Basic science for the clinician

Biomechanical stress in coronary atherosclerosis: emerging insights from computational modelling

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Received 26 September 2015; revised 7 November 2015; accepted 27 November 2015; online publish-ahead-of-print 22 February 2016

Coronary plaque rupture is the most common cause of vessel thrombosis and acute coronary syndrome. The accurate early detection of plaques prone to rupture may allow prospective, preventative treatment; however, current diagnostic methods remain inadequate to detect these lesions. Established imaging features indicating vulnerability do not confer adequate specificity for symptomatic rupture. Similarly, even though experimental and computational studies have underscored the importance of endothelial shear stress in progressive atherosclerosis, the ability of shear stress to predict plaque progression remains incremental. This review examines recent advances in image-based computational modelling that have elucidated possible mechanisms of plaque progression and rupture, and potentially novel features of plaques most prone to symptomatic rupture. With further study and clinical validation, these markers and techniques may improve the specificity of future culprit plaque detection.

Keywords Atherosclerosis • Coronary artery disease • Shear stress • Computational modelling • Plaque rupture

Introduction

While a number of advances have helped improve our understanding of atherosclerosis, cardiovascular disease remains the most common cause of death and a leading cause of chronic disease worldwide.1 This is largely due to silent atherosclerotic plaque progression leading to sudden rupture, occlusive thrombosis, and acute coronary syndrome. The earlier identification and treatment of plaques prone to catastrophic rupture is therefore an ideal approach to decrease cardiovascular morbidity and mortality. The ability to reliably detect these lesions currently remains limited, but is likely to improve with advances in plaque characterization.

According to current evidence, atherosclerosis is a highly complex disease marked by cycles of progressive endothelial insult, arterial inflammation, altered haemodynamics, and vascular remodelling, leading to plaque formation, progression, and rupture. While Virchow postulated the role of blood flow and stagnation in vascular thrombosis over a century ago, the idea that haemodynamic forces influence atherogenesis was introduced nearly 50 years ago.2 At that time, Caro, Fitz-Gerald, and Schroter had several key insights regarding endothelial shear stress (ESS): (i) atheromas develop in areas of low ESS even before the appearance of gross changes; (ii) up to a certain threshold, high ESS seems to protect against atheroma formation; (iii) endothelial injury occurs beyond this high ESS threshold; (iv) the high ESS induced by exercise may fall into the atheroprotective range; (v) intimal accumulation of lipid and other atherogenic material may be related to ESS.2 Although some debate persisted about the precise roles of high and low ESS, the following decades were marked by insightful experiments supported by increasingly realistic computational fluid dynamic (CFD) methods.3–5 A large body of evidence now suggests that ESS is a key instigator of endothelial injury,6–9 explaining why plaques often localize to characteristic areas such as the outer wall of bifurcations and inner arterial curvatures.7 A deeper understanding of this relationship has facilitated the earlier identification of potentially high-risk plaques.8,9

As many plaques undergo progressive atherosclerotic changes, they become increasingly vulnerable to rupture.10,11 Many advanced plaques display morphological characteristics indicating their vulnerability: thin overlying fibrous caps, large lipid cores with necrotic features, and potentially signs of inflammation, neo-angiogenesis, and intra-plaque haemorrhage.11–13 These lesions, termed thin-cap fibroatheromas (TCFAs), are most often responsible for acute
coronary syndrome and can be identified by intravascular imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT). However, the fact remains that most TCFAUs do not seem to cause symptomatic rupture.10 This paradox is beginning to be unravelled with detailed investigation of the relationship between vascular tissue stress and acute plaque rupture. Several clinical studies utilizing computational analyses have suggested novel markers of vulnerability and present additional tools that may further improve the identification of high-risk lesions.14–20

In this review, we examine the role of biomechanical stress in plaque evolution and rupture, with emphasis on the contribution and implications of image-based computational modeling on the prospective identification of high-risk coronary lesions.

Biomechanical stresses and their computational analysis

Pulsatile blood flow generates mechanical stresses in vascular tissue that directly and indirectly modulate vessel biology. Decades of research have brought increasing awareness of these stresses and the role they play in atherosclerotic plaque physiology and pathology. Rapid advances in medical imaging and computational methods have also allowed increasingly realistic in vivo estimation of these forces and other clinically significant measures, providing fundamentally and clinically relevant insights into plaque evolution. For instance, the recent FDA approval and clinical implementation of fractional flow reserve derived from computed tomography to non-invasively detect physiologically significant coronary lesions illustrates the feasibility and potential impact of computational methods.21 Significant theoretical, practical, and regulatory barriers remain, but with further work patient-specific computational vascular stress analyses may be similarly poised to impact clinical practice.

