Protection of the Vascular Wall

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Abstract
If one accepts that arterial glycocalyx dysfunction is the first step in the atherothrombotic process, screening of asymptomatic subjects could detect this change. Measurement of the arterial dilatation in response to increased arterial flow (FMD) is widely used in research and would seem to be a possible general non-invasive screening test in humans. Once there has been a break-down of this first line of protection, the second step in the atherothrombotic process might be effectively detected by measurement of blood platelet-platelet and platelet-leukocyte aggregates. While there is no clear treatment to counteract the first step other than exercise programmes, there is evidence to suggest that effective treatment of the second step could be achieved using 5HT2A antagonism.

Keywords: Vascular Wall; Arterial glycocalyx dysfunction; Atherothrombotic process

Abbreviations: EGL: Endothelial Glycocalyx; FMD: Flow Mediated Dilatation; Ach: Acetylcholine

Introduction
Primary prevention for vascular disease has, for some time now, been based on the administration of statins to people with high cholesterol levels or high-risk scores, e.g., NICE recommends wider use of statins for prevention of CVD [1]. However, this seems illogical in subjects free of vascular disease as these compounds have serious side effects, e.g., depression, myopathy and rhabdomyolysis. Should one be making normal people ill [2]? The policy is based on the theory that all vascular disease is caused by hyperlipidaemia, but other theories suggest more potent theories of causation, e.g., insulin resistance. There follows a commentary on the factors that are involved in disease of the arterial wall which might be more appropriate targets for preventative therapy.

Endothelial glycocalyx dysfunction
The smooth muscular structure of the vessel wall is separated from substances in the blood by two intimal layers - the endothelium and the Endothelial Glycocalyx (EGL). The theory that arterial glycocalyx dysfunction is the first step in the atherothrombotic process [3] has been found to be reasonable as summarised in 2018 [4]. For this to be compatible with the dogma that total cholesterol concentration is the cause of atherothrombosis, a search was made for the effect of this upon glycocalyx integrity. One such study suggests degradation of the endothelial surface layer by oxidised low density lipoprotein (Ox-LDL) as reflected in elevated capillary tube haematocrit [5,6]. A model of an arterial segment was developed to numerically simulate the flow and the transport of LDLs under normal and high pressure [7]; the transport parameters of the layers of the model were obtained from the hydrodynamic theory, the stochastic theory, and from the literature. The results showed that the increase in the thickness of the EGL could lead to a sharp drop in LDL accumulation in the intima. Aspects of these studies are (1) compatibility with the idea that LDL and not HDL may be involved in the genesis of atherothrombosis (2) patients should not be treated if the HDL is high, as only LDL is implicated in attacks on arterial protection. Further, there is no evidence that statins prevent glycocalyx dysfunction. Possibly rosuvastatin in heterozygous familial hypercholesterolemia [8] and sulodexide in patients with type 2 diabetes [9] may be effective in this regard. Administration of superoxide dismutase and catalase completely blocked the effect of Ox-LDL [5].

Development of a test of endothelial function
For primary prevention it would seem preferable to test endothelial-glycocalyx function than assess risk by conventional scores based on total serum cholesterol. Obvious risks such as smoking diabetes and hypertension are obvious risks that should be dealt with by stopping smoking, controlling blood glucose concentration and administration of anti-hypertensive drugs. The damaging effect of high lumenal glucose concentration was discovered by Kelly et al [10] whose experiments were carried out in the anaesthetized pig in which pressure, blood flow and diameter of the left iliac artery were measured at two sites. Infusion of glucose attenuated the shear stress-dependent dilatation in both sections of the artery with preservation of the responses to acetylcholine. They concluded from these results that the hyperglycaemia-impaired dilatation is consistent with loss of mechanotransducing properties of the Endothelial Glycocalyx (EGL) by hyperglycaemia and postulated that this was a possible...
The reason for regarding the glycocalyx as the important trigger for shear stress-dependent dilatation is that this response is attenuated when the gel structure of the glycocalyx is destroyed by hyaluronidase [11]. The attenuation of shear stress-dependent dilatation by glucose is presumably due to increased glycosylation of the glycoprotein of the glycocalyx gel. The shear stress-dependent dilatation is commonly called Flow Mediated Dilation (FMD), the mechanism of which has been discussed [12]. Impaired FMD is especially significant if the response to nitric oxide is normal.

