as multiple yellow flat spots and are composed of lipid-filled foam cells. Extracellular lipids are present in relatively smaller amounts than in plaques and proteoglycans, collagen and elastic fibres are found in variable amounts[29]. Fatty streaks have been seen in aortas of very young children (<1 year) and in all children older than ten years, regardless of geography, race, sex, or environment. Whatever the outcome of a specific fatty streak, the prevalence of these lesions early in life emphasize that atherosclerosis has its roots at a ery young age[6].

Atheromatous plaques

Focal intimal thickening and lipid accumulation produce the characteristic atheromatous plaques. Three principal components of atheromatous plaques are, cells (smooth muscle cells, macrophages and leukocytes), connective tissue extracellular matrix (collagen, elastic fibres and proteoglycans) and lipid deposits (intracellular and extracellular). These components occur in varying proportions in different plaques, giving rise to a spectrum of lesions. Usually, the superficial fibrous cap is composed of smooth muscle cells with a few leukocytes and relatively dense connective tissue. A cellular area beneath and to the side of the cap (the shoulder) consists of a mixture of macrophages, smooth muscle cells and T lymphocytes. A deeper necrotic core with disorganized mass of lipid material, cholesterol clefts, cellular debris, lipid-laden foam cells, fibrin, plasma proteins and a thrombus at various stages of organization[30-32]. The type of lipid found in plaques is primarily cholesterol.. The cholesterol esters and calcification appears to be related to the severity of stenosis and the age of the patient[33]. However, the composition of atheromas can vary, not only between different persons but also between arteries in the same person, same organ and even within same artery itself, affecting the vascular compliance[34]. Soft atheromas consist of necrotic debris whereas hard plaques usually present rigid fibrocalcific structures and can be designated as fatty, fibrofatty or fibrous based on relative contribution by soft and firm structural components (Figure 1).

