Atherosclerosis at arterial bifurcations: evidence for the role of haemodynamics and geometry

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Summary

Atherosclerotic plaques are found at distinct locations in the arterial system, despite the exposure to systemic risk factors of the entire vascular tree. From the study of arterial bifurcation regions, emerges ample evidence that haemodynamics are involved in the local onset and progression of the atherosclerotic disease. This observed co-localisation of disturbed flow regions and lesion prevalence at geometrically predisposed districts such as arterial bifurcations has led to the formulation of a 'haemodynamic hypothesis', that in this review is grounded to the most current research concerning localising factors of vascular disease. In particular, this review focuses on carotid and coronary bifurcations because of their primary relevance to stroke and heart attack. We highlight reported relationships between atherosclerotic plaque location, progression and composition, and fluid forces at vessel's wall, in particular shear stress and its 'easier-to-measure' surrogates, i.e. vascular geometric attributes (because geometry shapes the flow) and intravascular flow features (because they mediate disturbed shear stress), in order to give more insight in plaque initiation and destabilisation. Analogous to Virchow's triad for thrombosis, atherosclerosis must be thought of as subject to a triad of, and especially interactions among, haemodynamic forces, systemic risk factors, and the biological response of the wall.

Keywords

Atherosclerosis, biomechanics, shear stress, arterial bifurcation, haemodynamics

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Introduction

Atherosclerosis is a systemic inflammatory disease of the arterial system characterised by intimal lesion formation (atherosclerotic plaques) in the vasculature. Rupture of atherosclerotic plaques is responsible for the majority of the cardiovascular events (myocardial infarction, stroke), which are leading causes of morbidity and mortality in the Western world. Atherosclerotic plaques display a variety of phenotypes: highly inflamed lesions with a large lipid pool and a thin fibrous cap are recognised as most vulnerable to rupture, whereas fibrous plaques are generally considered more stable (1).

Atherosclerotic plaques develop at arterial locations with a dysfunctional endothelium and involves leukocyte recruitment, lipid accumulation, smooth muscle cell migration and proliferation, cell death and fibrosis (2, 3). Atherosclerotic plaque development occurs preferentially at geometrically predisposed areas, like the inner curvature of the aortic arch and close to arterial branch points, despite the fact that the entire arterial tree is exposed to systemic risk factors such as hypertension, hypercholesterolaemia and diabetes (4, 5).

There is ample evidence that haemodynamic factors are involved in the local onset and progression of atherosclerosis, often referred to as the 'haemodynamic hypothesis'. Haemodynamic factors regulate multiple aspects of vascular biology and physiology and play a key role in vascular homeostasis as well as in arterial disease development (6). In analogy to Virchow's triad on thrombosis, ▶Figure 1 shows a schematic representation of factors involved in atherosclerotic plaque formation, illustrating the complex interplay between a) haemodynamic factors, b) the biological response of the arterial wall, and c) systemic risk factors.

A haemodynamic factor that is widely recognised for its involvement in atherosclerotic plaque formation is endothelial shear stress, the frictional force per area exerted at the vessel wall by the flowing blood (▶Figure 2). In general, in the plaque initiation process low and oscillatory shear stress is considered atherogenic, whereas high shear stress is athero-protective (7).

Wall shear stress can be determined by calculating the gradient of the local blood flow velocity close to the vessel wall multiplied by the blood viscosity. Physical laws determine that blood flow velocities, due to the balance of centrifugal, pressure and viscous forces, are spatially distributed such that skewed, highly

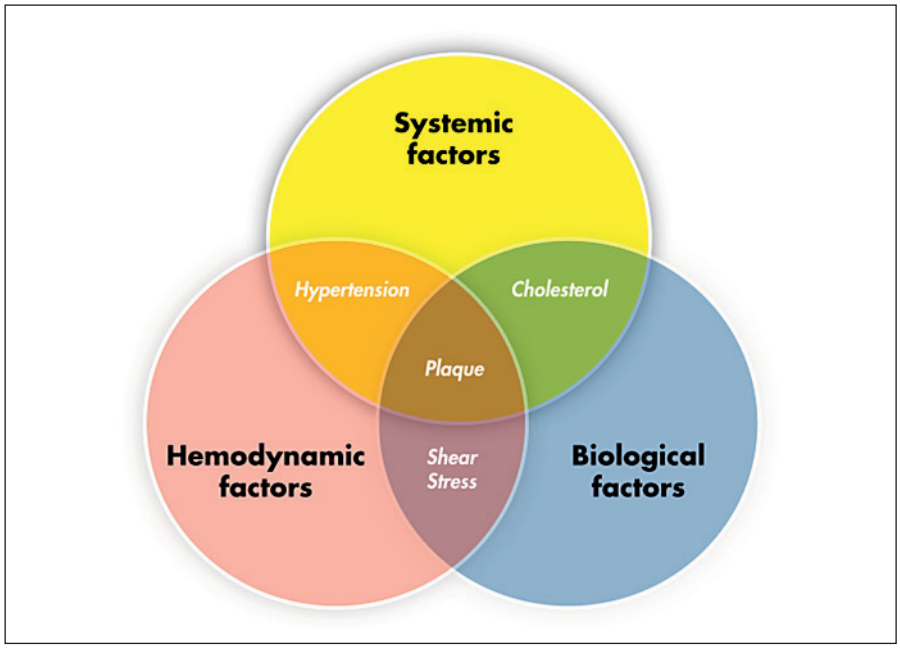

Figure 1: The complex interplay among systemic risk factors, biological factors and haemodynamic factors leading to vascular pathology and atherosclerotic plaque formation may be seen as a triad in analogy to Virchow's triad of thrombosis. The systemic risk factor most influencing atherosclerosis is hypertension, whereas shear stress locally influences the endothelial function and vascular biology. In turn, endothelial function is also influenced by systemic risk factors such as cholesterol levels.

asymmetric velocity profiles can be observed in bending arterial segments or at arterial branching (4, 8) and bifurcating regions, where flow separation and reattachment can occur, consequently leading to complex distinct patterns of low and high shear stress at the vessel wall (4, 9, 10).

