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Editorial

Has Neglect of Haemodynamics led to the Wrong Pathway for Treatment of Arterial disease?

Mark I.M. Noble*

University of Aberdeen, Foresterhill, Aberdeen AB25 2ZH, UK

***Address for Correspondence:** Mark I.M. Noble, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZH, UK, Tel: +016-748-40142; E-mail: mimnoble@abdn.ac.uk

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INTRODUCTION

The established treatment for arterial disease, such as coronary disease, is to establish the site of stenosis, to dilate the stenosis with angioplasty or surgery bypass, and to try to maintain the integrity of the arterial lumen with stents, mostly nowadays drug eluting stents, e.g., Percutaneous Coronary Intervention (PCI). The consequence is that a thrombogenic site remains, that has to be counteracted with dual anti-platelet therapy that carries bleeding complications with it. A recent a 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 re-admitted 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 [4]. Drug eluting stents are associated with lower rates of restenosis but may be associated with later vascular complications, such as in-stent thrombosis, bleeding at vascular access sites, intracranially, and in the upper gastrointestinal tract [5]. This is all very unsatisfactory, so we should question whether we have taken a wrong pathway in the treatment of arterial disease. Perhaps we should take a look at old fasioned harmodynamics [6] to find a clue to a better pathway to tread?

ARTERIAL STENOSIS

At an arterial narrowing (stenosis),

$$\partial P = a1Q + a2Q2$$

Where ∂P is the pressure drop across the stenosis, Q is the flow through the artery, a1 and a2 are proportionality parameters. This means that the relationship between the variables ∂P and Q is quadratic and stenotic resistance increases with flow. a1Q expresses viscous resistance, while a2Q2 expresses turbulence. Another 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 are of the open, normal artery; this can be expressed as a percentage as (1 - As/Ao)x100. 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. One can easily observe this phenomenon by watching a placid full river running into a gorge.

Acceleration is determined by force according to Newton's second law of motion,

$$F = ma$$

Where, F is force, m is mass and a is acceleration. 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, equal to the force divided by the area of the surface of the object.

Arterial Wall Stress

The effect of changes in wall stress on the arterial endothelium/glycocalyx complex has been described and discussed in a number of publications. In short, 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) [7] 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 [8], which is thought to be an anti-atherothrombosis factor by Louis Ignore (see his You-tube presentation), giving a scientific basis for the supposed beneficial effect of exercise [9].

Cells in Blood being Forced through a Stenosis

It is strange that 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 [10-14]. 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 Haemodynamics of stenosis that is the correct target for therapy. It follows from the discussion of arterial stenosis above, that platelets within a stenosis are subjected to force and turbulence and that 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 [15]. The reason for this is that platelets are also activated by serotonin through the 5HT2A receptor, so that serotonin released by stenosis haemodynamics activates more platelets which release more serotonin, setting up the well-known serotonin (in addition to other feedback mediators) positive feedback cycle [16]. The importance of serotonin in this platelet feedback process is its abolition by 5HT2A receptors, for which at least 20 references are available, although in this context two may be enough! [13,14].

Detailed Imaging of Arterial Stenosis

With the modern imaging of internal organs using magnetic resonance, one can obtain much greeted detail of the structure of stenosis, including complex ones at artery bifurcations together with the accompanying blood velocity patterns [17-19]. When this is combined with computational fluid dynamic measurements and multi-scale modelling [20-22] 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 haemodynamics of stenosis, which have a variety of patho-antomical features and abnormal blood flow patterns all activate platelets if the increase in shear stress and turbulence are sufficiently great.

Treatment of Arterial Stenosis-Induced Arterial Thrombosis based on Stenosis Haemodynamics

It follows immediately from the fact that stenosis thrombus growth is serotonin dependent, that treatment of arterial disease with 5HT2A 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 [17], as with dual antiplatelet therapy [5]. There is at least one of these drugs that has shown no change in bleeding time in patients [14,18].

Thus, the proposed treatment for the future is that patients with symptoms suggestive of arterial disease be prescribed a 5HT2A antagonist. If the symptoms are acute. i.e., possible acute coronary syndrome, stroke, leg Ischaemia, the drug should be given intravenously. If not acute, the patient would be given a course of oral 5HT2A antagonist. While the patient is thus protected, the patient undergoes investigation, e.g., angiography, MRI imaging [17-19], 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 5HT2A antagonist with no fear of excessive bleeding, only normal bleeding.

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