Current Concepts of Vascular Injury and Thrombosis in the Pathogenesis of Coronary Atherosclerosis

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Atherosclerosis (AS) is a complex disorder and is multifactorial in its pathogenesis. Interactions of blood cells, such as platelet and monocytes with arterial wall endothelial and smooth muscle cell involve complex autocrine and paracrine factors. A number of theories have been presented over the last 150 years to explain the pathogenesis of atherosclerosis (AS), however, none could completely account for all features of the disease. The currently held belief is the "response-to-injury" hypothesis, as presented by Ross in 1986[1].

VascuLar Injury and Repair - The Unifying Concept of Pathogenesis

The key event in the initiation of AS is injury to the vessel wall and the subsequent pathological changes are merely a reparative process[2]. Experimentally many factors have been shown to be injurious to arterial endothelium, intima or both producing lesion that in some aspects resemble those of human AS. These include chemical, metabolic, physical and biological forms of injury. Vascular injury with endothelial damage may be spontaneous, developing at sites of low hemodynamic shear stress and reversing flow, where the residence time of molecules (e.g., LDL) and cells (monocytes) may be prolonged[3]. An example of this may be bends in the arterial tree or areas where branches take off. Fuster et al. have classified, spontaneous vascular injury into 3 types, as illustrated in Figure 1[4].