Additionally, the direction and velocity of blood flow in arteries fluctuate throughout the cardiac cycle. Vascular locations that are exposed to low, oscillatory shear stress (i.e. varying in direction, with both forward and reverse velocities) during the cardiac cycle are considered as 'disturbed' shear stress regions.

Nowadays, shear stress is most commonly assessed using advanced computational fluid dynamics (CFD) (11). However, these methods are typically limited to engineering experts and can be sensitive to assumptions and uncertainties in input parameters including blood flow rates and vessel geometry. Other methods to estimate shear stress include magnetic resonance imaging (MRI)-

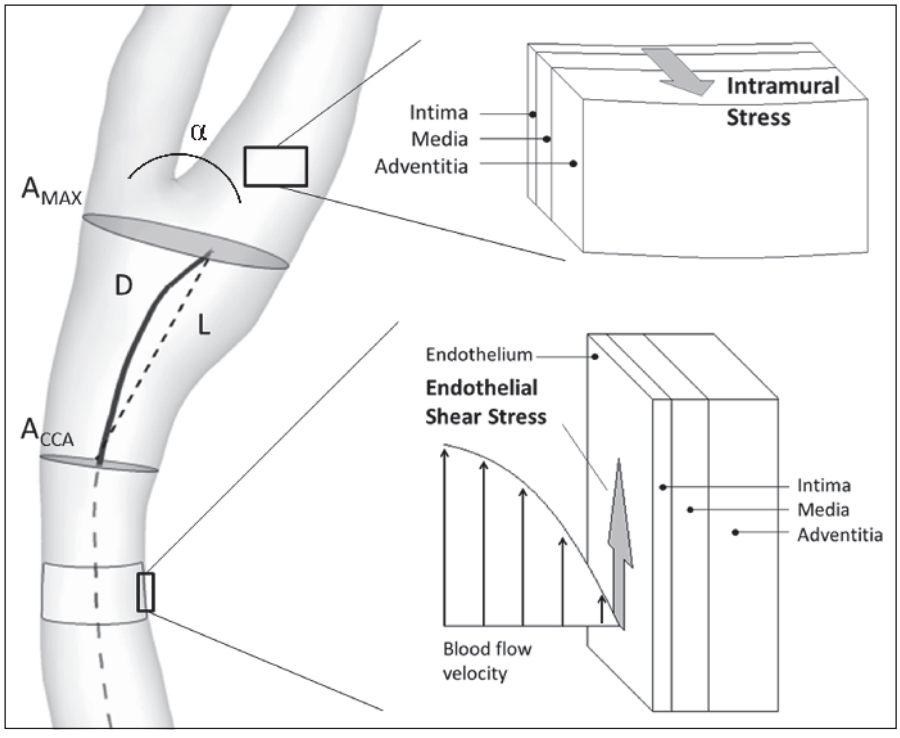

Figure 2: Definition of endothelial shear stress, intramural wall stress and geometric parameters in a schematic representation of carotid artery bifurcation. The shear stress is the gradient of the velocities close to the vessel wall multiplied by the viscosity, not to be confused with intramural stress (more markedly involved in plaque rupture) inside the vessel wall, also shown. The geometric parameters demonstrated for the carotid bifurcation as 'easy-to-measure' surrogates for shear stress are the ratio of maximal area at the bifurcation region (A_{MAX}) to the area at the common carotid artery (ACCA); and the ratio of the CCA centreline distance (D) to the shortest distance (L) between A_{CCA} and A_{MAX}. Also shown is the often-reported angle (α) between the two side branches.

based velocity measurements, but these can only be applied to larger arteries such as the carotid artery and aorta. Using MRI, absolute shear stress values are typically underestimated due to MRI's low spatial and temporal resolution; however, the relative distribution of low *vs.* high shear stress that can be obtained from the acquired phase velocities is generally correct (12).

Researchers have also investigated whether geometric features of arteries, as easier-to-measure surrogate markers of shear stress, might be able to predict risk for atherosclerotic plaque formation, the so-called 'geometric risk hypothesis' (13). More recently, attempts have been made to correlate specific geometric attributes of the carotid bifurcation with shear stress distribution (14–17) and with intimal thickness location (18). Descriptors of the intravascular flow itself, such as helical flow (which has been demonstrated to smooth out extremes of wall shear stress (19–21), have also been investigated as easier-to-measure surrogate markers of shear stress (20, 21).

This review focuses on carotid and coronary bifurcations because of their primary relevance to stroke and heart attack. We highlight reported relationships between atherosclerotic plaque location, progression and composition and shear stress or its surrogates, i.e. vascular geometry (because geometry shapes the flow) and helical flow (because it is instrumental in suppressing flow disturbances), in order to give more insight in plaque initiation and destabilisation.

Vascular biology and its relationship with shear stress

The luminal side of blood vessels is lined by a monolayer of endothelial cells, which regulate leukocyte adhesion and transmigration, mass transport/permeability, platelet aggregation and smooth muscle function through the release vasoactive substances, such as nitric oxide, endothelin-1 and prostacyclin, and by the expression of specific adhesion and junctional molecules (22–24). The endothelial cells are the only cell layer directly in contact with flowing blood, and shear stress influences vascular function by activating endothelial mechanoreceptors, which transmit biochemical signals in response to the shear stress. Three groups of potential shear stress sensors have been proposed over the past two decades: 1) cell membrane-associated molecules such as ion channels, receptors, adhesion molecules and the glycocalyx, 2) specific membrane microdomains, like primary cilia and caveolae, and 3) general cell supporting structures such as the cytoskeleton and the lipid bilayer membrane itself (25). There are substantial differences in the endothelial response in straight parts of arteries that are exposed to pulsatile laminar blood flow and in regions of disturbed shear stress near arterial bifurcations, which may be initiated by different sensing mechanisms. The endothelium in regions of disturbed shear stress displays increased expression and activation of the pro-inflammatory Nuclear Factor Kappa B (NF-κB), an increased oxidant/anti-oxidant balance, activation of the unfolded protein response and endoplasmic reticulum stress as well as low expression of protective factors such as endothelial nitric oxide synthase, thrombomodulin and Krüppel-like transcription factors (KLF2, KLF4) (26, 27). These disturbed shear stress-induced changes in endothelial cell behaviour result in increased susceptibility to injury and inflammation and limit the regenerative capacity of endothelial cells, this way explaining the focal nature of atherosclerotic lesion formation (6, 28).

