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Haemodynamical stress in mouse aortic arch with atherosclerotic plaques: Preliminary study of plaque progression

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ABSTRACT

Atherosclerotic plaques develop at particular sites in the arterial tree, and this regional localisation depends largely on haemodynamic parameters (such as wall shear stress; WSS) as described in the literature. Plaque rupture can result in heart attack or stroke and hence understanding the development and vulnerability of atherosclerotic plaques is critically important. The purpose of this study is to characterise the haemodynamics of blood flow in the mouse aortic arch using numerical modelling. The geometries are digitalised from synchrotron imaging and realistic pulsatile blood flow is considered under rigid wall assumptions. Two cases are considered; arteries with and without plaque. Mice that are fed under fat diet present plaques in the aortic arch whose size is dependent on the number of weeks under the diet. The plaque distribution in the region is however relatively constant through the different samples. This result underlines the influence of the geometry and consequently of the wall shear stresses for plaque formation with plaques growing in region of relative low shear stresses. A discussion of the flow field in real geometry in the presence and absence of plaques is conducted. The presence of plaques was shown to alter the blood flow and hence WSS distribution, with regions of localised high WSS, mainly on the wall of the brachiocephalic artery where luminal narrowing is most pronounced. In addition, arch plaques are shown to induce recirculation in the blood flow, a phenomenon with potential influence on the progression of the plaques. The oscillatory shear index and the relative residence time have been calculated on the geometry with plaques to show the presence of this recirculation in the arch, an approach that may be useful for future studies on plaque progression.
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1. Introduction

Atherosclerosis is a chronic and progressive inflammatory disease of the arterial wall involving various processes such as lipid deposition and oxidation, leukocyte infiltration, smooth muscle cell migration and extracellular matrix production [1–3]. The lipids form the core of the atherosclerotic plaque, while the smooth muscle cells and extracellular matrix produce an overlying fibrous cap. Rupture of the fibrous cap can induce thrombus formation on the plaque surface and can result in myocardial infarction or stroke. Plaque vulnerability to rupture depends on the fibrous cap thickness [4], in addition to luminal remodelling and blood haemodynamics. Depending on various factors, not yet all well identified, the plaques can remain stable for the whole life of the subject or can become vulnerable [5], leading eventually to a fatal acute syndrome. Therefore, understanding the plaque development processes and the vulnerable phenotype selection mechanisms is crucial.

Atherosclerosis is a complex and multifaceted disease. Aside from the complexity of the biological and biochemical processes involved in plaque development, it has been shown in the literature that plaque evolution is highly related to mechanical effects (see Assemat and Hourigan [6] for a review). Two main types of mechanical factors contributing to plaque development are reported in the literature: the haemodynamical stresses and the tissue (structural) stresses. Their relative contribution to plaque development is not well understood [7] and depends on the plaque age so that these contributions vary with the formation, progression or rupture stages.

Concerning the rupture, Maehara et al. [8] have shown the existence of two classes of rupture sites for vulnerable plaques: 63% of ruptures occur in the shoulder region, where the plaque joins the healthy intima,

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while the remainder (37%) occurs in the centre of the fibrous cap. Two types of vulnerable plaques have been identified in the literature: the rupture-prone and the erosion-prone [5]. For the first type, two theories have emerged from the mechanical point of view. Plaque rupture is due to a chronic fatigue structural damage (structural cyclic load) according to some [9, 10], or is due to an acute structural fracture failure (structural stress greater than the ultimate tensile stress limit [11, 12] or delamination [13]) according to others. Furthermore, besides the pure tissue stress aspect, the presence of microcalcifications [14–16], or intraplaque haemorrhages [17, 18] are thought to induce additional stresses that play a role in the rupture process. For the erosion-prone type, little is known, but in general, eroded plaques are scarcely calcified, rarely associated with expansive remodelling, and only sparsely inflamed [5, 19].

Concerning the formation aspect, it has been shown in the literature that plaques develop at particular sites in the arterial tree [20, 21] and it is widely accepted that this localization is influenced predominantly by the geometry [22, 23] and haemodynamic forces. Those forces are illustrated in the literature mainly by the calculation of haemodynamic parameters such as wall shear stress (WSS) [24, 25], oscillatory shear index (OSI) [20, 26] or relative residence time (RRT) [27, 28]. Whereas some pioneer studies [21] indicated that low WSS for plaque formation was inferior to 0.4 Pa and high WSS preventing the plaque formation superior to 1.5 Pa in human arterial tree, this hypothesis has been intensively discussed and there is currently no general agreement on the optimal haemodynamical factor or set of factors that can be correlated with precision with the plaque distribution in the arterial tree [27, 29]. Generally, plaques are found near bifurcations of large and medium size arteries and high curvature areas [20, 30]. In particular, plaques are mainly found in the carotid bifurcation, in the coronary bed, in the femoral, abdominal and iliac arteries, and in the aorta [31]. In the present paper, the region of interest is the aortic arch, which presents both a high curvature zone and bifurcations.