Axial, circumferential, and shear stress

Broadly speaking, blood flow generates axial, circumferential, and shear stress in blood vessels that, in combination, contribute to the overall strain distribution within vascular tissue (Figure 1). Axial stress arises from longitudinal stretching of vessels exposed to cyclical blood flow and cardiac motion. Historically, axial stress has been difficult to measure experimentally in vivo, leading to relatively poor characterization of its contribution to atherosclerosis compared with shear and circumferential stress.22 Recent evidence suggests axial stress plays a role in vascular homeostasis and minimizing overall tissue stress in normal arteries.22,23 However, flow obstructions generate pressure gradients across lesions with a resulting increase in axial stress and overall plaque strain that may contribute to rupture.24–26 (Figure 1A).

Circumferential stress arises from hydrostatic pressure exerting outward radial force on vessels. Arteries expand, distend, and recoil with cyclical variation in blood pressure, thereby generating stress within the vessel wall. The distribution of this stress depends on the mechanical properties and layered arrangement of the vessel wall components.27,28 In healthy arteries, circumferential stress is evenly distributed around the vessel wall.29 In atherosclerotic arteries, considerable changes in the mechanical properties of underlying tissues result in heterogeneous stress distributions as strain is offloaded from weak regions to stronger ones15,30–32 (Figure 1B). As a result, plaque shoulders generally exhibit high strain and are most often the site of plaque rupture.14,15,33

Endothelial shear stress is a measure of tangential frictional force exerted by blood flow at the vessel wall and is proportional to fluid viscosity and velocity. Blood viscosity is often approximated as a constant related to haematocrit, but blood actually exhibits variable shear-dependent viscosity. The biological significance of shear-thinning and other complex rheological behaviours has not yet been elucidated, but may have clinical implications in coronary arteries subject to complicated flow patterns (discussed later). Similarly, blood velocity is directly proportional to flow and inversely proportional to vessel diameter as described by Poiseuille’s law. Due to pulsatile flow, dynamic variation in coronary perfusion, complex vessel geometry, and flow obstructions, blood velocity changes magnitude and direction (Figure 1C). These changes in fluid velocity can result in areas of abnormally high and low ESS in addition to turbulence and flow reversal. Early atherosclerotic plaques form in these regions as a result of flow-induced endothelial injury and arterial inflammation.6,7,34

Computational solid and fluid mechanics

Fundamentally, computational methods are based on the idea that tissue stresses induced by solid and fluid motion can be accurately described by physical principles and mathematical equations. Computational fluid dynamics involves reconstruction of a three-dimensional arterial model from medical imaging, specifying boundary conditions, and making certain simplifying assumptions regarding the nature of blood and vessel mechanics. Subsequent solution of the Navier-Stokes equations governing fluid mass and flow allows extrapolation of parameters such as fluid velocity, pressure, and ESS in patient-specific models. Similarly, finite element analysis (FEA) is based on the solution of partial differential equations that describe the mechanics of solid bodies. By prescribing tissue geometry and elastic mechanical properties, it is possible to map various internal tissue stresses. In principle, the combination of CFD and FEA methods allows the simultaneous analysis of solid and fluid domains, termed fluid—structure interaction (FSI) analysis. Such image-based computational analyses are becoming increasingly relevant and insightful given the variety of information made available by emerging coronary imaging and diagnostic modalities.

Shear stress and plaque progression

Low endothelial shear stress and early atheroma

Although several orders of magnitude smaller than circumferential stress, the vascular endothelium responds dynamically to alterations in shear stress. Mechano-transduction of ESS through endothelial cell transmembrane proteins subsequently affects intracellular enzyme
activity, gene transcription, protein and micro-RNA synthesis, and release of bioactive mediators. These processes regulate endothelial cell structure and function, influence the surrounding cellular environment, and shift the balance between inhibition and promotion of atherosclerotic processes (Figure 2).

