Flow and atherosclerosis in coronary bifurcations

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Abstract
Coronary bifurcations are among the most frequent sites affected by atherosclerosis. In these regions, complex haemodynamic conditions prevail and local flow disturbances dictate the localisation and progression of atheroma. Endothelial shear stress (ESS) is the main flow-related factor affecting the distribution of atherosclerosis in a bifurcation. Plaques are more prevalent in low ESS areas, such as the lateral walls of the main vessel and side branches, while they are less common in the flow divider or carina, which is characterised by high ESS. However, the carina is not free of atheroma and is affected in up to one third of cases, but never in isolation. Lesions in the carina are likely to develop at a later stage of atherosclerosis, as result of circumferential expansion of plaques from the lateral wall. Pulsatile flow augments the local atherogenic environment by inducing low and oscillatory ESS. The geometrical configuration is also important as increased curvature and wide angles between the side branches of the bifurcation intensify flow perturbations, and highly curved segments show low ESS in the inner aspect of curvatures. Further research on the flow conditions which determine the initiation and progression of atherosclerosis in bifurcations will allow for more efficient prevention and management strategies.

Introduction
Even though the entire coronary tree is susceptible to the deleterious effects of the systemic risk factors for atherosclerosis, atherosclerotic lesions are focal and tend to localise in specific regions including the vicinity of branch points, the outer wall of bifurcations and the inner side of curvatures.1-3 Since systemic factors are essentially identical along the arterial bed, the non-random distribution of atherosclerosis has been attributed to the local effect of flow-related haemodynamic forces with endothelial shear stress (ESS) playing the most fundamental role. Coronary bifurcations are frequently affected by atherosclerotic disease, being involved in up to 20% of all percutaneous coronary interventions. Bifurcation lesions are among the most challenging lesion subsets because of the procedural complexity of their treatment and their preponderance towards in-stent restenosis and late stent thrombosis. As bifurcations are characterised by inherently complex haemodynamics, they exemplify a typical environment where flow disturbances dictate the localisation and progression of atheroma.4 While intravascular bifurcation anatomy and ESS patterns could previously only be investigated in vitro or ex vivo, novel, even non-invasive, methodologies now exist that enable ESS and detailed plaque features to be characterised in vivo. Better understanding of the interplay between local flow conditions and the formation and progression of plaque in bifurcations may define areas of angiographic interest in high-risk patients, enhance our ability to prospectively identify regions most likely to be inflicted by plaque and possibly facilitate the deployment of haemodynamically-driven treatment strategies with better clinical outcomes.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>µ</td>
<td>Blood viscosity</td>
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<tr>
<td>dV/dy</td>
<td>Radial gradient of axial blood velocity</td>
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<td>ESS</td>
<td>Endothelial shear stress</td>
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<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
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The purpose of the present review is to summarise current evidence regarding the distribution of plaque in coronary bifurcations, to investigate the critical effect of flow-related haemodynamics on the localisation and progression of atheroma in bifurcations and to analyse the potential determinants of flow perturbations in these regions.

**Evidence of plaque development and distribution in arterial bifurcations**

It has been documented in both autopsy and intravascular ultrasound studies that atherosclerosis in coronary bifurcations most frequently occurs in the lateral walls of both the main vessel and side branches, while it is uncommon in the flow divider (carina) region (Figure 1).\(^5\)\(^-\)\(^10\) The same distribution of lesions has been reported for carotid artery bifurcations.\(^11\) The carina, however, should not be considered as being consistently free of atherosclerosis. A contemporary classification scheme of bifurcation lesions proposed by Medina et al includes carina involvement in most types of lesions,\(^12\) and in an intravascular ultrasound study assessing the “floating-stent technique” for the treatment of left anterior descending ostial lesion the incidence of carina involvement was considerable (27%).\(^13\) In an autopsy study of coronary bifurcations there was no evidence of reduced intimal thickening in the flow divider region, although advanced atheroma was not present.\(^7\) Similarly, a degree of intimal thickening in the carina region has been recently reported in a histopathology study of coronary bifurcations by Nakazawa et al, although this was considerably less than that in the lateral walls; notably, intimal thickening at the flow divider region occurred in the absence of a necrotic core.\(^14\) In a multislice computed tomography study van der Giessen et al reported that plaque was documented in the carina region in 31% of cases (Figure 2). In cases where the carina was affected, there was invariably plaque in other areas of the bifurcation as well.\(^15\) Despite technical limitations in terms of the diagnostic accuracy of 64-multislice computed tomography as compared with intravascular ultrasound, the latter study suggests that the flow divider region is indeed less prone to atherosclerosis formation but it can still be affected under certain conditions.