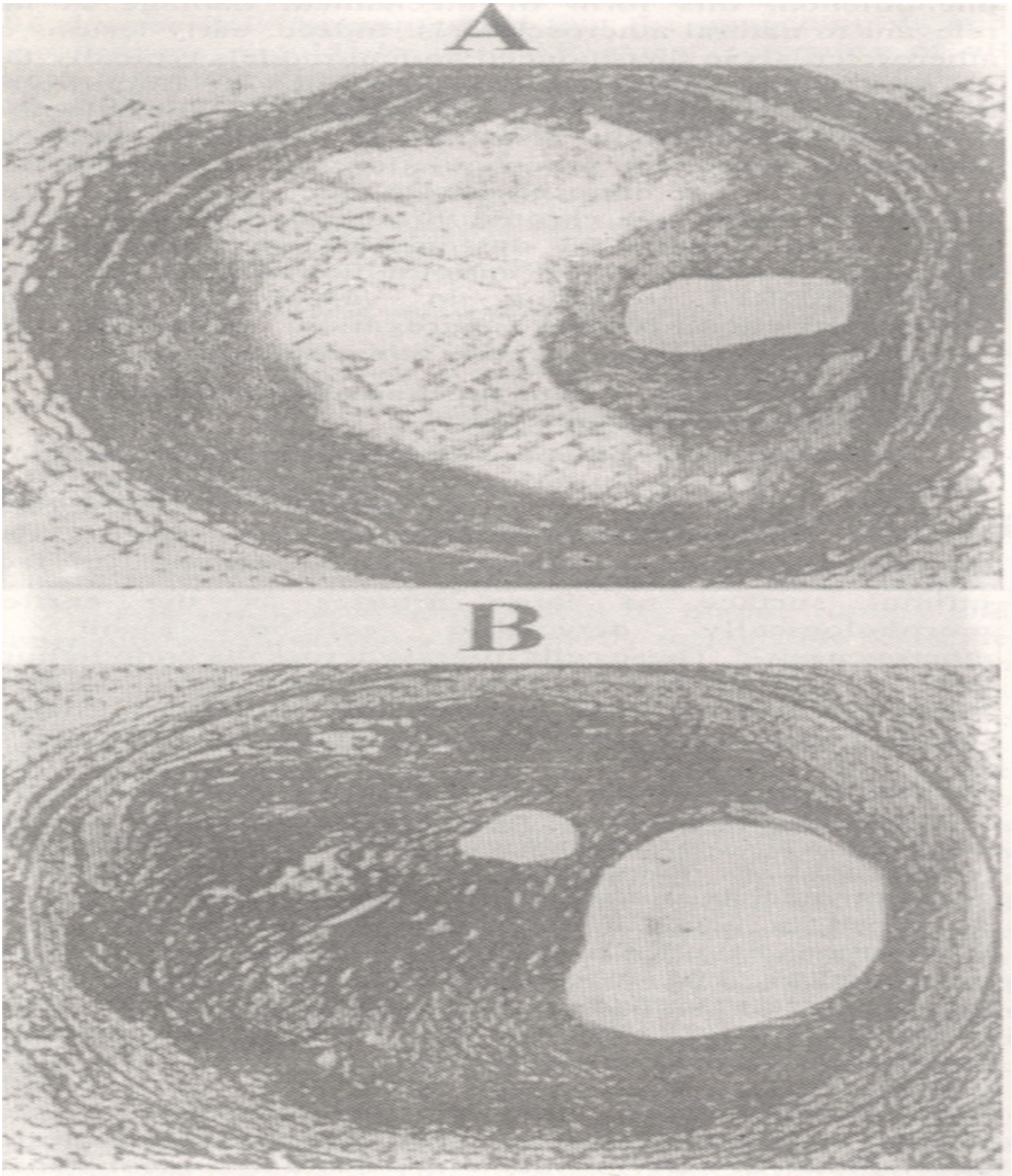

Figure 1. The composition of plaque in the coronary artery. A: Soft plaque showing the necrotic core mainly consisting of disorganized mass of lipid material, cholesterol clefts, cellular debri and lipid laden foam cells. B: hard plaque consisting of rigid fibrocalcific structures.