In healthy arteries exposed to physiologic or high ESS (15–70 dynes/cm²), endothelial structure and integrity remain intact, cells exist in elongated fusiform arrangement parallel to the direction of flow, and there is little cell turnover. Physiologic ESS also causes expression of vasodilators, fibrinolytics, and antioxidants, in addition to reduced expression of leukocyte adhesion molecules, inflammatory mediators, vasoconstrictors, and paracrine growth factors. The result is a largely athero-protective molecular environment.

Upon exposure to low ESS (<10 dynes/cm²), endothelial cells become misaligned, cell–cell junctions are disrupted, and the endothelium becomes permeable to circulating lipids and inflammatory mediators. Through mechanotransduction, low ESS decreases production of vasodilators, fibrinolytics, and antioxidants. Conversely, low ESS also increases expression of cell adhesion molecules, growth factors, vasoconstrictors, oxidative species, proteolytic enzymes, and acute inflammatory mediators.

The resulting endothelial dysfunction and acute inflammation may establish self-sustaining injury between endothelial, inflammatory, and smooth muscle cells (SMCs). In the setting of systemic risk factors, the complex interplay of these processes results in chronic inflammation, extracellular tissue degradation, endothelial proliferation, and apoptosis; intimal lipid accumulation and oxidation; platelet aggregation and thrombosis; plaque neovascularization and intraplaque haemorrhage (Figure 3 A and B). Over time, these processes contribute to plaque growth, arterial remodelling, and further altered ESS distribution.

**Endothelial shear stress and vascular remodelling**

**Adaptive remodelling**

In normal vessels, arterial remodelling may be a compensatory mechanism to restore physiologic ESS by narrowing or enlarging the vessel diameter, respectively. Areas exposed to low ESS normally undergo fibroblast and vascular smooth muscle-mediated growth of fibrous tissue resulting in vessel narrowing, or constractive
remodelling, which may return ESS to physiologic levels.\(^7^4\) Alternatively, areas exposed to high ESS tend to undergo expansive remodelling in which controlled metalloproteinase and cathepsin-mediated breakdown of the internal elastic lamina facilitates outward vessel growth to enlarge the lumen and decrease ESS.\(^7^4\) These findings are corroborated by IVUS-based CFD studies showing that early non-obstructive lesions exposed to low ESS subsequently develop plaque progression characterized by outward vessel remodelling, preserved lumen radius, and an increase in ESS.\(^3\,^8\,^9\,^7^5\,^7^7\) In contrast, areas exposed to high ESS at baseline show lumen and vessel enlargement with reduction in plaque thickness and ESS.\(^1\,^2\,^4\,^6\,^7^5\,^7^7\)

**Pathologic remodelling**

Whereas healthy arteries undergo adaptive remodelling to restore physiologic ESS, atherosclerotic arteries exposed to low ESS may demonstrate uncontrolled inflammation and matrix degradation leading to concurrent vessel and plaque enlargement, further reducing low ESS and augmenting endothelial dysfunction (Figure 3A).\(^7^8\,^7^9\) This response may be an attempt to maintain the lumen during early plaque growth, but may also facilitate a vicious cycle of self-sustaining endothelial injury leading to progressive plaque enlargement, expansive remodelling, and progressively worsening flow dynamics. Once the limit of expansive remodelling is reached, however, further plaque growth encroaches into the lumen. This results in increased ESS over the proximal lesion and persistently low ESS distally, which may coincide with the development of vulnerable features such as necrotic lipid core and thin fibrous caps.\(^4\,^8^0\)