Taken together, these data converge to the notion of a substantially lower incidence, and reduced extent, but not necessarily absence of plaque at the carina. Flow disturbances manifested as ESS variations in the respective regions are predominantly responsible for these plaque localisation patterns.

**The role of ESS in atherosclerosis development in coronary bifurcations**

**Definitions of ESS and blood flow patterns**

ESS is the tangential force exerted on the endothelial surface which results from the friction of the flowing blood. ESS is calculated as the product of the blood viscosity (\(\mu\)) and the radial gradient of axial blood velocity (dv/dy) at the endothelial surface (ESS=\(\mu dv/dy\)), and is expressed in units of force per area i.e. N/m\(^2\) or Pascal or dyne/cm\(^2\) (1 N/m\(^2\)=1 Pascal=10 dyne/cm\(^2\)).

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**Figure 1.** Representative histologic images of coronary plaque in bifurcation lesion. Reprinted from reference 14, with permission from Elsevier.
The pulsatile (unsteady) blood flow in combination with the complex geometric configuration of the coronaries determines the direction and magnitude of ESS. In relatively straight segments, ESS is pulsatile and unidirectional with a magnitude varying between 15 and 70 dyne/cm² over the cardiac cycle and yields a positive time-average. In contrast, in geometrically irregular regions, as coronary bifurcations, disturbed laminar flow occurs, and pulsatile flow generates low and/or oscillatory ESS. Low ESS refers to ESS which is unidirectional, but has a periodically fluctuating magnitude that results in a significantly low time-average (approximately less than 10-12 dyne/cm²). Low ESS typically occurs at the inner areas of curvatures and upstream of stenoses. Oscillatory ESS is characterised by significant changes in both direction (bidirectional) and magnitude over the cardiac cycle, resulting in a very low time-average, usually close to zero (Figure 3). Oscillatory ESS occurs primarily downstream of stenoses, at the lateral walls of bifurcations and in the vicinity of branch points.

Beside the temporal oscillations, ESS experiences significant spatial oscillations over short distances, especially in geometrically irregular regions, resulting in high spatial gradients, which also appear to be involved in atherosclerosis.

Association of ESS with atherosclerosis

A report as early as 40 years ago by Caro et al first implicated ESS in the localisation of atherosclerotic plaques. In the subsequent years, computational fluid dynamic studies in autopsy-based coronary models, carotid bifurcations or abdominal aortas showed that areas with low ESS were associated with atherosclerosis. The atherogenic role of low ESS was also confirmed in in vivo animal experiments. Human in vivo studies in arterial models derived from intravascular ultrasound or magnetic resonance imaging data also demonstrated the role of low ESS in the initiation and progression of atherosclerosis.
atherosclerosis. More recent basic research studies have shed light on the precise pathways by which low ESS leads to atherosclerosis, as well as the formation of thin cap fibroatheromas, suspected “vulnerable plaques”, responsible for acute coronary syndromes.16

Flow patterns and spatio-temporal ESS variability in coronary bifurcations

An arterial bifurcation or branching point imposes an anatomical substrate for the development of disturbed flow. This is because a proportion of blood flow is subject to an abrupt change in direction from purely axial to the direction of the side branches. As a result, flow separation occurs and secondary flow patterns develop, often manifesting as vortices. These events lead to a low and oscillatory ESS as well as a low wall pressure gradient along the lateral walls of the main vessel and side branches.4,19,20 On the other hand, high ESS develops in the carina region.21 This spatial variation in ESS is generally consistent with the anatomical distribution of atherosclerosis in coronary bifurcations. As low ESS promotes atherosclerosis, it is an important factor responsible for the more frequent localisation of plaques in the lateral wall of bifurcations than in the carina. Conversely, high ESS has been associated with endothelial denudation, and this may be responsible for a subsequent acute luminal occlusion arising from a carina lesion which would clinically manifest as an acute coronary syndrome.