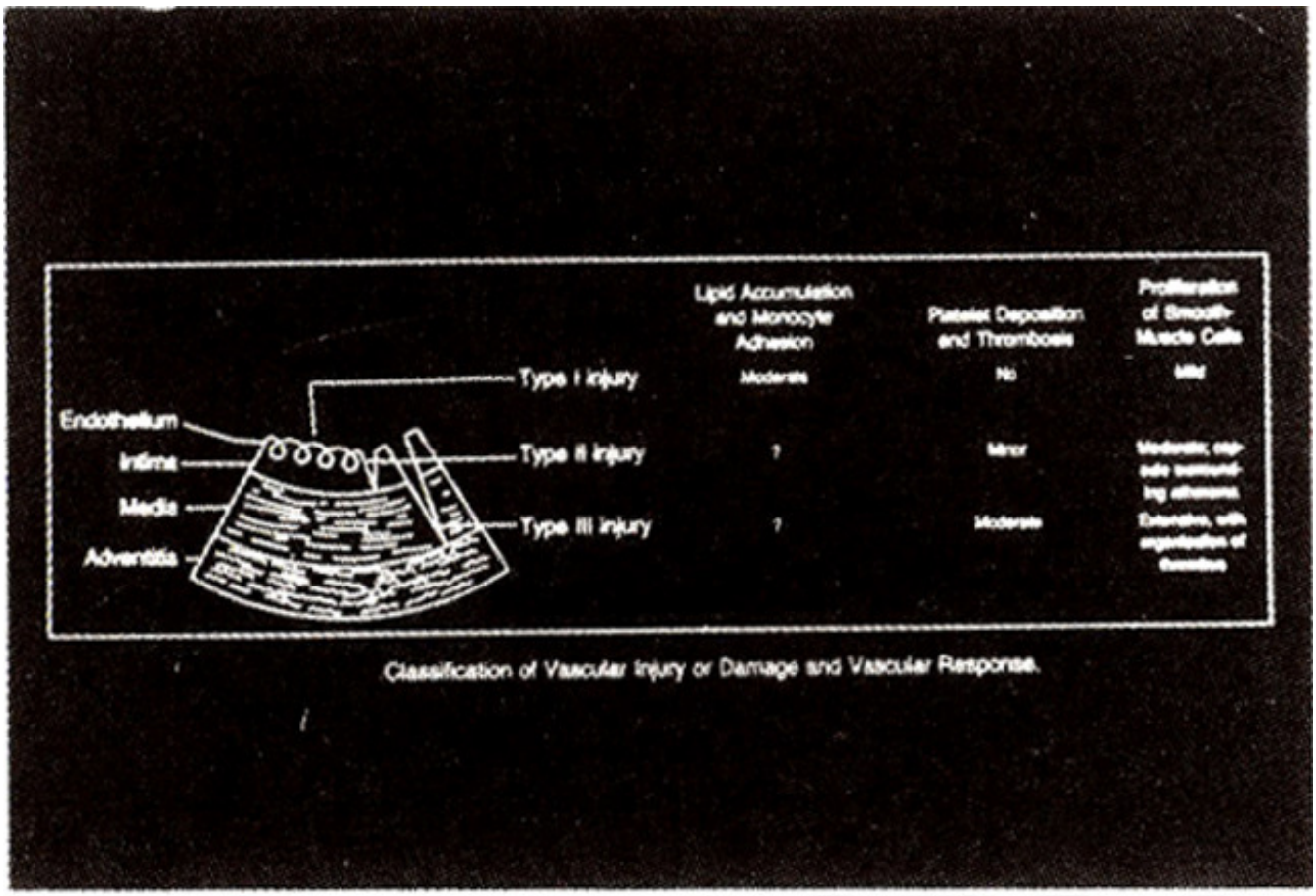

Figure 1. Pathogenic classification of vascular injury. Type I. Consists of functional alterations of endothelial cells without morphologic changes. Type II. Endothelial denudation and intimal damage with an intact internal elastic lamina. Type III. Endothelial denudation with damage to both the intima and media with rupture of the internal elastic lamina.

A type III lesion with its predominantly lipid core surrounded by a thin capsule can be easily disrupted leading to thrombus formation. When these thrombi are small they can become organized and contribute to the growth of AS plaque. When thrombi are large and occlusive, they can lead to acute coronary syndromes such as unstable angina, myocardial infarction and sudden ischemic death. Compared to spontaneous AS, a more aggressive and accelerated version of coronary atherogenesis is seen in patients with cardiac transplantation where a local immune-mediated vascular injury appears to be responsible for AS[5]. Similarly in patients undergoing percutaneous coronary angioplasty (PTCA), the mechanical trauma of stretch to the arterial wall with antecedent rupture of the internal elastic lamina appears to be the trigger for the formation of neo-intimal fibro fatty lesion.

Risk Factors for Coronary Artery Disease (Table I)

Risk factors for clinical coronary artery disease may promote atherogenesis, thrombosis or both. Some of the traditional risk factors are enlisted in Table I.

Table I. Risk factors for CAD.

- Age
- Male sex
- Hypercholesterolemia (iLDL-C)
- Low levels of HDL-C (<35 mg%)
- Hypertension
- Diabetes mellitus
- Cigarette smoking
- Family history of CAD before 55 years
- Obesity (>30% ideal body weight)
- Sedentary lifestyle
- Type A personality (hostility, icirculating epinephrine)
- History of cerebrovascular or peripheral vascular disease

Others:

- Hyperfibrinogenemia
- Hypertriglyceridemia

A more detailed discussion on this topic is beyond the scope of this review. It is important to point out that a major contribution of cardiovascular epidemiologic studies has been the concept of risk factors and the probability for occurrence of clinical illness.

Coronary Artery Plaque Morphology

The earliest lesions of atherosclerosis can usually be found in young children and infants in the form of a lesion called the 'fatty streak' whereas the advanced lesion, the 'fibro fatty plaque' generally appears during early adulthood and progresses with age.

Fatty streak:

These were first demonstrated by Stary[6] in a series of children and young adults, These fatty streaks consist primarily of lipid laden macrophage (foam cells), together with varying (but small) number of lipid filled smooth muscle cells (SMC). The bulk of this lipid is in the form of cholesterol and cholesteryl-esters, which enters the fatty streak by transport of lipoprotein from the plasma via the endothelial cells, after which it is taken up by macrophage and SMC. The plasma lipids present in the intima are ingested by the macrophage and are hydrolyzed and reesterified once they have been taken up by these cells (Figure 2).