Shear stress may not only affect the initiation of atherosclerosis, but may also directly modify plaque composition and thereby its vulnerability (29). Indeed, the pattern of (imposed) shear stress disturbance appeared by itself crucial for plaque phenotype in mice (30), i.e. plaques in a low shear stress region contained low amounts of smooth muscle cells and collagen, high quantities of macrophages and a large lipid core, corresponding to a vulnerable plaque phenotype in human. In contrast, oscillatory shear stress induced smaller plaques with a more stable phenotype.

The relationship between shear stress and atherosclerosis is reciprocal, since plaque formation leads to alterations in local shear stress. During early atherogenesis, outward vessel wall remodelling can compensate for plaque growth, thus minimizing changes to the vessel lumen (31). Since the geometry of the lumen determines blood flow patterns, this implies that shear stress will not alter significantly during this period. As a result of persisting low shear stress, plaques with a large lipid core, intense inflammation and a thin fibrous cap are found at such locations in porcine coronary arteries (32). When expansive remodelling is exhausted, further plaque growth leads to narrowing of vessel lumen, resulting in marked alteration of the shear stress patterns. The upstream segment of the plaque to the point of maximal stenosis is exposed to high shear stress, whereas the downstream segment is subjected to low and oscillatory shear stress. Although defined successive alterations in shear stress patterns have not (yet) been experimentally imposed in animal models, the distribution of leukocytes in human carotid atherosclerotic lesions seems to relate to shear stress (33).

Upstream segments of plaques at the carotid bifurcation show enhanced macrophage accumulation and apoptosis, intraplaque haemorrhage, thinner fibrous caps and greater incidence of plaque rupture (33, 34). Increased smooth muscle cell and collagen content in the downstream segment seems to stabilise the plaques at this location. Several mechanisms have been proposed (35) that potentially are responsible for the high shear stress-induced fibrous cap destabilisation. High shear stress leads to an increased NO production and may thereby enhance MMPs expression by macrophages, which can promote cap rupture (36). Also, plasmin, which is produced by the endothelium in response to high endothelial shear stress (37) is a strong activator of specific MMPs (i.e. MMP-1, –3, –9, –10 and –13) (38).

It is important to note that the mechanisms governing advanced plaque progression and vulnerability are almost certainly different from those for initiation and early progression. In fact, the hypothesis that atherosclerosis initiation correlates with low and/or oscillatory shear stress cannot explain why intermediate and advanced plaques continue to grow under the elevated high shear stress condition caused by severe stenosis-driven altered flow conditions (39–41).

Carotid bifurcation

Variation in geometry and its influence on shear stress

The carotid bifurcation is the vascular connection where arterial blood from the common carotid artery (CCA) is distributed to the intracranial and extracranial circulations via the internal (ICA) and external (ECA) carotid artery branches, respectively. The presence of this bifurcating vessel, and in particular the dilatation of the region where the ICA stems from the CCA (the so-called carotid bulb) causes complex intravascular flow structures, including flow separation and recirculation, consequently leading to low and oscillatory shear stress.

Early CFD studies using idealised geometries of the bifurcation demonstrated the impact of bulb diameter and bifurcation angle (16, 17) on the size and intensity of disturbed shear stress at the carotid bulb. Later, a more systematic approach using a parametric geometry demonstrated interactions among bulb diameter, bifurcation angle, and branch diameters in predicting low shear stress (42). Investigations using patient-specific geometries showed that bifurcation planarity had only a minor influence on disturbed shear stress compared to artificially straightened counterparts (43). A more comprehensive study of 50 young adults showed that the interaction between bifurcation area ratio and CCA tortuosity significantly predicts exposure to disturbed shear stress at the carotid bulb (14). Interestingly, in that study bifurcation angle did not show correlation with disturbed shear stress. These findings were corroborated by *in vivo* (MRI) imaging of blood flow in an independent cohort (44), and were later shown to be strengthened either by prudent combination of selected geometric parameters (45), or by refining the definitions of individual geometric parameters (►Figure 2) to better reflect their influence on the shear stress distribution at the luminal surface (46).

Plaque localisation, growth, composition vs shear stress

Autopsy specimens of carotid bifurcations (9, 10) have revealed that there are preferred sites for lesion location. Intimal thickening was 1) more pronounced along the outer wall, opposite of the flow divider of the bifurcation, 2) eccentric and greater than elsewhere in the carotid bulb, and 3) minimal and in general uniformly distributed at the common carotid and distal internal carotid levels.

In vitro studies on haemodynamics in adult carotid bifurcations have clarified that regions where maximum intimal thickening and atherosclerotic plaque formation occur were associated with low and oscillatory shear stress (9, 10, 47), whereas the minimally affected arterial lesions were exposed to high flow velocities and thus high shear stress (9). These observations suggested that low shear stress may enhance atherogenesis in the carotid bifurcation. CFD analysis on postmortem human carotid bifurcations with early atherosclerosis have also confirmed the existence of wall alterations at low shear stress regions (48).

Recent studies point to a link between shear stress and plaque composition, and thus plaque stability/rupture in carotid arteries (49, 50). For instance, at the upstream side of the plaque, presumably exposed to high shear stress, a more vulnerable plaque phenotype is observed (33, 34), as is the majority of ulcerations (51). This observation has been confirmed by using MRI-based modelling of the shear stress, showing plaque ulcers being located at the high shear stress sites of the plaque (52).

Geometric risk factors and plaque localisation and growth

Vascular geometry might serve as a risk factor for the early development of atherosclerosis disease because of its strong influence on local haemodynamics (13, 53). Early tests of this geometric risk hypothesis were equivocal (54–60), owing to small sample sizes (N< 100) and difficulties in controlling for systemic risk factors or possible secondary effects of plaque on lumen geometry. Larger studies from the early 2000s reinvigorated the search for geometric risk factors (61–63). In a recent study, proximal ICA radius and ICA angle were reported to be significant independent predictors of stenosis development (64), but the inclusion of cases with up to 90 % stenosis makes it difficult to exclude the impact of plaque on geometry. This importance of cause vs effect was highlighted in a recent study demonstrating that so-called 'haemodynamically-inspired' geometric risk parameters were significant *independent* predictors of early carotid bulb wall thickening, but only after carefully excluding cases with possibly inward remodelling (18).