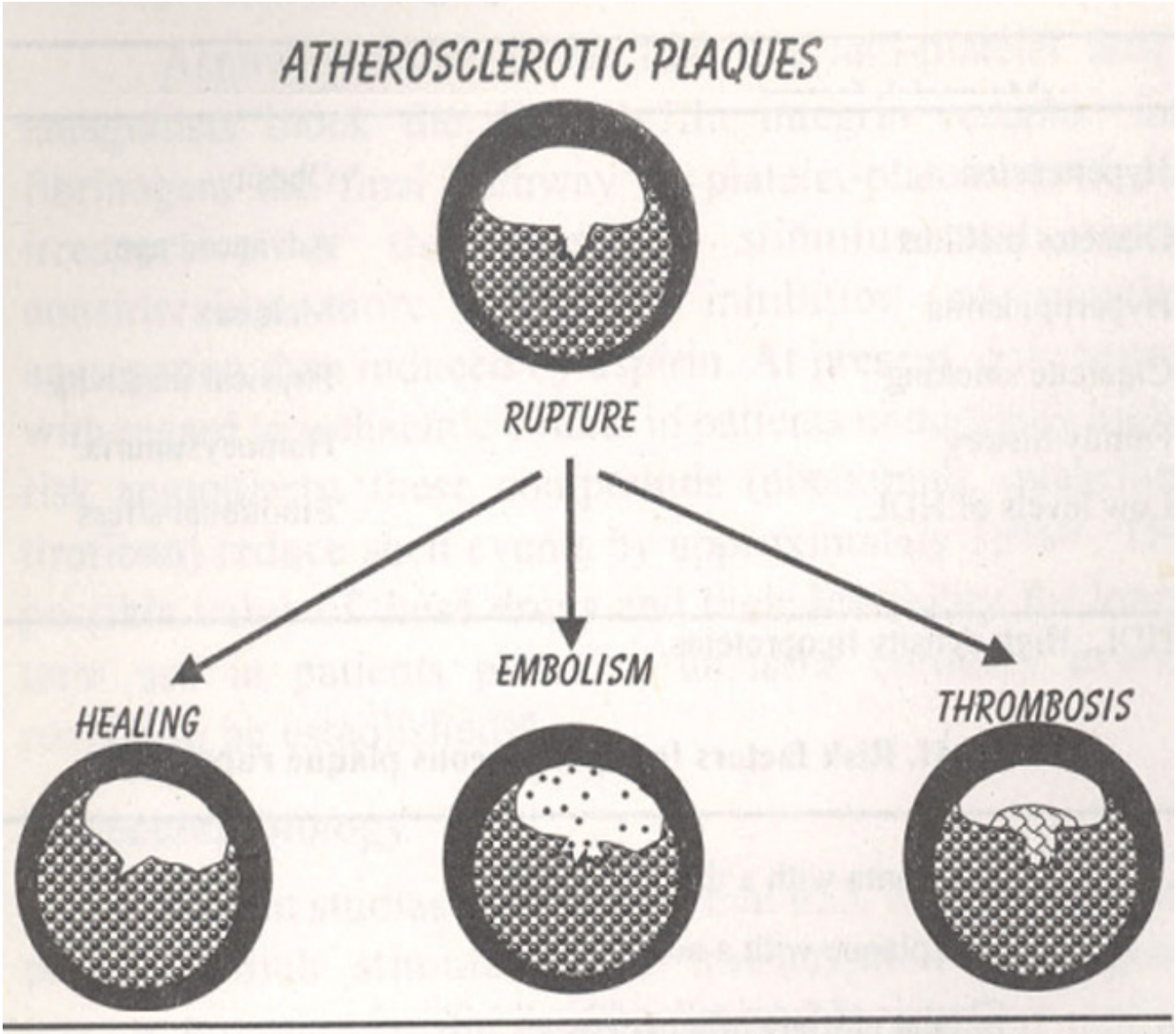

Figure 2. Schematic drawing showing different possibilities of the fate of ruptured plaques in the artery.

Unstable atherosclerotic plaques

Numerous studies have demonstrated that coronary thrombosis, the immediate cause of acute coronary syndromes is a consequence of plaque disruption[35]. Stable plaques may become unstable lesions when dynamic alterations occur which directly or indirectly lead to luminal narrowing. The four most frequently encountered alterations are plaque rupture, plaque hemorrhage, thrombosis and medial spasm (Figure 2). It has been shown that these alterations generally act in concert[36,37]. Furthermore, plaque rupture often results in thrombosis and through the release of various mediators, promote thrombosis. This is turn, may cause mechanical stresses that extent the size of plaque rupture and the cycle continues[37].

Plaque rupture

The causes of plaque rupture are complex as given in Table[11,38,39].

Numerous clinico-pathologic studies have shown that surface injury is the most common feature of unstable plaques, ranging from minimal surface erosions to lacerations that extend deep within the

plaque[38,40]. Regardless of the extent of injury, it results in exposure of the luminal blood to thrombogenic surface, thereby setting the stage of acute thrombotic obstruction. The consequences of plaque rupture depend upon the extent of thrombus formation and may result in unstable angina, acute myocardial infarction or sudden death. Plaque rupture has been associated with a trigger event in about half of the patients with myocardial infarction[41,42]. Physical exertion and emotional stress can trigger plaque disruption by surges in sympathetic activity with an increase in blood pressure, pulse pressure, blood flow, heart rate and coronary tone[42]. Vasospasm, in itself can produce endothelial damage and patients are more likely to have a secondary myocardial infarction who suffer vasospasm during cardiac catheterization

Prevention of plaque rupture

During management of patients with coronary artery disease, a reasonable goat is to prevent destabilization of coronary plaques. If this goal cannot be accomplished, then a second option is to counteract thrombus formation. Current efforts to prevent acute ischaernic syndromes have been limited by our inability to identify those plaques prospectively which are prone to rupture. The development of intravascular ultrasound has allowed the assessment of plaque morphology and composition[45]. However, at present no technology exists that can discriminate a plaque that will rupture from those with least tendency to rupture. Application of nuclear magnetic resonance microscopy may allow non-invasive assessment of atherosclerotic plaque in future[46] but studies have shown that the vulnerability of plaque to disruption appears to be determined by the presence of a dense lipid-rich core, a thin fibrous cap and an inflammatory cellular infiltrate rather than by the size of the plaque or the severity of stenosis[35].