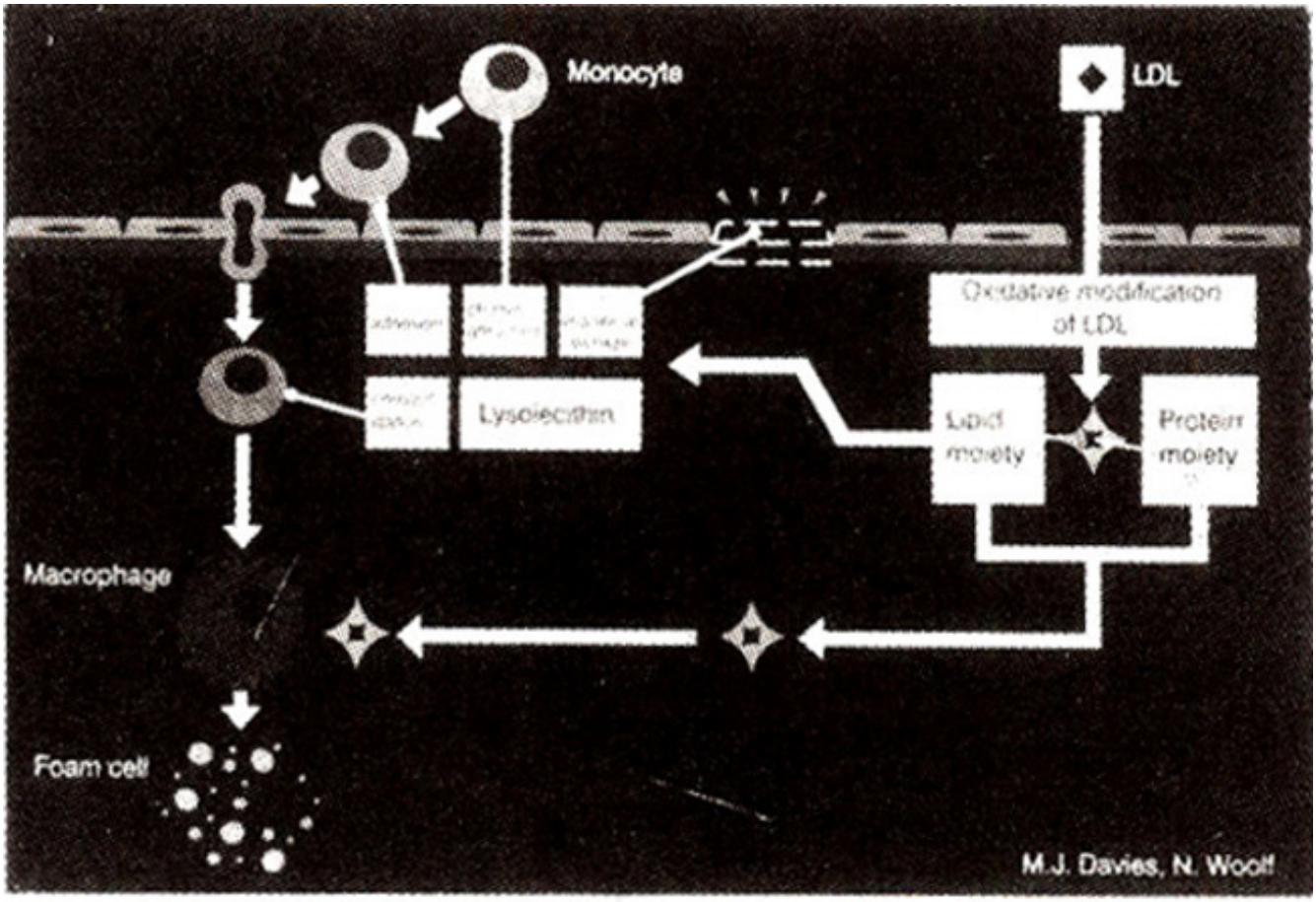

Figure 2. A diagram showing the events surrounding the modification of LDL and its interaction with macrophage to form foam cells.

A number of coronary artery fatty streaks regress However, in the majority it is the precursor lesion that becomes convened into the advanced occlusive torm of AS. It is noteworthy that foam cells, pathognomonic of early lesion development but not limited to earlr lesions are largely of monocyte-macrophage lineage. Intimal monocyte-macrophage express a membrane receptor called the scavenger receptor which recognizes epitopes of oxidatively modified LDL (Ox-LDL) and other lipoprotein. Scavenger receptors do not down regulate in rdsponse to increasing lipid incorporation into macrophage; if Ox-LDL is abundant, uptake continues until macrophage become foam cells.