Helical flow velocity and plaque localisation and growth

The main geometric characteristics of the carotid artery bifurcation contribute to the onset and development of helical flow patterns (i.e. pitch and torsion of the streaming blood) (20, 21, 65). Recent findings on a dataset of 50 models of human carotid bifurcations showed that helical flow intensity suppress flow disturbances at the carotid bifurcation and thereby is potentially protective for atherosclerotic plaque build up (21). Since it was demonstrated that intravascular helical flow can be reliably assessed *in vivo* (66), the quantitative analysis of helical flow patterns could offer a practical way to predict local risk on atherosclerosis in large scale clinical studies, as already done in other arterial districts (66, 67) (►Figure 3).

Coronary bifurcation

Variation in geometry and its influence on shear stress

The coronary circulation provides the heart with blood and, in general, it consists of two-to-three major branches: the right side of the heart is fed by the right coronary artery (RCA), whereas the left side is fed by 1) the left main coronary artery (LM), which bifurcates into the left anterior descending artery (LAD) and the left circumflex (LCx), or 2) the LAD and LCx when they stem directly

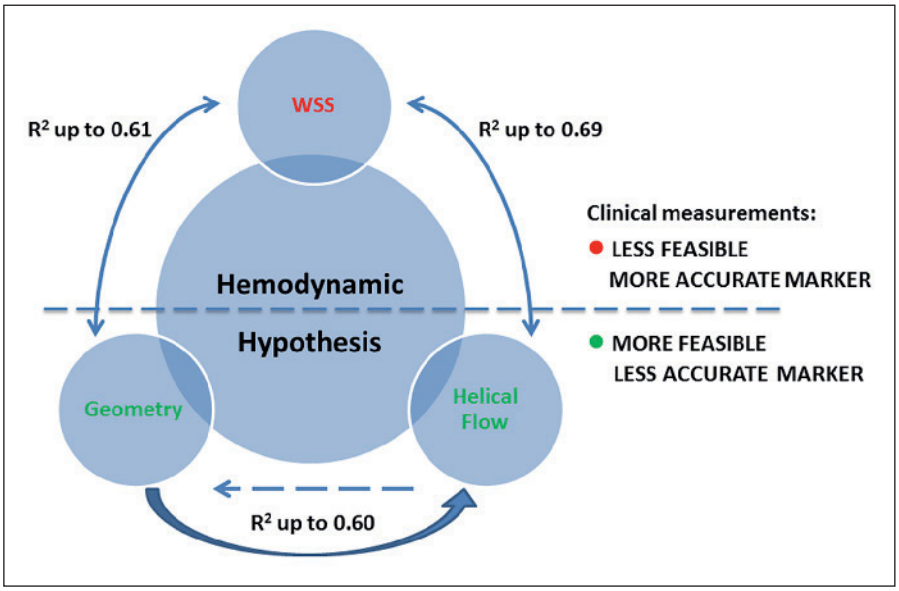

Figure 3: Schematic representation of the relationship between shear stress, geometry and helical flow in carotid arteries. It is hypothesised that 1) the local shear stress is associated with either the local geometry of the bifurcation (R^2 up to 0.61) (46) or the helical flow (R^2 up to 0.69) (21) and that 2) local geometry and helical flow are also correlated (R^2 up to 0.60) (65). Quantitative analysis of geometric vascular attributes and helical flow is feasible and reliable in a clinical setting. However, they could be less sensitive or specific than shear stress, for inferring vascular disease.

from the aorta. Of all bifurcations in the coronary circulation, LM-LAD-LCx bifurcations are most often affected by disease (68).

Data on geometrical attributes influencing shear stress in coronary artery bifurcations is limited, with the only patient data available focusing on the LM bifurcation. A recent study of LM bifurcations from eight patients showed that LM-LAD tortuosity, appeared to be a good predictor for low shear stress (69), whereas LM-LCx tortuosity, bifurcation angle or area ratios were not predictive of shear stress. Interestingly, other studies have observed an association between LAD-LCx angle and low and oscillatory shear stress regions (70, 71). A positive correlation between regions exposed to high shear stress and LAD-LCx and LM-LCx angles (69) has also been observed. In addition to the bifurcation angle, the sharpness/smoothness of the artery branching off has been shown to significantly influence the local shear stress: the sharper the bifurcation the lower the shear stress (72). Although the out of plane course of the coronary arteries (planarity) is potentially of influence on the local shear stress distribution, this geometric parameter has not been studied for coronary arteries.

As noted earlier, the presence of stenosis in the bifurcation region potentially changes the local well-defined shear stress distribution. As an example, a study investigated the shear stress distribution in the bifurcation region in the presence of lumen narrowing in the proximal (main) vessel, main distal vessel or side branches (73). Intuitively the lowest shear stress values were expected when all vessels had a significant stenosis. However, it was observed that significant stenosis in the proximal vessel in combination with stenosis in the side branch resulted in the lowest shear stress values (i.e. an intense atherogenic environment) in the side branch, in the flow recirculation zone immediately distal to the stenosis (73).

Shear stress and plaque localisation and growth

In the left coronary arteries, plaques are most commonly located at the lateral wall (74–76). Based on a coronary CT study, it was speculated that the plaques grow from the opposite of the flow divider (low shear stress) circumferentially towards the flow divider, presumably the high shear stress region (77). Interestingly, early plaques located near bifurcations were found to be associated with high shear stress. A possible explanation for this observation is that in the bifurcation region positive remodelling is limited, leading to lumen narrowing and shear stress increase already with early disease (78).