Pharmacologic interventions

Once a vulnerable plaque is identified, antilipodaemic drug therapy, antioxidants (vitamins E, C), B-adrenoceptor blockers, angiotensin-converting enzyme inhibitors and thrombolytic therapy can be used to reduce the incidence of plaque rupture apart from elimination of risk factors. Some regression of atherosclerosis has been shown to substantially reduce the incidence of myocardial infarction, unstable angina and cardiac death[47].

Hypolipidaemic theory: Low density lipoprotein (LDL) is oxidized in vascular endothelial cells to a highly injurious product that results in characteristic cell dysfunction (loss of dilation, constriction, thrombosis and inflammation), before and during the development of atherosclerosis, in particular during plaque rupture[48,49]. During the several decades, studies have focused on the effects of serum lipids on atherogenesis[50]. There is strong evidence in recent trials on patients showing that treatment of serum lipids can improve clinical outcomes (e.g. acute coronary events) in 18 months to 3 years[49,51]. Lowering of total serum cholesterol, low-density lipoproteins, cholesterol and triglycerides, as well as increasing high-density lipoprotein cholesterol can be achieved with anticholesterolemic drugs[52]. Aggressive lipid lowering regimens have demonstrated an alteration in the progression of established atherosclerosis and regression of atheroma in some patients. A significant reduction in cardiac events in these studies have been thought to be related with plaque stabilization and restoration of endothelial vasodi lation[50-52]. Therapeutic lowering of serum cholesterol, LDL and oxidized LDL have recently been shown to improve endothelium-dependent dilation in the forearm vasculature of patients with hypercholesterolemia[53]. These observations are interesting because they show that atherogenic lipids can interact with blood vessel function even more rapidly than previously suspected. This study also shows that the relationship between atherogenic lipids and vascular dysfunction is dynamic and subject to change within minutes. This finding has important implications regarding the pathogenesis of ischemic syndromes and use of potent and rapidly acting lipid-lowering therapies in patients[53].

B-Adrenoceptor blockers

B-adrenoceptor and calcium channel blockers have been commonly used as first-line therapy for treatment of hypertension for more than two decades now. Statistically significant and clinically relevant reductions of mortality and reinfarction have been shown in prospective, double-blind, placebo-controlled trials[54,55]. Experimental studies suggest that beta blockers may have antiatherosclerotic effect in animals fed on atherogenic diet and subjected to stress[54]. There is substantial evidence that B-adrenoceptor blockers reduce the incidence of plaque rupture by reducing circumferential plaque stress as a result of reduction in blood pressure and blunting hypertensive pressure surges. B-adrenoceptor blockers increase plaque tensile strength by reducing heart rate and may also prevent plaque rupture by increasing the ability of the plaque's fibrous cap to withstand stress[54-56].

Angiotensin-converting enzyme inhibitors

Angiotensin II is a growth factor for vascular smooth muscle cells and may play a role in the initiation of plaque rupture. A strong association between vascular angiotensin generation and the development of coronary atherosclerosis in humans has been found using immunohistochem ical techniques[57]. Angiotens in converting enzyme (ACE) in hypercellular lesions, atheromatous plaques and ruptured plaques contributes to the further progression of atherosclerosis via an increase in vascular angiotensin 11 formation and inactivation of bradykinin[58].

