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Commentary: On the Pathophysiology of Coronary Heart Disease

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Abstract

This article highlights some important aspects of the pathophysiology of coronary artery disease, namely:

- The distribution of lesions within the arterial tree at sites of low wall shear stress.
- The potential role of low flow-mediated arterial dilatation at sites of low wall stress.
- Low flow-mediated dilatation leads to low nitric oxide production by the arterial endothelium and consequent reduced protection against lesion formation.
- Flow-mediated dilatation is reduced by high lumenal glucose concentration.
- The role of the glycocalyx dysfunction in mediating flow-mediated dilatation and consequent reduced NO production by the arterial endothelium and cell adhesion.
- Stenoses cause convective acceleration of blood velocity and a consequent increase in platelet shear stress.
- Increased platelet shear stress activates platelets with release of serotonin.
- Serotonin activates more platelet activation *via* the $5HT_{2A}$ platelet receptor causing a positive feedback and thrombus growth.
- Arterial thrombus growth is abolished by $5HT_{2A}$ receptor antagonists, the key to improved treatment of the disease.
- One $5HT_{2A}$ receptor antagonist has been shown in humans to be safe and to cause no excess bleeding from wounds.

Keywords: Wall shear stress; Glycocalyx; Nitric oxide; Convective acceleration; Platelet shear stress; Serotonin

Pathology of Coronary Artery Atheromatous Lesions

This subject requires only brief mention as a reminder before examining the resulting pathophysiology. Post-mortem and surgical observation of coronary artery disease have shown characteristic lesions within the arterial walls which have been called "atheroma"; "atherosclerosis"; or "atherothrombosis". The accumulation of degenerative material in the inner layers of artery walls, that increases with age, are mostly described as containing macrophages, lipids, calcium and fibrous connective tissue. There is a list of conflicting theories as to causation, e.g., tissue damage starts off the process, infection similar to that which causes stomach ulcers is causative, or there is an immunological cause. The conventional hypothesis in the 1990's proposed that the atheromatous plaque is a response to vessel injury initiated by leucocytes and involves infiltration of the vessel wall by lipid laden macrophages. However, because the proponents of this theory were studying animals with high lipid (cholesterol) blood levels, the role of lipid involvement at the start of lesion development understandably dominated their thinking.

Macrophages in atheromatous lesions indicate the presence of inflammation, progression of which would lead to fibrosis and calcification. The presence of lipids led to the idea that lipid abnormalities are responsible for the start of this pathological process, implying that toxic lipids in the blood are sucked up by the arterial wall. The presence in younger cadavers of "fatty streaks", irregular yellow-white discolorations on the luminal surface of an artery led the "fat causes atheroma" theorists to think that it is these fatty streaks that develop into atheroma lesions. Unfortunately for the theory, the distribution within the arterial tree of the atheromatous lesions is different from the distribution of fatty streaks; they have the wrong "geography".

The importance of flow mediated arterial dilatation (FMD)

The distribution of atheromatous lesions within the arterial tree is of potential importance in trying to explain the pathophysiology. The lesions occur mainly at places in the arterial tree where there is low shear stress [1]. Caro et al. [1] showed that atheromatous lesions were distributed preferentially within the arterial tree to these sites of low shear stress. Caro thought it was related to increased lipid uptake into the arterial wall where shear stress was low. The velocity of blood flow is lower, e.g., on the inside of a bend or branch, so that there is less force exerted by the blood flow upon the inside of the artery wall. The layer of cells in contact with the blood is the endothelium, which is highly metabolically active and controls the underlying smooth muscle.

The low shear stress site distribution of mature lesions was combined with the lipid theory by finding that there was more lipid uptake at low shear stress sites [1]. However, one might well interpret the findings in a different manner. There is another layer between the endothelial cells and the blood within the artery lumen, a layer of gel

called the glycocalyx [2], a gel based on glycoproteins. An important function of the glycocalyx-endothelium combination is what is popularly known as "Flow mediated dilatation" [3], but should really be called "Shear stress mediated dilatation". When more blood flow is demanded by the organ supplied by the artery, the increased blood flow causes the artery to widen, by relaxation of the smooth muscle in the arterial wall, in order to accommodate more blood.