Although the impact of shear stress on plaque progression has been investigated for non-bifurcated segments of the coronary arteries (79), no studies have been dedicated to the bifurcation region. The largest such plaque progression study ever, the PREDICTION study of 500 patients, showed a positive relationship between lumen area change and shear stress, and an inverse relation between plaque burden (percentage of plaque area with respect to the total vessel area) change and shear stress (80). Other studies have shown that low shear stress in combination with a plaque burden greater than 50 % was a hallmark of plaque area increase over a period of six months (81), whereas high shear stress was found to be related to plaque area decrease (82).

Shear stress and plaque composition

In a porcine study, low shear stress was observed to be correlated with increased inflammation and lipid content, suggesting that low shear stress initiates plaque onset and the generation of vulnerable plaques (32). Similar data have been obtained in a number of patient studies, suggesting a co-localisation of low shear stress and vulnerable plaque components such as necrotic core, plaque burden and calcium (5, 82, 83). On the other hand, plaques

characterised by a plaque burden greater than 40 %, at which point lumen narrowing is typically observed, showed a co-localisation of high shear stress (i.e. a consequence of lumen narrowing) and the lipid core. This corroborates the hypothesis that shear stress remains low until the plaque encroaches into the lumen, leading to high shear stress exposure at the upstream side of the plaque (84). Interestingly, high shear stress has been associated with plaque rupture sites (85, 86).

Several studies propose strain, the wall deformation caused by wall stress (►Figure 2), as a surrogate marker for plaque composition. Low strain or low tissue deformation presumably corresponds with 'stable' fibrous tissue and was found to be co-localised with low shear stress (83). In contrast high strain (or deformation), indicating weaker underlying materials such as lipid-filled macrophages was associated with high shear stress regions (87). In a later study, high shear stress was found to be correlated with an increase in strain over time, suggesting that high shear stress modulates plaque compositional growth (88). Using virtual histology, high shear stress has also been associated with increase in necrotic core area and decrease in overall plaque area, potentially leading to increase in plaque vulnerability (81).

Plaques that are located close to the bifurcation can extend from the main mother vessel into the distal main branch. Interestingly, plaques show a clear difference in composition comparing plaques located proximal from the bifurcation versus distal from the bifurcation. Plaques containing larger lipid pools are predominantly located at the proximal site of the bifurcation, and lesions appear to be longer at this site (89–92). In general, the thinnest caps are observed at the proximal site of the bifurcation (90, 91), except for a study where the thinnest caps were found to be located at the distal site (93). Summarising the above, one would classify atherosclerotic lesions at the proximal site of the bifurcation as vulnerable and thus more prone to rupture.

Geometric risk factors and plaque localisation

Already in 1997, geometrical parameters were identified as possible risk factors for plaque localisation (94). Based on vascular casting techniques of the left coronary artery bifurcation (LM-LAD-LCx), the presence of plaques in the LAD segment correlated best with an interaction term that included the planarity of the bifurcation and the LCx-LAD branch angle. Another study in 245 right coronary arteries correlated the shape of the coronary artery (C-shape vs sigma shape) to the presence of disease. Although multivariate analysis showed that C-shape was an independent predictor of significant coronary artery disease (95), the measure was not sensitive enough to be used as predictor (96).

Discussion

Since atherosclerotic plaques are observed at distinct locations in the vasculature, in particular around bifurcations, a link between local haemodynamics and the initiation and progression of plaques has been suggested. For instance, in the bulb region of a carotid artery bifurcation the local flow velocity distribution and thus the local shear stress environment is complex, but well defined. This is not to imply that haemodynamic factors are the sine qua non; additionally, systemic risk factors must also be recognised in the onset and progression of atherosclerosis. As shown in ►Figure 1, the interplay among haemodynamics, systemic risk factors and vascular biology may be visualised analogously to Virchow's triad. All factors go hand in hand towards vascular pathology. For instance, the endothelial response to shear stress is modulated by systemic risk factors, such as hypercholesterolaemia, influencing the endothelial function and thereby the susceptibility to atherosclerotic plaque formation (7). This synergistic effect of hypercholesterolaemia on shear stress induced plaque progression was elegantly shown in an atherosclerotic animal model of plaque progression (97) corroborating the interaction among the three different factors. The same risk factors are also responsible for the extent of plaque growth, as has been convincingly demonstrated in clinical studies reducing cholesterol levels and systemic inflammation by statin therapy (98) .

Surrogate markers of 'haemodynamic risk'

Present methods to assess endothelial shear stress directly *in vivo* suffer from limitations of imaging technology (44, 99). On the other hand, acquisition of helical patterns or certain geometric features of vascular segments are clinically feasible and may be considered as potential surrogate markers for atherosclerosis risk, by virtue of their influence on near-wall flow patterns (20, 21). ►Figure 3 shows an overview of the interplay between geometry on one hand and helical flow and the endothelial shear stress on the other, indicating the strength of associations reported by investigations of the carotid arteries. The possibility to screen risk from the bifurcation geometry or helical flow as promoters/surrogates of disturbed shear stress is attractive in terms of translation of biomechanical principles into clinical practice. However, a better understanding of the interaction of biomechanical risk factors, systemic factors and factors related to vascular biology are needed to fully capture the total risk, as visualised in ►Figure 1.

Coronary arteries vs carotid arteries

Geometric features dictate the local haemodynamic environment and thereby plaque initiation and progression, irrespective of the vascular bed. The geometric features the carotid and coronary bifurcations have in common, which influence low shear stress, is tortuosity (46, 69). At the level of the bifurcation, marked differences are present: a larger area ratio was clearly associated with low disturbed shear stress for the carotid (46), but not for coronary bifurcation (69) owing to the dominant influence of the carotid bulb, which is unique to the carotid bifurcation. Geometric features predominantly associated with plaque in the coronary arteries were planarity and large bifurcation angle. The carotid bifurcation, on the other hand, is largely planar (15), while the influence of bifurcation angle on haemodynamics is negated by the competing influences of area ratio and tortuosity (45).

Identical twins studies have underlined the 'haemodynamic hypothesis' by showing plaque at similar locations even in pairs with different coronary risk profiles (100). In twin pairs with similar anatomy the location of plaque was most often in concordance contrasting the twin pairs of which the anatomy was not in concordance (101). These observations highlight again the importance of geometry and thus haemodynamics in addition to genetic and systemic risk factors in the generation of plaques.