Apart from the above evident spatial ESS gradients in coronary bifurcations, temporal ESS variations are also particularly important. ESS is low and oscillatory during systole, while in diastole it rapidly increases up to a maximum value and then slowly declines. It would be thus reasonable to suggest that the systolic phase of cardiac cycle exposes the endothelium to flow conditions which favour the atherosclerotic process, whereas the diastolic phase exerts an athero-protective role.4,22

Molecular, cellular and vascular effects of low ESS

Endothelial cells sense the local ESS stimuli through mechanoreceptors on their luminal, junctional and basal surfaces. Mechanoreceptors trigger numerous intracellular pathways, in a process known as mechanotransduction, leading to activation of several transcription factors. These bind positive or negative responsive elements at promoters of mechanosensitive genes, inducing or suppressing gene expression and ultimately regulating cellular behaviour. In regions with non-disturbed flow and high ESS, endothelial cells express various atheroprotective genes, and suppress pro-atherogenic ones. In contrast, where disturbed flow and low and/or oscillatory ESS occur, the atheroprotective genes are suppressed, while the pro-atherogenic genes are upregulated, thus promoting atherogenesis.16,23

The role of ESS in the pathophysiology of early atherosclerosis is summarised in Figure 4.16 Low ESS reduces the bioavailability of nitric oxide and upregulates endothelin-1, thereby inducing endothelial dysfunction. It also promotes low density lipoprotein cholesterol (LDL-C) uptake and synthesis by the endothelium, leading to subendothelial accumulation of LDL-C. Low ESS also mediates the production of reactive oxygen species within the intima which are responsible for the oxidative modification of LDL-C. Furthermore, it upregulates several adhesion molecules, chemotactant chemokines, and pro-inflammatory cytokines thereby promoting infiltration of circulating monocytes within the intima. There, they differentiate to macrophages and evolve to foam cells which sustain the atherosclerosis progression. Over-expression of proteases associated with extracellular matrix degradation (metallopeptinases and cathepsins) is also mediated by low ESS. Low ESS upregulates the expression of potent mitogens, as platelet derived growth factor, endothelin-1, and vascular endothelial growth factor which promote vascular smooth muscle cell

Figure 4. Role of low endothelial shear stress (ESS) in atherosclerosis. Reprinted from reference 16, with permission from Elsevier.
migration and proliferation. Ultimately all these mechanisms contribute to the focal formation and progression of plaque.\textsuperscript{16}

**Mechanisms of plaque distribution and progression in coronary bifurcations**

The disturbed flow patterns are responsible for the preponderance of the outer bifurcation walls to plaque formation. The carina involvement in bifurcation atherosclerosis, however, remains a controversial issue and the subject of an ongoing debate, as previous studies may seem contradictory. Since the ESS distribution in the bifurcation clearly defines the carina as a high (i.e., athero-protective) ESS region and the lateral wall as a low (i.e., athero-prone) ESS environment, the question arises: what is the mechanism responsible for the formation of any extent of plaque at the carina?

One can speculate on the mechanisms underlying the conundrum of the plaque-protected, but not necessarily plaque-free carina. One possible explanation of the “carina paradox” might be that plaque grows from the low ESS regions and extends to the high ESS carina wall. Reports indicate that atherosclerosis in the carina is not seen in isolation, but always coexists with lesions elsewhere in the bifurcation area. The relatively reduced involvement of the carina may have to do with the stage of the atherosclerotic process at the time of study. In early atherosclerosis, plaque is shown at the lateral walls opposite to the carina.\textsuperscript{6} In older populations, where it is reasonable to expect a more advanced overall stage of atherosclerosis, intimal thickening is similar in the carina as in the other walls.\textsuperscript{7} Such an explanation is further supported by the findings by van der Giessen et al who studied middle-aged individuals, 75\% of whom had stable or unstable angina. Advanced atherosclerosis would be expected in some proportion of this population and this may account for a carina involvement in nearly one third of cases. Moreover, in the above study, the carina was always free of atheroma in minimally diseased cases, was affected in 29\% of mildly diseased segments, in 45\% of moderately diseased, and in 100\% of severely diseased segments.\textsuperscript{15} The insight gained by these findings indicate that atherosclerosis initially develops in the lateral walls of the bifurcation. As plaque expands, it circumferentially grows from the lateral walls towards the carina region, which is ultimately affected. Furthermore, local flow patterns are not only determined by geometric configurations, but also by plaque-induced changes of local anatomy and by the arterial remodelling response to plaque; local ESS patterns therefore may not only promote atherogenesis, but also change in response to the developing lesion.\textsuperscript{24}