Recent studies have shown an effect of ACE inhibition on the development of atherosclerosis in animal models. Captopril and Cilazpril prevent myointimal proliferation after vascular injury in rat. Captopril reduces aortic cholesterol content and percentage intimal aortic surface covered by lesions in Watanabe heritable hyperlipidemic rabbits. Captopril also significantly reduces the progression of carotid and coronary lesion in monkeys fed a high cholesterol diet[59]. The clinical usefulness of ACE-inhibitors in preventing the recurrence of myocardial infarction had been observed in large randomized trials. Results from these studies have suggested that ACE-inhibitors show vasculoprotective effects, possibly by preventing angiotension II induced vascular proliferation and therefore suppressing the development of atherosclerosis[60,61]. It is also conceivable that the blood pressure effects of ACE-inhibitors could play a role in the antiatherosclerotic effects shown by these drugs[59].

Antioxidants: There is mounting evidence that oxidation of low-density lipoprotein cholesterol may be instrumental in atherogenesis. Oxidized LDL is an initiator of macrophage accumulation within the plaque. A number of studies have been undertaken to evaluate the effects of antioxidants vitamins, beta carotene and selenium on coronary artery disease. Results in many instances have been promising, particularly in case of vitamin E supplements[62]. It is thought that the antioxidants inhibit the formation of oxidized LDL[63,64].

Anticoagulation therapy

The coagulation system is activated in vivo by exposure to tissue factors. This occurs when atherosclerotic plaque ruptures or when the endotheliurn is damaged by angioplasty. Endogenous thrombin is a major trigger for thrombosis in acute coronary syndromes[38,39]. Heparin is a potent inhibitor of thrombin and thrombin generation but its ability to accelerate thrombolysis is relatively limited clinically. Use of aspirin is most impressive in the early stages of symptomatic unstable coronary artery disease, a period when prothrombotic forces are most apparent[65]. When added to the B-adrenoceptor blocker-based treatment of patients with stable angina pectoris, aspirin significantly decreases the likelihood of developing fatal as well as non- fatal myocardial infarction[66].

Aspirin remains as the first line anti-platelet drug. Other approaches involving glycoprotein (GP) lIb-Illa antagonists block the GP lIb-IIIa integrin receptor for fibrinogen, the final pathway to platelet-platelet bridges, irrespective of the causative stimulus and cause considerably more effective inhibition of platelet aggregation than induced by aspirin. At present, only tested with regard to ischaemic events in patients undergoing high-risk angioplasty, these compounds (abciximab, integrilin, tirofiban) reduce

such events by approximately 35%[67]. The possible value of these drugs and their feasibility for long-term use in patients prone to unstable coronary events remain to be established[68].

Molecular Biology

Recent studies have shown that p53, a gene regulator protein which stimulates the transcription of a gene encoding cyclin-dependent kinase inhibitor protein called p21, is involved in the control of proliferation of human vascular smooth muscle cells (VSMCs) in atheromatous plaques. It has been demonstrated that VSMCs undergo apoptosis in the human atheromatous plaques, particularly at areas prone to rupture, suggesting that VSMC apoptosis may promote plaque rupture and subsequent thrombosis leading to myocardial infarction[69,70].

More recent studies have suggested that many plaque cells are in a process of apoptosis as determined by positive deoxyribonucleotide-transferase-mediated dUTP end labelling[71]. With the advent of molecular biology techniques, it has now become possible to clone differentially expressed genes in vessels with or without atherosclerosis. This would help to characterize the molecular and cellular mechanisms of this disease. In addition, the search for such candidate genes could form the basis of future genetic interventions during the development of atherosclerosis.

Conclusion

Plaque rupture is usually the initial event in the formation of coronary thrombi, responsible for acute coronary syndromes. From the present discussion, it can be speculated that to prevent or minimize the development of atherosclerosis, the elimination or control of chronic risk factors is important. Once the disease is symptomatic, drug therapy is generally directed towards relieving the obstruction and prevention of plaque rupture and its complications. Further insight into the causes of plaque rupture may provide information regarding the prevention of disease. The current research and treatment modalities are directed towards understanding and controlling the risk
factors for acute plaque rupture and ultimately transformation of unstable plaques into stable and quiescent lesions[72].