Application of FMD to humans

The main method that has been adopted from this is to measure diameter changes of the brachial artery in response to increased flow, i.e., FMD, using ultrasound [13]. An alternative method of assessing endothelial function is to measure the response of flow to the endothelium-dependent vasodilator Acetylcholine (ACh), but this does not detect dysfunction arising from the glycocalyx. Nevertheless, the use of these methods has produced a large literature on conditions in which endothelial dysfunction has been detected. It is no surprise that aging is one such. According to Seals et al. [16], several lifestyle and biological factors modulate vascular endothelial function with aging, including regular aerobic exercise, dietary factors (e.g. processed compared with non-processed foods), body weight/fatness, vitamin D status, menopause/oestrogen deficiency and a number of conventional and non-conventional risk factors for CVD. Given the number of older adults now and in the future, these authors call for more information is on effective strategies for the prevention and treatment of vascular endothelial aging. According to Celemajer et al. [17], loss of endothelium-dependent dilation in the systemic arteries occurs in the preclinical phase of vascular disease and is associated with interaction of the same risk factors known to predispose to atherosclerosis and its complications in later life. Once age, smoking diabetes and hypertension have been excluded, endothelial function testing would seem to be an encouraging way of assessing risk.

The principle idea for maintaining arterial integrity based on the evidence available is to encourage exercise programmes to promote FMD which is mediated by nitric oxide, thought to be an anti-atherosclerotic agent.

The next step in the process of disease when glycocalyx protection has been overcome

Degradation of the endothelial was found to cause adhesion to the endothelium of platelets and leukocytes [18]. This can be interpreted as the second step in the atherothrombotic process. How can one protect the arterial wall from this process? At this stage, there may be no symptoms, but one postulates that the adhered platelets and leukocytes form aggregates on the endothelium, it is possible that they break free and circulate; they can be detected without the need for microscopic analysis of blood smears [19]; samples can be fixed for later analysis [20,21] and could be the best marker of this stage of the process before angiography can detect full atheromatous lesions. Circulating platelet-leukocyte and platelet-platelet aggregates are found in inflammatory bowel disease by authors who claim this increases cardiovascular risk [22]. That risk can be detected by this method in the presence of normal angiography is shown in diabetic patients [23]. Less surprising is the detection of circulating aggregates in myeloproliferative disorders [24], transient cerebral ischemia [25] and full-blown coronary disease [26].

The evidence for a pre-thrombotic condition is compatible with the theory of thrombosis as a unitary hypothesis of cardiovascular risk [27] and in the absence of any evidence that statins inhibit the formation of aggregates, one might think it logical to treat these patients with anti-thrombotic drugs. However, we are discussing a sort of borderline state between asymptomatic people who may be developing an unprotected state of the vessel wall, so that to expose such people to the considerable risk of a worse outcome due to bleeding complications is unwise.

Possible treatment of patient with platelet aggregates indicating the likelihood of platelet-leucocyte adherence to the endothelium

This possibility comes from the work of Menys [28], who showed that aggregate growth in vitro is inhibited by a serotonin 5HT2A receptor antagonist. The reason for this is that aggregate and platelet rich thrombus growth occurs when activated platelets release serotonin from the dense granules, such serotonin activates more platelets via the platelet 5HT2A receptor [29]. The antagonist used by Menys was also shown to inhibit and disperse growing thrombi in the coronary artery [30]. The great advantage of this approach is that the drug used by McAuliffe et al [30] has no effect on bleeding from wounds [31] which do not contain serotonin. If the screening and institution of 5HT2A antagonism could be organised, one might be able to prevent progression to the development of atherothrombotic lesions that would necessitate secondary prevention with statins and dual anti-platelet treatment.

Conclusion

Protection of the arterial wall from initiation and progression of the first manifestations of vascular disease is theoretically possible, but fraught with practical difficulties. It would be a programme that would make primary prevention with statins unnecessary.

*ICI170809, now patented by Thromboserin Ltd with the trade name Artedere.

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