Finally, while the focus of this review paper was on wall shear stress and the haemodynamic hypothesis, it is worth making brief mention of mass transport, because it would appear that the transport of species (e.g. lipid-carrying macromolecules), their uptake into the arterial wall, as well as the adhesion of bioactive substances, can be strongly influenced by the fluid phase (102–104). These observations on the existence of a mechanism involving arterial wall lipid metabolism and shear-dependent blood-wall mass transport, paralleled by the acknowledgment that blood-wall transport occurs by different routes (103), have led to the formation of the 'mass transport hypothesis', which is thought to partially underlie or at least complement the haemodynamic hypothesis.

Conclusions

Disturbed haemodynamics, in particular low and oscillatory shear stress, is recognised as one of the most important determinants in plaque initiation and progression. In particular, arterial bifurcations can be markedly exposed to disturbed shear stress and thereby affected by local plaque formation, which reflects a complex interplay among the triad of haemodynamics, biological and systemic risk factors. Simply using geometrical factors or intravascular flow features might give a first indication on risk of plaque, but the interplay with biological and systemic risk factors should be taken into consideration.

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Conflicts of interest

None declared.

References

1. Ylä-Herttuala S, et al. Stabilisation of atherosclerotic plaques. Position paper of the European Society of Cardiology (ESC) Working Group on atherosclerosis and vascular biology. Thromb Haemost 2011; 106: 1–19.
2. Libby P, et al. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. Immunity 2013; 38: 1092–1104.
3. Van Vre EA, et al. Apoptotic Cell Death and Efferocytosis in Atherosclerosis. Arterioscler Thromb Vasc Biol 2012; 32: 887–893.
4. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circ Res 1990; 66: 1045–1066.
5. Eshtehardi P, et al. Association of coronary wall shear stress with atherosclerotic plaque burden, composition, and distribution in patients with coronary artery disease. J Am Heart Assoc 2012; 1: e002543.
6. Kwak BR, et al. Biomechanical factors in atherosclerosis: mechanisms and clinical implications. Eur Heart J 2014; 35: 3013–3020.
7. Malek AM, et al. Hemodynamic shear stress and its role in atherosclerosis. J Am Med Assoc 1999; 282: 2035–2042.
8. Glagov S, et al. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. Arch Pathol Lab Med 1988; 112: 1018–1031.
9. Zarins CK, et al. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localisation with flow velocity profiles and wall shear stress. Circ Res 1983; 53: 502–514.
10. Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis 1985; 5: 293–302.
11. Taylor CA, Steinman DA. Image-based modeling of blood flow and vessel wall dynamics: applications, methods and future directions: Sixth International Bio-Fluid Mechanics Symposium and Workshop, March 28–30, 2008 Pasadena, California. Ann Biomed Eng 2010; 38: 1188–1203.
12. Cibis M, et al. Wall shear stress calculations based on 3D cine phase contrast MRI and computational fluid dynamics: a comparison study in healthy carotid arteries. NMR Biomed 2014; 27: 826–834.
13. Friedman MH, et al. Arterial geometry affects hemodynamics. A potential risk factor for athersoclerosis. Atherosclerosis 1983; 46: 225–231.
14. Lee S-W, et al. Geometry of the carotid bifurcation predicts its exposure to disturbed flow. Stroke 2008; 39: 2341–2347.
15. Thomas JB, et al. Variation in the carotid bifurcation geometry of young versus older adults: implications for geometric risk of atherosclerosis. Stroke 2005; 36: 2450–2456.
16. Perktold K, Resch M. Numerical flow studies in human carotid artery bifurcations. J Biomed Eng 1990; 12: 111–123.
17. Perktold K, et al. Pulsatile non-Newtonian blood flow in three-dimensional carotid bifurcation models: a numerical study of flow phenomena under different bifurcation angles. J Biomed Eng 1991; 13: 507–515.
18. Bijari PB, et al. Carotid bifurcation geometry is an independent predictor of early wall thickening at the carotid bulb. Stroke 2014; 45: 473–478.
19. Caro CG, et al. Non-planar curvature and branching of arteries and non-planar-type flow. Proc R Soc Lond A 1996; 452: 185–197.
20. Morbiducci U, et al. Helical flow as fluid dynamic signature for atherogenesis in aortocoronary bypass. A numeric study. J Biomech 2007; 40: 519–534.
21. Gallo D, et al. Helical flow in carotid bifurcation as surrogate marker of exposure to disturbed shear. J Biomech 2012; 45: 2398–2404.
22. Félétou M, et al. Nitric oxide: Orchestrator of endothelium-dependent responses. Ann Med 2012; 44: 694–716.
23. Weber C, et al. The role of junctional adhesion molecules in vascular inflammation. Nat Rev Immunol 2007; 7: 467–477.
24. Zarbock A, Ley K. Mechanisms and consequences of neutrophil interaction with the endothelium. Am J Pathol 2008; 172: 1–7.
25. Ando J, Yamamoto K. Flow detection and calcium signalling in vascular endothelial cells. Cardiovasc Res 2013; 99: 260–268.
26. Boon RA, Horrevoets AJG. Key transcriptional regulators of the vasoprotective effects of shear stress. Hamostaseologie 2009; 29: 39–43.
27. Davies PF, et al. The atherosusceptible endothelium: Endothelial phenotypes in complex haemodynamic shear stress regions in vivo. Cardiovasc Res 2013; 99: 315–327.