References

1. Majno G, Joris JZ, Atherosclerosis: New horizons. Human. Pathol., 985;1 6:3-5.
2. Schwartz CJ, Valente AJ, Sprague EA., et al. The pathogenesis of atherosclerosis and overview. Clin. Cardiol., 1991; 14:1 -16.
3. Ross R. Atherosclerosis: A defencc mechanism gone awry. Am. J. Pathol., 1993;1 43:987-1002.
4. Davies Mi, Woolf N. Atherosclerosis, what is it and why does it occur? Br. Heart J., 1993;69:S3-S1 1.
5. Strong JP. The natural history of atherosclerosis in childhood. Ann. N.Y. Acad. Sci., 1991;623:9-15.
6. World Health Organization. Classification of atherosclerotic lesions. WHO Tech. Report. Series, 1985:153-220.
7. Neaton JO, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking and death from coronary heart disease. Overall findings and differences by age for 316099 white men. Arch. Inten. Med. 1992:152:56-64.
8. Kennel WB. Contributions of the Framingham study to the conquest of coronary artery disease. Am. J. Cardiol., 1988;62:1 109-22.
9. Lipid Research Clinics Program: The lipid research clinics coronary primary prevention trial results.
1. Reduction in incidence of coronary heart disease. JAMA, 1984:251:351-64.
10. Kane JP, Malloy Mi, Ports TA, et al. Regression of coronary atherosclerosis during treatment of

familial hypercholesterolemia with combined drug regimens. JAMA: 1990:264:3007-12.
11. Chobanian AV. The influence of hypertension and other hemodynamic factors in atherosclerosis. Prog. Cardiovasc. Dis., 1983;26:177-86.
12. McGill H. The cardiovascular pathology of smoking. Am. Heart J., 1988:115:250-57.
13. Bierman EL. Atherogenesis in diabetes. Arterioscler. Thromb., 1992:12:64756.
14. Clarke R, Daly L, Robinson K, et al. Hyperthroinbocysteinemia: An independent risk factors for vascular disease. N. EngI .1. Med., 1991:324:1149-55.
15. Von-Rokitansky CA. Manual of pathological anatomy. Vol. 4, Translated by Day GE. London, The Sydenham Society, 1852.
16. Virchow R, Gesammelte Abhandlungen zur WisscnschafIlichen Medizin. Phlogose und thrombose in gefassystem. Berlin, Meidinger Sohn and Co., 1856, pp. 458-63.
17. Ross R, Glomset JA. Atherosclerosis and arterial smooth muscle cell. Science, 1973:180:1332-39.
18. Ross R. The pathogenesis of atherosclerosis, an update. N. EngI. J. Med., 1986:314:488-500.
19. Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990. Nature, 1993:362:801-9.
20. Simionescu M, Simionescu N. Proatherosclerotic events: Pathobiochemical changes occurring in the arterial wall before monocytc migration. FASEB. J., 1993:7:1359-66.
21. Luscher TF, Vanhouette PM., eds. The endothelium. Modulator of cardiovascular function. Boca Raton, FL : CRC Press, 1990.
22. Abrams J. Role of endoihelial dysfunction in coronary artery disease. Am. J, Cardiol., 1997:79:2-9.
23. Cybulsky Ml, Gimbrone MA. Endothelial leukocyte adhesion molecules in acute inflammation and atherogenesis. In: Simionescu N. Sitnioneseu M, eds. Endothelial cell dysfunctions. New York, Plenum l'ress, 1992:129-40.
24. Faggiotto A, Ross R, Harker L. Studies of hvpcrcholesterolemia in nonhuman primates. 1. Changes that lead to fatty streak formation. Arteriosclerosis, 1984:4:323-40.
25. Springer TA. Adhesion receptors of the immune system. Nature, 1990:346:425-34.
26. Cybulsky Ml, Gimbrone MA. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis . Science, 1991 ;25 1:78891.
27. Poston RN, Haskard DO, Coucher JR, et al Expression of intercellular adhesion molecules-I in atherosclerotic plaques. Am. J. Pathol., 1992;140:665-73.
28. Stary HC. Evolution and progression of atherosclerotic lesions in children and young adults. Arteriosclerosis., 1 989;99(Suppl 1): 1:19-32
29. Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol: modification of low-density lipoprotein that increases atherogenicity. N. EngI. J. Med., 1989;320:915-24.
30. Davies Mi, Woolf N, Rowles PM, et al. Morphology of the endotheliurn over atherosclerosis plaques in human coronary arteries. Br. Heart J., 1988;60:45964.
31. Kragel AH, Reddy SO, Wittes JT, et al. Morphometric analysis of the composition of coronary arterial plaques in isolated unstable angina pectoris with pain at rest. Am. J. Cardiol., 1990:66:562-67,
32. Kragel AH, Reddy SG, Wittes JT, et al. Morphornetric analysis of the composition of atherosclerotic plaques in four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. Circulation, 1989;80:1747-56.
33. Ornish D, Brown SE, Scherwitz S. et at. Can lifestyle changes reverse coronary artery disease? The lifestyle Heart Trial. Lancet, 1990;336:129-33.
34. Blackenhorn DH, Nessim SA, Johnson RL, et at. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA., 1987:257:3233-40.
35. Shah PK. New insights.into the pathogenesis and prevention of acute coronary syndromes. Am. J. Cardiol., 1997:79:17-23.
36. Kohchi K, Takebayashin-Hiroki T, Nobuyoshi M. Significance of adventitial inflammation of the coronary artery in patients with unstable angina. Results at autopsy. Circulation, 1985:71:709-16.
37. Baroldi G, Silver MD, Mariani F, et al. Correlation of morphological variables in the coronary