As plaques develop, they may cause luminal narrowing, leading to a reduction in vessel volume, or undergo expansive remodelling to maintain lumen diameter [2, 24, 32, 33]. This remodelling has been first underlined by Glagov et al. [34] for coronary arteries in which Chatzizisis et al. [2] suggest that low WSS causes intense inflammation, excessive wall and lumen expansion inducing outward plaque formation, and that arterial sections with slightly low WSS induce limited inflammation and lipid accumulation, leading to stenotic shape remodelling. In that study, the authors indicate that the vulnerable plaques are associated with a biomechanical self-feeding cycle causing an excessive expansive remodelling (outward remodelling) whereas stenotic remodelling induces stable plaques. Similar conclusions related to the link between vulnerability and remodelling are presented by Phinikaridou et al. [33] in a study conducted on white rabbit abdominal aortas. However, WSS amplitude does not seem to be the only criterion for plaque stability and mouse cuff models have been developed to study the oscillatory characteristics of the wall shear stress [35]. Cheng et al. [36], in a study involving an ApoE −/− cuff model (right common carotid artery), have suggested that vulnerable plaques are related to areas of lowered WSS (upstream of the cast), whereas stable ones are found in zones of high oscillatory shear stress (downstream of the cast). Their study indicates that the instantaneous dynamics also seems to play a role in the phenotype selection. This instantaneous dynamics can be calculated using numerical methods as described in the present paper.

Finally, the details of the processes of the growth of plaques after their initiation and, in particular, the influence of their presence on the blood flow, remain poorly understood. In their position paper, the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology [5] underlines that “the natural history of vulnerable plaques such as speed of development, lifetime (persistency) and fate is presently mostly unknown.” Few papers give some insight into the question of plaque progression, and limitations are found in these papers. These limitations are mainly related to the number of time points used to define the plaque progression, to the number of samples, to the image resolution or to the excessive simplification of the numerical model or to the diversity of locations in the arterial tree. In the aortic arch region, Harloff et al. [37] have conducted an in vivo study at one time point and revealed a good correlation between cross section planes with critical WSS (defined as WSS below an individual threshold) and plaque positions but limited correlation between critical WSS and plaque angular positions. Hoi et al. [38] and Tomita et al. [39] have, for their part, commented on the importance of the geometry specificities for the location of plaques, in addition to haemodynamical factors. Although it is well known that haemodynamical factors are coupled with the geometrical features, in complex geometry this relation is non-trivial and investigations of the specific geometry could also give a clue to understanding plaque growing processes. The three previously cited articles do not consider the time evolution of plaques, and two of them underline the necessity of developing numerical methods that calculate blood flow in aortic arch with plaques.

To summarize this review introduction, the calculation of wall shear stress seems to have an influence on the formation, on the development and on the rupture of plaques so its knowledge is a first step towards the prediction of acute events. In addition, according to the literature, the phenotype of the plaques seems to be dependent on haemodynamical stresses, so that it is important to develop methods to calculate their distribution in realistic geometries in the presence of plaques. To the authors' knowledge, except for the related work published by our team [40], no numerical study has been yet conducted for this purpose in aortic arches with plaques, a restriction perhaps due to the challenge of generating high resolution 3D geometries with plaques (small size of plaques compare to the resolution). Another difficulty is to generate meshes that enable the numerical methods to converge in highly complex geometries (bifurcations, high curvature zones, plaques). The present paper will give some insight into these questions and address some of the challenges described in Tang et al. [41], who underline the lack of the data necessary to develop clinical efficient predictive models of plaque vulnerability.

The purpose of the present study is, in addition to develop a methodology, to investigate the haemodynamics of blood flow through the mouse aortic arch with plaques. The focus is to improve understanding of plaque development and vulnerability in a realistic geometry and provide insight into the influence of plaque on haemodynamics. In addition, plaques in aortic arches have been shown to increase stroke frequency in patients suffering from cardiovascular diseases [42, 43]. In particular, it multiplies by six the risk of stroke after cardiopulmonary bypass operations [44], therefore understanding plaque development in this region is highly important. Furthermore, while the results presented here are based on the rigid wall assumption, this paper seeks to validate a numerical approach that is adaptable to the implementation of fluid structure interaction methods. The results show the plaque changes observed between mice fed after 10, 12, 14 and 16 weeks of fat diet, and the blood flow dynamics in a geometry with and without plaque obtained with numerical calculations. The emphasis of the present work is to develop tools and undertake a preliminary study that will allow the detailed investigation of plaque progression in future studies with a larger number of subjects.

2. Material and methods

2.1. Animal preparation

An apolipoprotein E knockout (ApoE −/−) mouse model sourced from Dr Grant Drummond colony (Monash University) was used as a model of spontaneous atherosclerosis development. Mice were fed with a high fat diet at 5 weeks of age (HFD SF00-219, 21% fat; 0.15% cholesterol) for 10, 12, 14 or 16 weeks. Mice were perfusion fixed at 100 mm Hg via the left ventricle of the heart. The first perfusion solution was heparinised saline (50 mL) to clear blood from the vessel and this was followed perfusion fixation with 50 mL of a low osmolarity

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