Fibro-fatty plaque:

The advanced form of AS is called a fibro fatty plaque. These lesions primarily consist of a large number of intimal SMC, together with numerous macrophage and T-lymphocytes. The predominant lipids in the macrophage or SMC are in the form of cholesterol and cholesteryl esters. The proliferated SMC are surrounded by collagen, elastic fibers and large amounts of proteoglycan. Usually in the third decade of life, some of these lesion either become predominantly ‘fibromuscular’, whereas other become \'fibrolipid\' surrounded by a cap of SMC and collagen, over single or multiple lipid cores.

Plaque progression

The progression of atherosclerotic lesion to clinically manifest enlarging plaque such as those causing exertional angina unstable angina and acute myocardial infarction are often more rapid in individuals with multiple risk factors. Recent evidence indicates that plaque progression follows recurrent minor fissures of the most fatty or atheromatous plaque with subsequent thrombus formation and fibrotic organization[4].

-Table II. Processes contributing to atherosclerosis lesion progression

- Lipoprotein oxidation: generation of cytotoxic components including aldehydes
- Foam cell necrosis; formation of an extracellular necrotic lipid core
- Smooth muscle cell migration and a phenotypic shift from a resting 'contractile' to a proliferating 'synthetic' type
- Fibrillar (collagen) and non-fibrillar connective tissue synthesis
- Plaque ulceration with intraluminal mural thrombus formation and subsequent incorporation.

A list of processes are given in Table II which putatively contribute to fatty streak lesion transition and progression. Asides from these processes, a number of growth factors and mitogen have been identified which positively and negatively regulate arterial cell function and are listed in Table III.

Table III. Biological growth factors and mitogen involved in arterial cell function.

Promoters
- Transforming growth factorb (TG F-b)
- Platelet derived growth factor (PDGF)
- Fibroblast growth factor a-b (FGF)
- Smooth muscle cell growth factor (SMCGF)
- Endothelial cell growth factor (ECGF)
- IL-I, IL-6
- LDL-C
- Epinephrine, angiotensin II, endothelin, serotonin, neuropeptides
- Thrombin
- Leukotrienes B4, C4 and D4
- Prostaglandin
Inhibitors
- TGF–β
- Heparin and heparin like factors
- Endothelium derived relaxing factor (EDRF)
- α -Interferon
- Prostaglandin e.g., prostacyclin

Role of Plaque Disruption/Ulceration and Occlusive Thrombus Fonnation in Acute Coronary Syndromes

Atherosclerotic plaque may predominantly be a lipid rich or a fibrous lesion and again these can either be concentric or more usually eccentric lesion. Plaque rupture or fissuring which initiates thrombogenesis plays a fundamental role in the pathogenesis of unstable angina, acute MI and sudden cardiac death. Occlusive thrombosis in coronary arteries is present in over 95% of transmural Q wave MI\'s. Interestingly recent evidence from angiography shows that occlusive thrombi do not necessarily occur with the most severe coronary stenosis (e.g., 80-90% stenosis), they more commonly result from small or intermediate (40-60% stenosis) lipid rich plaques. In addition it appears that the ongoing thrombotic process once initiated may be dynamic and repetitive. Thus in some patients with unstable angina, plaque disruption may lead to intermittent or transient vessel occlusion and ischethia by a labile thrombus. In others, more severe vascular damage in the form of a large ulcer may lead to the formation of a fixed thrombus and a more stable occlusion resulting in acute MI. However, even these thrombotic occlusion may resolve with thrombolytic therapy as well as spontaneously. Within hours or days they can recur, both pathologically and clinically. Plaque rupture or fissuring which initiates thrombosis usually occurs at plaque shoulders, next to sites where macrophage/foam cell density is greatest and the collagenous cap thinnest (Figure 3).