28. Schober A, et al. MicroRNA-mediated mechanisms of the cellular stress response in atherosclerosis. Nat Rev Cardiol 2015; 12: 361–374.
29. Ylä-Herttuala S, et al. Stabilisation of atherosclerotic plaques: An update. Eur Heart J 2013; 34: 3251–3258.
30. Cheng C, et al. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. Circulation 2006; 113: 2744–2753.
31. Glagov S, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987; 316: 1371–1375.
32. Chatzizisis YS, et al. Prediction of the localisation of high-risk coronary atherosclerotic plaques on the basis of low endothelial shear stress: an intravascular ultrasound and histopathology natural history study. Circulation 2008; 117: 993–1002.
33. Dirksen MT, et al. Distribution of inflammatory cells in atherosclerotic plaques relates to the direction of flow. Circulation 1998; 98: 2000–2003.
34. Cicha I, et al. Carotid plaque vulnerability: A positive feedback between hemodynamic and biochemical mechanisms. Stroke 2011; 42: 3502–3510.
35. Slager CJ, et al. The role of shear stress in the destabilisation of vulnerable plaques and related therapeutic implications. Nat Clin Pract Cardiovasc Med 2005; 2: 456–464.
36. Death AK, et al. Nitroglycerin upregulates matrix metalloproteinase expression by human macrophages. J Am Coll Cardiol 2002; 39: 1943–1950.
37. Kenagy RD, et al. Increased plasmin and serine proteinase activity during flow-induced intimal atrophy in baboon PTFE grafts. Arterioscler Thromb Vasc Biol 2002; 22: 400–404.
38. Lijnen HR. Plasmin and matrix metalloproteinases in vascular remodeling. Thromb Haemost 2001; 86: 324–333.
39. Tang D, et al. Quantifying effects of plaque structure and material properties on stress distributions in human atherosclerotic plaques using 3D FSI models. J Biomech Eng 2005; 127: 1185–1194.
40. Tang D, et al. A negative correlation between human carotid atherosclerotic plaque progression and plaque wall stress: in vivo MRI-based 2D/3D FSI models. J Biomech 2008; 41: 727–736.
41. Tang D, et al. Image-based modeling for better understanding and assessment of atherosclerotic plaque progression and vulnerability: data, modeling, validation, uncertainty and predictions. J Biomech 2014; 47: 834–846.
42. Bressloff NW. Parametric geometry exploration of the human carotid artery bifurcation. J Biomech 2007; 40: 2483–2491.
43. Thomas JB, et al. On the influence of vessel planarity on local hemodynamics at the human carotid bifurcation. Biorheology 2002; 39: 443–448.
44. Markl M, et al. In vivo wall shear stress distribution in the carotid artery: effect of bifurcation geometry, internal carotid artery stenosis, and recanalisation therapy. Circ Cardiovasc Imaging 2010; 3: 647–655.
45. Zhang Q, et al. Use of factor analysis to characterize arterial geometry and predict hemodynamic risk: application to the human carotid bifurcation. J Biomech Eng 2010; 132: 114505.
46. Bijari PB, et al. Improved prediction of disturbed flow via hemodynamically-inspired geometric variables. J Biomech 2012; 45: 1632–1637.
47. Ku DN, Giddens DP. Pulsatile flow in a model carotid bifurcation. Arterioscleros 1983; 3: 31–39.
48. Goubergrits L, et al. Atherosclerosis and flow in carotid arteries with authentic geometries. Biorheology 2002; 39: 519–524.
49. Schulz UGR, Rothwell PM. Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4,627 carotid stenoses. Cerebrovasc Dis 2003; 15: 244–251.
50. Lovett JK, Rothwell PM. Site of carotid plaque ulceration in relation to direction of blood flow: an angiographic and pathological study. Cerebrovasc Dis 2003; 16: 369–375.
51. De Weert TT, et al. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. Stroke 2009; 40: 1334–1340.
52. Groen HC, et al. Plaque rupture in the carotid artery is localized at the high shear stress region: a case report. Stroke 2007; 38: 2379–2381.
53. Raso AM, et al. Geometry of aortoiliac bifurcation in healthy men and women as possible atherogenic risk factor. Panminerva Med 1981; 23: 33–37.
54. Harrison MJG, Marshall J. Does the geometry of the carotid bifurcation affect its predisposition to atheroma? Stroke 1983; 14: 117–118.
55. Spelde AG, et al. Pathological-anatomical study concerning the geometry and atherosclerosis of the carotid bifurcation. Eur J Vasc Surg 1990; 4: 345–348.
56. Fisher M, Fieman S. Geometric factors of the bifurcation in carotid atherogenesis. Stroke 1990; 21: 267–271.
57. Smedby O, et al. Two-dimensional tortuosity of the superficial femoral artery in early atherosclerosis. J Vasc Res 1993; 30: 181–191.
58. Smedby O. Geometric risk factors for atherosclerosis in the aortic bifurcation: a digitized angiography study. Ann Biomed Eng 1996; 24: 481–488.
59. Smedby O. Geometrical risk factors for atherosclerosis in the femoral artery: a longitudinal angiographic study. Ann Biomed Eng 1998; 26: 391–397.
60. Ravensbergen J, et al. Localizing role of hemodynamics in atherosclerosis in several human vertebrobasilar junction geometries. Arterioscler Thromb Vasc Biol 1998; 18: 708–716.
61. Schulz UG, Rothwell PM. Major Variation in Carotid Bifurcation Anatomy A Possible Risk Factor for Plaque Development? Stroke 2001; 32: 2522–2529.
62. Polak JF, et al. Segment-Specific Associations of Carotid Intima-Media Thickness With Cardiovascular Risk Factors: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Stroke 2010; 41; 9–15.
63. Sitzer M, et al. Internal Carotid Artery Angle of Origin. A Novel Risk Factor for Early Carotid Atherosclerosis. Stroke 2003; 34: 950–955.
64. Phan TG, et al. Carotid artery anatomy and geometry as risk factors for carotid atherosclerotic disease. Stroke 2012; 43: 1596–1601.
65. Gallo D, et al. An insight into the mechanistic role of the common carotid artery on the hemodynamics at the carotid bifurcation. Ann Biomed Eng 2015; 43: 68–81.
66. Morbiducci U, et al. Mechanistic insight into the physiological relevance of helical blood flow in the human aorta: an in vivo study. Biomech Model Mechanobiol 2011; 10: 339–355.
67. Frydrychowicz A, et al. Interdependencies of aortic arch secondary flow patterns, geometry, and age analysed by 4-dimensional phase contrast magnetic resonance imaging at 3 Tesla. Eur Radiol 2012; 22: 1122–1130.
68. Boucek RJ, et al. Clinical and Pathologic Features of Obstructive Disease in the Predominant Right and Left Coronary Circulations in Man. Circulation 1980; 62: 485–490.
69. Malvè M, et al. Tortuosity of Coronary Bifurcation as a Potential Local Risk Factor for Atherosclerosis: CFD Steady State Study Based on In Vivo Dynamic CT Measurements. Ann Biomed Eng 2015; 43: 82–93.
70. Chaichana T, et al. Computation of hemodynamics in the left coronary artery with variable angulations. J Biomech 2011; 44: 1869–1878.
71. Dong J, et al. Fluid-structure interaction analysis of the left coronary artery with variable angulation. Comput Methods Biomech Biomed Engin 2015; 18: 1500–1508.
72. Perktold K, Peter R. Numerical 3D-simulation of pulsatile wall shear stress in an arterial T-bifurcation model. J Biomed Eng 1990; 12: 2–12.
73. Frattolin J, et al. Numerical study of stenotic side branch hemodynamics in true bifurcation lesions. Comput Biol Med 2015; 57: 130–138.
74. Svindland A. The localisation of sudanophilic and fibrous plaques in the main left coronary bifurcation. Atherosclerosis 1983; 48: 139–145.
75. Kimura BJ, et al. Atheroma morphology and distribution in proximal left anterior descending coronary artery: In vivo observations. J Am Coll Cardiol 1996; 27: 825–831.
76. Badak O, et al. Characteristics of atherosclerotic plaque distribution in coronary artery bifurcations: an intravascular ultrasound analysis. Coron Artery Dis 2003; 14: 309–316.
77. Van der Giessen AG, et al. Plaque and shear stress distribution in human coronary bifurcations: a multislice computed tomography study. EuroIntervention 2009; 4: 654–661.
78. Gijsen FJH, et al. 3D reconstruction techniques of human coronary bifurcations for shear stress computations. J Biomech 2014; 47: 39–43.
79. Molony DS, et al. An assessment of intra-patient variability on observed relationships between wall shear stress and plaque progression in coronary arteries. Biomed Eng Online 2015; 14: 1–14.
80. Stone PH, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation 2012; 126: 172–181.
81. Corban MT, et al. Combination of plaque burden, wall shear stress, and plaque phenotype has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability. Atherosclerosis 2014; 232: 271–276.
82. Samady H, et al. Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. Circulation 2011; 124: 779–788.