A previously described mechanism for longitudinal plaque progression assumes that the low ESS downstream of a lumen-protruding lesion accentuates an adverse haemodynamic environment that promotes additional plaque growth downstream of the lumen stenosis, and it is plausible that such a mechanism might also account in part for the longitudinal progression of plaque in the atherosclerotic bifurcation.\textsuperscript{25} Initially, in atherosclerosis-susceptible bifurcation segments where low ESS occurs (i.e., in the lateral walls) a lesion starts to develop (Figure 5A). Progressively, and under the combined influence of other risk factors, plaque develops in these regions (Figure 5B). At the post-stenotic regions across the lateral walls low and disturbed flow occurs and the effects of pulsatile flow lead to the generation of an oscillatory ESS. The latter further amplifies the local atherogenic environment facilitating the progression of the lesion downstream (Figure 5C). We could also speculate that atherosclerosis may not only extend downstream of the bifurcation, but also upstream towards the main vessel as low ESS in this area favours local plaque growth and vulnerability.

![Figure 5. Hypothetical model of the longitudinal progression of atherosclerosis in coronary bifurcations.](image)
In a wider perspective, one should not be dogmatic when assessing the cause-effect relation between haemodynamic factors and atherosclerotic disease. While the identification of low ESS regions, including the complex milieu of the bifurcation, provides a safe estimation of the sites with a relatively higher probability of plaque formation and progression, some plaque formation is still possible even in regions exposed to putatively athero-protective shear conditions, such as the flow divider of a bifurcation, likely mediated by other mechanisms that yet remain to be determined.

**Role of ESS in plaque destabilisation in coronary bifurcations**

In addition to the role of low ESS in plaque initiation and growth, more recently, ESS has been linked to the formation of advanced rupture-prone high-risk plaque. Computational fluid dynamics and histopathology studies have identified baseline local ESS patterns which resulted in vulnerable atherosclerotic lesions. Cheng et al. showed in a mouse carotid model that lesions with characteristics of vulnerability, including increased plaque size and lipid content, and reduced smooth muscle cells and collagen, developed in regions of low, but not directionally oscillatory ESS. This concept was further advanced in a study that serially analysed coronary arteries in a human-like, porcine model. This study showed that low ESS segments resulted in inflamed, thin-capped atheromata, with a dose-response relationship between the magnitude of low ESS, and the severity of high-risk plaque characteristics. Additional analyses showed a mechanistic link between low baseline ESS, heightened expression and activity of elastolytic enzymes, internal elastic lamina degradation and excessive expansive arterial remodelling, which further accentuated the adverse, low ESS environment. A recent in vivo study highlighted the dynamic nature of the local haemodynamic milieu, and showed that phenotypic de-differentiation of intimal smooth muscle cells and increased expression of collagenolytic enzymes was associated with collagen depletion, fibrous cap thinning, and ultimately the formation of rupture-prone coronary lesions in regions of persistently low ESS.

The value of the above studies linking ESS patterns with plaque destabilisation lies in the demonstration of low ESS as an ongoing adverse stimulus that decisively influences the focal evolution towards rupture-prone lesions. Atherosclerotic plaques are known to be heterogeneous, and even presumed high-risk lesions of similar morphology, as assessed by currently available imaging modalities, may carry a different risk of eventually causing an acute coronary event. In vivo identification of regions with low ESS may be utilised for the prospective detection of areas most likely to acquire a high-risk, rupture-prone phenotype.

**Determinants of disturbed flow in coronary bifurcations**

**Geometrical configuration**

The angulation of the side branch take-off has been reported to influence the severity of atherosclerosis in coronary bifurcations as larger angles have been associated with increased plaque. Data from computational fluid dynamics studies have confirmed this finding by demonstrating that even in the absence of alterations in the amount of branch flow, a wide angle between the side branches intensifies flow perturbations, increases the spatial ESS variations in the bifurcation region and the low ESS in the lateral walls, thereby augmenting the atherosclerosis-prone environment. The magnitude of reversed flow, the extension of the recirculation zone and the duration of flow separation during the pulse cycle comprise other haemodynamic parameters which are important in atherogenesis and are amplified by an increased bifurcation angle. Apart from the angle of side branch take-off, an increased ratio of the side branch dimensions in proportion to those of the main vessel and an increased bifurcation tortuosity have been reported to contribute in the formation of a low and/or oscillatory ESS environment in the bifurcation region in coronary arteries.