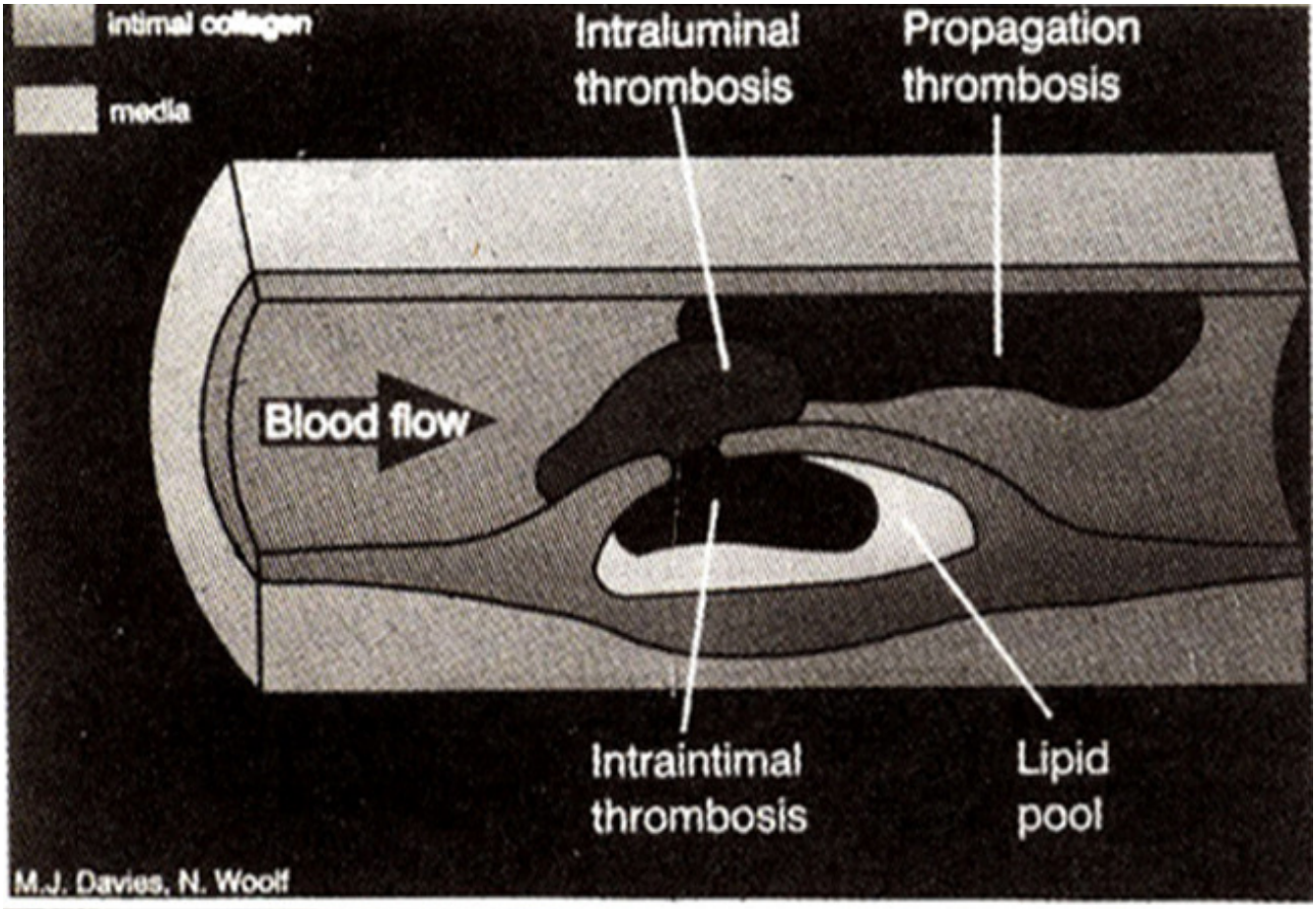

Figure 3. Plaque fissuring at the shoulders of a lipid rich pool intima. This massive thrombus has both an intraintimal and an intraluminal component. Notice the extension and propagation of the thrombu to totally occlude the artery.

This intriguing anatomical association may reflect participation of macrophage derived proteolytic enzymes (collagenases) in the events leading to plaque fissuring. Superficial plaque disruption leads to formation of a thrombus that is labile and could be partially dislodged by the laminar flow of blood.