atherosclerotic plaque with clinical patterns of ischernic heart disease. Am. J. Cardiovas. Pathol., 1988;2:159-72.
38. Fuster V, Stein B, Ambrose JA, et al. Atherosclerotic plaque rupture and thrombosis: Evolving concepts. Circulation, 1990;82 (Suppl l1):47-59.
39. Davies MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischeniic death. N. Engl. J. Med., l984;310:1 137-40.
40. Fuster V, Badimon L, Badimon JJ, et at. The pathogenesis of coronary artery disease and the acute coronary syndromes. N. Engl. J. Med., 1992:326:24250.
41. Gerlernt MD, Hochrnan JS. Acute myocardial infarction triggered by emotional stress. Am. J. Cardiol., 1992;69:1512-13.
42. Muller JE, Tofler OH, Edelman E. Probable triggers of onset of acute myocardial infarction. Clin. Cardiol., 1989:12:473-75.
43. Joris I, Majno 0. Endothelial changes induced by arterial spasm. Am. J. Pathol., 1981:102:346-58.
44. Alpert iS. Coronary vasornotion, coronary thrombosis, myocardial infarction and camel's back. J. Am. CoIl. Cardiol., 1985:5:617-18.
45. Liebson PR, Klein LW. Intravascular ultrasound in coronary atherosclerosis: a new approach to clinical assessment. Am. Heart J., 1992;123:1643-50.
46. Perlman JD, Southern JF, Ackerman JL, Nuclear magnetic resonance microscopy of atheroma inhuman coronary arteries. Angiology, l991;42:726-33.
47. Watts GF, Lewis B, Brunt IN, et at. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in St. Thomas' Atherosclerotic Regression Study STARS. Lancet, 1 992;339:563-69.
48. Saeed SA, Mernon RA, Gilani AH, et al. Effects of lipoprotcins on cyclooxygenasc and lipoxygenase pathways in human platelets. J. Pak. Med. Assoc., l997;47:84-88.
49. Selwyn AP, Kinlay 5, Libby P, et at. Atherogenic lipids, vascular dysfunction and clinical signs of ischemic heart disease. Circulation, 1997;95:5-7.
50. Brown G, Albert JJ, Fisher LD. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N. EngI. J. Med., 1990:323:1289-98.
51. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering therapy in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study 4S. Lancet, 1994:344:1383-89.
52. Bjelajac A, Goo AK, Weart CW. Prevention and regression of atherosclerosis: Effects of HMG-Co reductase inhibitors. Ann. Pharmacother., 1996;30:1303-15.
53. Tamai 0, Matsuoka H, Nishida H, et at. Single LDH-apheresis improves endothel ium-dependent vasodi lation in hypercholesterolemic humans. Circulation, 1997:95:76-82.
54. Hanson L. Review of state-of-art beta-blocker therapy. Am. J. Cardiol., 1991;67:43B-46B.
55. Ynsuf S, Peto J, Lewis J, et al. Beta blockade during myocardial infarction. An overview of randomized trials. Cardiovasc. Dis., 1985:27:335-71.
56. Frishman WH, Lazar EJ. Reduction of mortality, sudden death, non-fatal reinfarction with beta-adrenergic blockers in survivors of a myocardial infarction: A new hypothesis regarding the cardioprotective action of betaadrenergie blockade. Am. J. Cardiol., 1 990:66:66G-70G.
57. Powell JS, Clozel JP, Muller RKM, et at. Inhibition of angiotensin-converting enzyme prevent myocardial proliferation after vascular injury. Science, 1989;245: 186-88.
58. Ohishi M, Ueda M, Rakugi H, et at. Enhanced expression of angiotensinconverting enzyme is associated with progression of coronary atherosclerosis in humans. J. Hypertens., 1997; I 51295-1302.
59. Ambrosioni E, Bacchelli S, Degli ED,et al. ACE-inhibitors and atherosclerosis. Eur. J. Epiderniol., 1992:8:129-33.
60. Pfeffer MA, Braunwald E, Moye LA, et at. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction and myocardiat infarction: results of the Survival and