This function depends on the endothelial cells producing nitric oxide (NO) [4], which relax the smooth muscle of the arterial wall, and thus increase the lumen diameter [5]. The NO is rapidly removed by haemoglobin, as its accumulation would be toxic. It is generally recognised that NO opposes the atheromatous process. Thus, it is possible that the areas of low shear stress develop more disease because there is less NO production. Exercise may retard the progress of the disease with ageing by causing greater NO production by arterial endothelium.

From this theory, one would predict that circumstances that inhibit this process would be associated with a more rapid development of atheromatous disease with ageing. One such factor is the concentration of glucose in the blood within the artery. Kelly et al. [6] showed that after soaking the inside of the artery with blood with a high concentration of glucose, flow mediated dilatation was much reduced, or even abolished. High glucose concentration is a characteristic feature of diabetes mellitus and patients with this disease have a more rapid development of atherothrombosis. The hypothesis is that increased glycosylation of the glycoproteins in the glycocalyx impairs the mechanical properties of the gel acting as a transducer transmitting the signal to the endothelial cells. Noble et al. [7] postulated that arterial glycocalyx dysfunction is the first step in the atherothrombotic process. Consistent with this theory, flow-mediated dilatation is impaired is impaired in patients with coronary disease [8]. There is thinning of the glycocalyx in diabetes [2] and heterozygous familial hypercholesterolemia [9], both diseases characterised by proneness to coronary disease. Constantinescu et al. [10] demonstrated thinning of the glycocalyx by oxidised LDL.

Progression of the lesions

Further experiments with high blood glucose concentrations, this time prolonged, have shown a thinning of the glycocalyx, the gel layer between the arterial endothelium and the blood. It has also been shown that areas of glycocalyx denudation lead to adhesion of blood cells such as platelets and leucocytes. Thus there is the possibility that not only high levels of some lipoproteins, but also high glucose levels are an important trigger for the process.

Cell adhesion may be the part of the process in which tissue damage plays a role in lesion progression rather than in the initiation of the process. Such adhesion of cells to endothelium bare of a full thickness protective glycocalyx would be expected to set up inflammation, the damage which is observed by pathologists. The tissue damage hypothesis for the initiation of the process does not indicate what caused the tissue damage in the first place, but as a part of the progression of the lesions, it makes much more sense. The emphasis on the role of lipids has led to the general assumption that all lesions are full of lipid. The conventionally envisaged "plaque" has a crescent of obstruction of the lumen on one side of the artery.

Causative factors in patients

In the 1990's, before I retired, we looked at all the coronary angiograms of the patients admitted with an acute coronary syndrome (ACS) in a busy hospital clinical practice with a coronary care unit that I supervised, and found that only half were sort-of eccentric. The other half were concentric. In a cross-section of a concentric lesion, one sees a small central lumen in the stenosis surrounded by overlapping layers of non-lipid material. Rokitansky's hypothosis [11] in 1885 stated that these layers constitute the remains of organised thrombi and led me to postulate a much greater influence of thrombosis in the development of the disease than had hitherto been considered so important [12]. The evidence that not all arterial lesions are lipid laden and that a large number of patients admitted with acute coronary syndromes have normal blood cholesterol levels led me to postulate that the progression of atheromatous lesions, at least sometimes, might be largely due to covert thrombosis. In 1980, a study by Meade et al. [13] showed that blood fibrinogen correlated more strongly with coronary deaths than blood cholesterol. Progression of disease, if it involves covert thrombosis, might cause an increase in blood fibrinogen, i.e., the raised fibrinogen may be the result rather than the cause of the progression. An interesting observation is that patients with haemophylia are protected against coronary disease [14].

