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Commentary

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Initiation of Arterial Stenotic Thrombosis

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Introduction

Current practice in arterial disease is to establish the site of stenosis, to dilate the stenosis with angioplasty or surgical bypass, and to try to maintain the integrity of the arterial lumen with stents. There are either bare stents or drug eluting stents which are more thrombogenic requiring long term dual antiplatelet therapy with its risk of increased bleeding. For coronary disease, this is called Percutaneous Coronary Intervention (PCI). A recent study showed that heart stents for stable angina show no benefit over placebo [1,2]. It has also been shown that 12% of PCI patients are readmitted within 30 days [3]. A study of 60 day re-admission after PCI showed that among 1193 enrolled patients, 71 (6.0%) underwent unplanned 60-day re-admission for unstable angina (35.3%), chest pain (21.1%), heart failure (14.1%), and acute Myocardial infarction (11.3%); 40.8% patients underwent repeated PCI. Drug eluting stents are associated with lower rates of restenosis but may be associated with later in-stent thrombosis, and/or bleeding at vascular access sites, intracranially, and in the upper gastrointestinal tract [4]. This is all very unsatisfactory. Have we have taken a wrong pathway in the treatment of arterial disease?

Arterial Stenosis cause damaging increases in Shear Stress

At an arterial narrowing (stenosis), the relationship between the pressure drop and the flow is both proportional and quadratic due to turbulence. A quantitative expression of a stenosis is the area ratio As/Ao , where As is the cross-sectional area of the stenosis and Ao is the cross-sectional area of the open, normal artery; this can be expressed as a percentage as $(1 - As/Ao) \times 100$. As the same flow has to go through both the normal section, Ao and the much smaller As of the stenosis, the blood has to go faster, i.e., velocity of blood flow increases; this is called convective acceleration. Think of watching a placid full river running into a gorge. So we envisage a mass of fluid accelerating into a narrowing of the artery exerting greater force, and just as objects in a river gorge feel force, so do blood cells in a stenosis. This effect is called shear stress. Shear stress applied to blood platelets activates them, initiating thrombus growth in such sites even in the absence of plaque rupture. This explains why coronary thrombosis occurs in stenosis in contrast to the lack of thrombosis in sites of endothelial damage but no narrowing.

Shear stress at the normal arterial wall may be beneficial

An increase in flow through an artery, due to an increase in downstream demand, causes the artery to dilate. This is commonly known as Flow Mediated Dilatation (FMD) [5] and is commonly used to assess arterial endothelial function. It has been suggested that this effect of increased shear stress at the arterial wall is beneficial because the dilatation is mediated by nitric oxide [6], which is thought to be an anti atherothrombosis factor by Louis Ignarro (see his You-tube presentation), giving a scientific basis for the supposed beneficial effect of exercise [7].

What happens in a stenosis?

No-one seems to have queried the mechanism of predilection of arterial thrombosis to occur in stenosis. Here the analogy of the river gorge does not hold. Whereas objects in the gorge are swept downstream, in an arterial stenosis there occurs a platelet rich thrombus growth. When developing an experimental model of coronary arterial thrombosis, we all experienced the fact that endothelial damage alone does not produce thrombosis. One has to apply a stenosis to set off thrombus growth [8-12]. Why has this fact been ignored? Why is current drug therapy based on the results of platelet aggregation only in response to endothelial damage? Is it not likely that there is something about the presence of arterial narrowing and the hemodynamics of stenosis that is the correct target for therapy? Platelets within a stenosis are subjected to force and turbulence and these factors activate them. The response of platelet activation is release of serotonin which is packed into their dense granules. Reduction of secretion of these dense granules is associated with marked protection from the development of arterial thrombosis, inflammation and neointimal hyperplasia after vascular injury [13]. The reason for this is that platelets are also activated by serotonin through the 5HT_{2A} receptor, so that serotonin released by stenosis shear stress activates more platelets which release more serotonin, setting up the well-known serotonin (in addition to other feedback mediators) positive feedback cycle [14]. The importance of serotonin in this platelet feedback process is its abolition by 5HT_{2A} receptors, for which at least 20 references are available [11,12].

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Imaging of arterial stenosis

Modern imaging of internal organs using magnetic resonance, yields images with much greater detail of the structure of stenosis, including complex ones at artery bifurcations together with the accompanying blood velocity patterns [15-17]. This is combined with computational fluid dynamic measurements and multi-scale modeling [18-20] with which one perceives the exciting possibility that the force applied to each platelet might be calculated. Leading to a prediction of which platelets are likely to be activated by the shear stress and release serotonin to trigger thrombus growth. Already, these techniques have been useful when applied to the study of atheromatous lesion growth and post stenting disease. Nevertheless, in practical cardiology today, it is predicted that the altered hemodynamics of stenosis, which have a variety of patho-anatomical features and abnormal blood flow patterns, all activate platelets if the increase in shear stress and turbulence are sufficiently great.

Can arterial stenosis-induced arterial thrombosis be treated specifically?

Since stenosis thrombus growth is serotonin dependent, that treatment of arterial disease with 5HT_{2A} receptor antagonists is urgently required. The additional benefit of this approach is that, there being no serotonin in wounds, the prediction is that there will be no bleeding complications, as occurs with dual antiplatelet therapy [4]. There is at least one of these drugs that has shown no change in bleeding time in patients [12,21,22].

The proposed treatment for the future is that patients with symptoms suggestive of arterial disease be prescribed a 5HT_{2A} antagonist. If the symptoms are acute, i. e. , possible acute coronary syndrome, stroke, leg ischemia, the drug should be given intravenously. If not acute, the patient would be given a course of oral 5HT_{2A} antagonist. While the patient is thus protected, the patient undergoes investigation, e. g. , angiography, MRI imaging [15-17], exploratory surgery, which will induce only normal operative bleeding. Any stenosis that is shown, resting, or upon stress testing, may then undergo an appropriate procedure to remove stenosis. Post intervention treatment will be chronic administration of a 5HT_{2A} antagonist with no fear of excessive bleeding, only normal bleeding.

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