Ventricular Enlargement Trial. N. EngI. J. Med., 1992;327:669-77.
61. The SOLVD investigators. Effects of Enalarpil on mortality and development of heart failure in asymptomatic patients with reduced ventricular ejection fractions. N. EngI. J. Med., 1992;327:685-91.
62. Mehra MR, Levie CJ, Ventura HO, et at. Prevention of atherosclerosis . The potential role of antioxidants. Postgrad. Med., 1995:98: 1 75-84.
63. Chesebro JH, Zotdhetyi P, Fuster V. Plaque disruption and thrombosis in unstable angina pectoris. Am. J. Carcliol., 1991 :68:9C-l 5C.
64. Esterbaur H, PuhI H, Dieber R, et at. Effect of antioxidants on oxidative modification ofLDL. Ann. Med., 1991:23:573-81.
65. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet, 1990:336:827-30.
66. Juul-Moller 5, Edvardsson N, Jahnmatz B, et at. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable angina pectoris. The Swedish angina Pectoris Aspirin Trial SAPAT group. Lancet, l992;340: 142 1-25.
67. Tcheng JE, Glycoprotein lib/lilA receptor inhibitors: Putting the EPIC, IMPACT II, RESTORE and EPILOG trials into prospective. Am. J. Cardiol., 1 996;78:35-40.
68. Ryden L,, Hamsten A. The way ahead in the management of unstable coronary artery disease. Am. J. Cardiot., l997;80: 5A:64E-67E.
69. Isner J, Kearney M, Bortman S. etat. Apoptosis in human atherosclerosis and restenosis. Circulation, 1995:91:2703-11.
70. Martin RB, Littlewood TD, Schwartz PL, et al. Increased sensitivity of human vascular smooth cells from atherosclerotic plaques to p53-mediated apoptosis. Circ., Res., 1997;81:591-99.
71. Jovinge S. Crisby M, Thyberg J, et at, DNA fragmentation and ultrastructural changes of degenerating cells in atherosclerotic lesions and smooth muscle cells exposed to oxidized LDL in vitro. Arterioscler. Thromb. Vase., Biol., 1 997;1 7:2225-31.
72. MacIsaac Al, Thomas JD, Topol EJ. Towards the quiescent plaque, J. Am. Coil. Cardiol., 1993;22:1228-41.