Unfortunately, in our coronary care practice, we were not able to measure serum fibrinogen, but we were able to sample blood from ACS patients before treatment, which in those days involved, among other things, the administration of a thrombolytic drug in an attempt to remove thrombus from the coronary arteries. With a four year follow up, we were unable to find a correlation between subsequent coronary events and total serum cholesterol, which is still extolled as the most important risk factor. The profession does not seem to have caught up with the fact that there are beneficial lipoproteins of high density (HDL). The factors in non-diabetic patients that subsequent events did correlate with were: infarct size (as assessed by troponin [15], previous ACS, insulin resistance [16], plasma homocysteine rose above normal [17] and raised lipoprotein(a) [18]. Of particular interest was the link between raised homocysteins and pro-thrombosis [19].

The importance of convective acceleration

We were particularly interested in the question, "Why does a coronary stenosis exist for some time and then suddenly become blocked by thrombus to cause an ACS?" The conventional answer was that this was the result of plaque rupture leaking lipid and inflammatory material into the lumen, thus stimulating platelets to initiate the thrombus. Acting upon this idea, anti-platelet drugs blocking the thromboxane and P_2Y_{12} platelet receptors were added to thrombolysis and, later and now, primary angioplasty. However, this explanation did not explain the thrombosis that blocks concentric lesions (approximately half of those admitted).

The factor that is common to all stenoses, whatever their anatomical details, is convective acceleration. When a calmly flowing river enters a gorge, the water speeds up, i.e., convective acceleration [20]. This also occurs in arterial stenoses, and the increased velocity exerts an increase in shear stress upon the platelets which are, consequently, activated. Platelets contain large quantities of serotonin (5-hydroxytryptamine, 5HT) in the dense granules, which are released upon platelet activation. Serotonin, in contrast to the thromboxane, purine or glycoprotein mediators, does not influence the formation of haemostatic layers, although it is implicated in shear-induced

aggregation and thrombus propagation by positive feedback from the large amount of intra-platelet serotonin. It is important to distinguish between the serotonergic receptor subtypes [21]. Serotonin stimulates endothelial $5HT_1$ receptors that respond with endothelium dependent nitric oxide mediated vasodilatation. $5HT_{2A}$ receptors activate platelets and mediate smooth muscle contraction. Thus in arterial lesions in which vascular smooth muscle is bared, vasoconstriction exacerbates arterial occlusion by thrombus; relief of such vasoconstriction by $5HT_{2A}$ antagonists is a bonus. However, surprisingly to date, serotonin antagonism has not progressed to clinical application. Platelets are the richest source of serotonin in the body outside the brain, acquiring serotonin from the plasma by means of the cell membrane serotonin uptake mechanism. Inhibition of this mechanism by serotonin re-uptake inhibitors (SSRIs) causes depletion of platelet serotonin [22].

The importance of platelet serotonin positive feedback

Upon platelet activation (especially with high shear) high concentrations of serotonin in the platelets are released from the dense granules [23], and act upon platelet serotonin $5HT_{2A}$ receptors to activate more platelets, thus constituting a positive feedback mechanism leading to thrombus growth [24]. The serotonin theory [25] supposes that this serotonin mediation is essential for thrombotic occlusion of diseased coronary arteries, owing to the fact that such occlusions are abolished by antagonism of the platelet $5HT_{2A}$ receptor [26,27], even when the major stimulus of adrenaline is applied [28] and also in the circumstances where thrombolysis has failed to clear a complete thrombotic occlusion [29].

Examination of patients undergoing angiography has showed that a high plasma serotonin level was significantly associated with coronary artery disease in patients younger than 70. In nearly four years of follow up, high serotonin levels were also associated with cardiac events. This association persisted after adjustment for conventional risk factors [30].

Conclusion

As convective acceleration is common to all arterial stenosis and results in serotonin dependent thrombus growth, the logical treatment for coronary disease is serotonin antagonism. This is reinforced by the fact that all present anti-thrombotic drugs used in this disease cause increased bleeding. There is unpublished data showing that, in humans, the $5HT_{2A}$ antagonist used in the study of McAuliffe [28] had no effect on haemostasis, which is consistent with the serotonin theory of Noble and Drake-Holland [25]. This drug, at least, could provide protection from thrombosis during surgical operations without affecting operative bleeding.

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