Coronary bifurcations are not planar, but they follow a three-dimensional configuration across the surface of the beating heart thereby producing curved regions. An implication of the effects of vascular curvature on the development of disturbed flow came initially from studies documenting that atherosclerosis in coronary bifurcations is more pronounced in the myocardial than in the epicardial aspect of the arteries. These areas constitute the inner curvature regions, where impaired flow conditions occur and atherosclerosis is favoured. Therefore, as the curvature is higher the plaque accumulation in the respective regions is more prominent. In curved arteries, low ESS is noted in the inner curvature while high ESS in the outer curvature. Arterial curvature over the myocardial surface contributes to a skewed local velocity profile which denotes impaired flow conditions. It is noteworthy that the effects of arterial curvature in coronary flow are higher downstream of the bifurcation than near the branching point. Overall, despite the invariable effects of geometry in coronary flow in bifurcating vascular regions one could not argue that there is a uniform simple geometric risk factor which determines the creation of disturbed flow. Wide inter-individual variations rather exist, and further research to elucidate these parameters is warranted.

**Pulsatile flow**

Coronary circulation is subject to a pulsatile blood flow pattern. As a result of different forces exerted in the large epicardial coronary arteries across the cardiac cycle, forward flow mostly occurs during diastole whereas a marked deceleration or even flow reversal may be noted in systole. Since ESS is proportional to the flow velocity gradient at the endothelial surface, it is conceivable that phasic blood flow alterations correspond to respective ESS variations and expose specific coronary regions to low and oscillatory ESS during systole. The effects of the complex three-dimensional geometrical structure of bifurcations in flow properties are augmented by pulsatile flow. The low ESS near the lateral walls is more easily affected, and can completely reverse direction even if there is no reversal in the overall volume flow rate. Therefore, in these atherosclerotic-prone regions of a bifurcation the pulsatile flow generates an oscillatory ESS which constitutes a clear pro-atherogenic factor.
Rate of dynamic flow alterations over the cardiac cycle

The effects of pulsatile blood flow in the haemodynamic environment of coronary bifurcations may further account for the pathogenetic role of increased heart rate in the development of atherosclerosis in these regions. Within normal resting heart rates, the diastolic phase possesses about two thirds of the cardiac cycle duration, the remaining one third covered by the systolic phase. However, in conditions of a raised heart rate, the increase occurs at the expense of the diastolic phase duration which is reduced and eventually becomes equal to that of the systolic phase. The latter event is translated as an increase in the total time per minute which the myocardium spends in the systolic phase. Consequently, a high heart rate prolongs the exposure of the coronary endothelium to the impaired systolic flow conditions of low and/or oscillatory ESS thereby promoting atherosclerosis.22

Dynamically changing three dimensional geometry over the cardiac cycle

High heart rate also promotes the development of atherosclerosis by inducing changes in the coronary geometry. The perpetual motion of the pulsating myocardium affects the shape of the coronary arteries in a periodic manner. This causes a respective variance in the haemodynamic forces exerted on the endothelium and further enhances the regional atherogenic environment. In the left anterior descending artery, curvature is maximal in systole and relatively low in diastole. In highly curved regions, ESS is low in systole, and increases in diastole as curvature decreases, and vice versa. Thus, the cumulative duration of systole as the heart rate increases, augments the curvature of coronary arteries, which in turn leads to a low ESS and progression of atherosclerosis. Cyclic alterations in coronary torsion also account for flow disturbances. Plaque is more evident in regions exhibiting higher torsion than normal segments. Also, changes in coronary torsion during the cardiac cycle may contribute to low regional ESS, which further supplies the vicious cycle of geometry deformations, disturbed flow and atherosclerosis progression.22

Conclusions

Coronary bifurcations are of the most complex regions in the coronary tree in terms of flow conditions, and an overall understanding of the pathophysiology of atherosclerosis initiation and progression in these areas remains a challenge. ESS is the main factor determining the distribution of atherosclerosis, while the effects of pulsatile flow and local geometry also contribute significantly. Knowledge of these parameters is therefore critical in determining the focal susceptibility of specific portions of the bifurcation milieu to develop clinically relevant plaque. Advances in the current imaging modalities of the coronary arteries are expected to enable the development of more accurate models for the study of geometry and flow conditions in coronary bifurcations. Further research on these factors will allow for more efficient prevention and management strategies.

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