83. Wentzel JJ, et al. In vivo assessment of the relationship between shear stress and necrotic core in early and advanced coronary artery disease. EuroIntervention 2013; 9: 989–995.
84. Wentzel JJ, et al. Extension of increased atherosclerotic wall thickness into high shear stress regions is associated with loss of compensatory remodeling. Circulation 2003; 108: 17–23.
85. Fukumoto Y, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008; 51: 645–650.
86. Gijsen F, et al. Shear stress and advanced atherosclerosis in human coronary arteries. J Biomech 2013; 46: 240–247.
87. Gijsen FJH, et al. Strain distribution over plaques in human coronary arteries relates to shear stress. Am J Physiol Heart Circ Physiol 2008; 295: H1608–1614.
88. Gijsen FJH, et al. High shear stress induces a strain increase in human coronary plaques over a 6-month period. EuroIntervention 2011; 7: 121–127.
89. Papadopoulou SL, et al. Assessment of atherosclerotic plaques at coronary bifurcations with multidetector computed tomography angiography and intravascular ultrasound-virtual histology. Eur Heart J Cardiovasc Imaging 2012; 13: 635–642.
90. Diletti R, et al. Assessment of coronary atherosclerosis progression and regression at bifurcations using combined IVUS and OCT. JACC Cardiovasc Imaging 2011; 4: 774–780.
91. Gonzalo N, et al. In Vivo Assessment of High-Risk Coronary Plaques at Bifurcations With Combined Intravascular Ultrasound and Optical Coherence Tomography. JACC Cardiovasc Imaging 2009; 2: 473–482.
92. García-García HM, et al. A comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary lesions: An in vivo assessment using intravascular ultrasound radiofrequency data analysis. EuroIntervention 2010; 6: 321–327.
93. Jia H, et al. Insights into the spatial distribution of lipid-rich plaques in relation to coronary artery bifurcations. Coron Artery Dis 2015; 26: 133–141.
94. Ding Z, et al. Influence of the geometry of the left main coronary artery bifurcation on the distribution of sudanophilia in the daughter vessels. Arterioscler Thromb Vasc Biol 1997; 17: 1356–1360.
95. Dvir D, et al. Degrees of severe stenoses in sigma-shaped versus C-shaped right coronary arteries. Am J Cardiol 2003; 92: 294–298.
96. Demirbag R, Yilmaz R. Effects of the shape of coronary arteries on the presence, extent, and severity of their disease. Heart Vessels 2005; 20: 224–229.
97. Koskinas KC, et al. Synergistic effect of local endothelial shear stress and systemic hypercholesterolemia on coronary atherosclerotic plaque progression and composition in pigs. Int J Cardiol 2013; 169: 394–401.
98. Goldstein JL, Brown MS. A Century of Cholesterol and Coronaries: From Plaques to Genes to Statins. Cell 2015; 161: 161–172.
99. Cibis M, et al. Wall shear stress calculations based on 3D cine phase contrast MRI and computational fluid dynamics: a comparison study in healthy carotid arteries. NMR Biomed 2014; 27: 826–834.
100. Gullu AU, et al. The comparison of angiographic lesions and clinical outcomes in identical twins. Interact Cardiovasc Thorac Surg 2007; 6: 575–576.
101. Nathoe HMW, et al. Angiographic findings in monozygotic twins with coronary artery disease. Am J Cardiol 2002; 89: 1006–1009.
102. Dull RO, Davies PF. Flow modulation of agonist (ATP)-response (Ca2+) coupling in vascular endothelial cells. Am J Physiol 1991; 261: H149–H154.
103. Tarbell JM. Mass transport in arteries and the localisation of atherosclerosis. Ann Rev Biomed Eng 2003; 5: 79–118.
104. Coppola G, Caro CG. Oxygen mass transfer in a model three-dimensional artery. J RS Interface 2008; 5: 1067–1075.