ATHEROTHROMBOSIS – ALL CLOGGED UP, MAKING SENSE OF IT

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To understand atherothrombosis, we need to revisit its definition. Atherothrombosis is the process of thrombus formation on an atherosclerotic plaque. The clinical expression of atherothrombosis in vascular disease can be acute coronary syndromes (myocardial infarction and unstable angina), transient ischaemic attack and stroke or peripheral artery disease. Thrombosis in vessels is also a common problem in various cancers and after major surgery where there is prolonged immobilization after the procedure.

Pathogenesis

Atherothrombosis is a progressive disease characterized by the accumulation of lipids, fibrous materials and minerals in to the arterial wall leading to narrowing of the arterial lumen. 150 years ago in 1845, Virchow described the process of atherogenesis based on three prerequisites: (1) abnormal blood flow, (2) vessel wall abnormalities, and (3) blood constituent abnormalities. Know as the Virchow triad, this concept has evolved today with modern technology and knowledge of endothelial function, flow characteristics, blood constituents, haematological factors, clotting factors, and platelet physiology.

Atherosclerosis plaque formation is no longer thought of as a passive clogging of the vessels as the vessel walls thickened. It is in fact an active biological entity brought on by inflammatory process that occurs in the wall of the vessels filled with lipids. The plaque contains intrinsic vascular wall cells (endothelial and smooth muscle wall cells), and inflammatory leucocytes (monocytes/macrophages and T-lymphocytes). The interactions among these cells are critical in atherogenesis. This process of atherogenesis develops over many years even decades. Early lesion formation may even occur in adolescence.

The process of inflammation participates in all phases of atherothrombotic disease of lesion initiation, lesion progression, and thrombotic complication. The process of atherogenesis starts with leucocytes migration into the intrinsic layer of the vessel. The accumulation of leucocytes and subsequent death lead to a lipid core covered by a fibrous cap (atheroma). Once the atheroma is well established, it crosses the threshold to clinical manifestations such as unstable angina and acute myocardial infarction. Thrombotic complication of the atheroma in the cerebrovascular or peripheral arteries results in transient ischaemic attack or stroke and critical limb ischaemia respectively.

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Thrombosis of the atheroma results from weakening of the fibrous caps and the enhanced thrombogenecity of the lipid core. The weakening of the fibrous caps and the subsequent plaque disruption is thought to be caused by the ability of the inflammatory cells in the intima in inhibiting the production of collagen by the smooth muscle cells and the release of proteolytic enzymes capable of degrading collagen and other structurally important constituents of the fibrous cap[1,2].

Diagnostic tools

Identification of vulnerable atherosclerotic plaque and measurement of the extent of atherosclerosis are subjects of ongoing studies and experimentation. The tools available range from invasive angiographic techniques to non-invasive techniques such as ultrasonography, magnetic imaging techniques and analysis of coronary calcium.

Atherosclerosis is a systemic disease affecting not only the heart but also brain and peripheral vessels. Epidemiological studies show that peripheral arterial disease (PAD) is a marker for systemic vascular disease. PAD can be diagnosed accurately, quickly, and non-invasively in most patients in the office setting through Ankle – Brachial Index (ABI). The ABI has emerged as one of the most useful early warning markers of diffuse atherosclerosis. This is a simple technique that is easy to perform using a handheld Doppler and Sphynomonometer.

As we understand more about the biology of atherothrombosis, we need to move beyond standard cholesterol screening if we are to appreciate the promise of preventive early intervention therapies. While hyperlipidemia, hypertension, and diabetes, as well as the behavioral risk factors of smoking and diet, remain major critical modifiable risk factors for vascular disease, we have learnt over the years that many haemostatic and thrombotic markers such as lipoprotein (a), D-dimer, and homocysteine, inflammatory markers such as C-reactive protein (CRP), fibrinogen, and interleukin-6, and genetic markers are all part of the evolving understanding of cardiovascular risk.

Antithrombotic therapy

At the present moment the therapeutic approaches available are often unable to prevent short and longer term progression of disease and ischaemia. This is because the agents available are not potent enough to block thrombus formation.

The agents presently available[3] are:

1. Antiplatelet agents; (a) aspirin, (b) dipyridamole, (c) ticopidine and clopidogrel, and (d) glycoprotein IIb/IIIa

receptor inhibitors e.g., abciximab (intravenous)
2. Anticoagulant drugs: (a) warfarin, and (b) heparin
3. Thrombolytic agents: (a) Streptokinase, and (b) Tissue plasminogen activator.

Unfortunately, the agents are not potent enough and are unable to block all the factors contributing to the process of atherothrombosis. Some cannot be administered for extended period of time without risk of causing bleeding.

Other strategies

Behavioral modification and therapeutic lifestyle changes still remain important actions to take to prevent atherosclerosis (diet, exercise, weight control, stop smoking and control of hypertension and diabetes). For those individuals who are symptomatic of heart, brain and peripheral artery atherothrombosis, specific aggressive intervention will be needed.

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