Risk Factors for Thrombosis

However, exposure of blood to fibrillar collagen,. as in deep plaque rupture leads to a dense platelet thrombus that is fixed and not dislodgable A number of local and systemic factors have now been recognized which suggest that an antecedent hypercoagulable or thrombogenic state of the circulation can favour focal thrombosis. Thus, platelet aggregation and the generation of thrombin may be activated by circulating catecholamines. This mechanism and catecholamine-dependent vasoconstriction may be of major importance in humans because they may link emotional stress, circadian variation, catecholamine effects and the development of arterial thrombosis and vasoconstriction. Other risk factors identified include cigarette smoking, cholesterol levels, Lp (a), fibrinogen, plasminogen-activator inhibitor type 1 (PA 1-1), etc.

Injury Response of Artery following Angioplasty

Animal models and human pathologic material have provided information on the cell type, growth factors, cytokines and genetic regulatory- changes involved in the process of repair following aggressive controlled barotrauma injury to the vessel wall. PTCA causes endothelial cell denudation and stretch injury to the surrounding vessel wall media. Rupture of the internal elastic lamina is common. Activated platelet adhere to the damaged vessel wall with subsequent secretion of growth factors enabling further thrombus formation. An inflammatory response ensues, with monocytes

infiltrating the lesion. Cell injury and mitogens appear to activate previously quiescent proto-oncogenes, including proliferation of SMC and elaboration of extracellular matrix. Proliferation of SMC is associated with a phenotypic shift from a contractile to a synthetic type. Recently Steele et al. [9] have described three phases of repair following percutaneous angioplasty. Phase I is the deposition of platelet thrombi, occurring in minutes and is complete within 24 hours. Subsequently SMC's are activated and they begin to proliferate and undergo hypertrophy as indicated by an increase in DNA synthesis. Phase 2 begins on the 4th day and is marked by the migration of SMC's from the media into the intima. This process continues until day 14. Phase 3 of repair is somewhere between days 14 to 3 months and is marked by continued intimal thickening. Proliferation and hypertrophy of SMC continue, however, now with elaboration of abundant extracellular matrix. The matrix contributes, not only td the fibrotic organization of the thrombi, but also to be composition of the growing atherosclerotic plaque. Induction of collagen genes appear to peak 7 days following arterial injury.

Conclusion

In conclusion; therapy for coronary artery plaque progression must target atherosclerosis, thrombosis and other mechanisms associated with cardiac mortality and morbidity. Emerging understanding of the mechanisms underlying atherogenesis has pointed to several therapeutic targets other than LDL-cholesterol levels. Regression of atherosclerotic plaque which is now a reality (as observed in multiple experimental and angiographic human studies) should include, retardation of the key events in lesion initiation; enhance plaque stabilization; retard key events in lesion transition and progression and enhance removal of plaque constituents, i.e., lipids,fibrin and collagen.

References

1. Ross, R. The pathogenesis of atherosclerosis - an update. N.Engl.J.Med., 1986;314:488-500.
2. Haust, M.D. Injury and repair in the pathogenesis of atherosclerotic lesions. Atherosclerosis; proceedings of second international symposium. Springer, New York, Heidelberg, 1970; pp. 12-20.
3. Richardson, PD., Davies, M.J. and Born, G.V.R. Influence of plaque configuration and stress distribution or fissuring of coronary atherosclerotic plaques. Lancet, 1989;2:941-44.
4. Fuster, V., Badimon, L., Badimon, J.J., et at. The pathogenesis of coronary artery disease and the acute coronary syndromes. N.Engl.J.Med., 1992;326:242-50.
5. Ip, J.H., Fuster, V., Badimon,L., et al. Syndromes of accelerated atherosclerosis: role ofvascularinjury and smooth muscle cell proliferation.J.Am.Coll.Cardiol., 1990;15:1667-87.
6. Stary, H.C. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis. 1989;9(suppl):1-32.
7. Schwartz! C.J. and Valente, A.J. The pathogenesis of atherosclerosis; an overview. Clin.Cardiol., 1991 ;41:11-16.
8. Grigrani, 0., Soffiantino, F. and Zucchella, M. Platelet activation by emotional stress in patients with coronary artery disease. Circulation, 1991 ;83(suppl):Il-128.
9. Steele, P.M., Chesebro, J.H., Standon, A.W., et al. Balloon angioplasty; natural history of the pathophysiological response to injury in a pig model. Circl.Res., 1985;57:105-12.