**High endothelial shear stress and advanced atheroma**

Whereas higher ESS values are generally considered athero-protective in healthy arteries, in the setting of an obstructive plaque these same processes may promote further vulnerable changes leading to TCFA morphology and plaque destabilization."
Figure 3  (A) Arterial bifurcations are marked by well-defined flow disturbances including low endothelial shear stress at the outer walls and high endothelial shear stress at the carina (inset; red and blue shading of endothelial cells in main figure). Low endothelial shear stress induces endothelial dysfunction including production of inflammatory cell adhesion molecules, cytokines, oxidative species, increased lipid uptake, endothelial permeability, and blood stagnation (blue shaded boxes). These processes result in chronic arterial inflammation, lipid accumulation and oxidation, intimal proliferation and apoptosis, and extracellular matrix and internal elastic lamina degradation, which contribute to the development and progression of lipid plaques, expansive arterial remodeling, and persistent endothelial shear stress disturbances. Due to expansive arterial remodeling, early atheroma may not be accompanied by luminal obstruction (ESS, endothelial shear stress). (B) Advanced atheromas often cause luminal obstruction with subsequent alteration in endothelial shear stress distribution over the plaque (indicated by red and blue shading of endothelial cells). Proximal plaque regions exposed to high endothelial shear stress undergo smooth muscle cell apoptosis, macrophage activation, and increased activity of matrix-degrading MMPs leading to fibrous cap and extracellular matrix degradation, plaque and fibrous cap calcification, endothelial disruption and platelet activation (red-shaded boxes). Distal segments of advanced plaques are exposed to flow stagnation and low endothelial shear stress, which may increase risk for thrombosis in addition to progressive atherosclerotic changes. As a result, advanced plaques often demonstrate features associated with high risk of rupture including thin fibrous caps, large necrotic lipid core, inflammation, neo-angiogenesis, intraplaque hemorrhage, and endothelial disruption with or without thrombosis (ESS, endothelial shear stress; SMC, smooth muscle cell; MMP, metalloproteinase).
show that higher strain regions are exposed to high ESS at the proximal and lateral plaque shoulders, and that prolonged exposure to high ESS results in progressive rise in strain. Other IVUS-based CFD studies demonstrate that plaques exposed to high ESS undergo regression of fibrous and fibrofatty components and harbour more necrotic core, dense calcium, and other indicators of vulnerability.

**Endothelial shear stress and detection of future culprit lesions**

The landmark Providing Regional Observations to Study Predictors of Events in Coronary Tree (PROSPECT) study demonstrated that although most adverse clinical outcomes arise from TCFAs, only a small fraction (4.9%) of TCFAs progress to cause clinical events over 3 years. In addition to IVUS-detected TCFA morphology, both large plaque burden (>70%) and small minimal lumen area (<4 mm²) are also independent predictors of progressive lesions; however, even in combination these features do not confer high specificity in detecting future culprit lesions. Thus, while these morphological characteristics are key features of vulnerable plaques, additional markers are needed to identify plaques progressing to clinical relevance.

Given the relationship between ESS and plaque progression, the predictive capacity of local ESS distribution has been examined as an additional clinically relevant marker of high-risk plaque. The Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics (PREDICTION) study, an IVUS-based CFD analysis of 506 Japanese patients, showed that a large plaque burden and low ESS at baseline were independently associated with an interval increase in plaque burden, a decrease in lumen area, and could predict lesions progressing to require percutaneous clinical intervention during the 6- to 10-month follow-up period. Importantly, most of these interventions (n = 39/53, 74%) occurred in asymptomatic patients treated for significant angiographic progression of stenosis during follow-up vascular profiling; therefore, the precise predictive capacity of ESS to detect lesions progressing to clinical events remains unclear.

Whereas PREDICTION demonstrated that low ESS may incrementally improve detection of plaques that progress angiographically, CFD analyses of ruptured plaques demonstrate the potential role of high ESS in future culprit plaque detection. An IVUS-based CFD study of ruptured culprit plaques in 20 patients with acute coronary syndrome demonstrated a strong correlation between focal elevation in ESS and the site of plaque rupture (κ = 0.79). A more recent OCT-based CFD analysis demonstrated similar results. Although spatial co-localization is not mechanistic evidence of causality, these studies suggest that identifying focal areas of high ESS over atheroma harbouring other advanced morphologic
features may improve detection of plaques prior to symptomatic rupture. Additional large, prospective, image-based CFD studies evaluating the morphology, composition, and natural history of atheroma will be critical.

Despite the intriguing and often convincing evidence correlating ESS with progressive atherosclerosis, the fact remains that ESS as it is currently determined does not contribute high enough specificity to accurately predict clinically significant progression or vulnerable transformation of individual plaques. Notwithstanding a possibly fundamental limitation of ESS as a predictive marker, this may be due to a combination of suboptimal imaging, limited 3D reconstruction techniques, and necessary assumptions in CFD methodology.

**Ongoing advances in image-based computational fluid dynamic**

**Imaging and three-dimensional reconstruction**

Although IVUS and angiography-based CFD has provided considerable insight into ESS and atherosclerosis, these modalities lack adequate resolution to image fine details of lumen and plaque morphology. Given the high resolution of OCT (10–15 μm), the development of OCT-angiography fusion-based CFD may provide further insight into the relationship between ESS and plaque evolution. Optical coherence tomography-based three-dimensional reconstruction of coronary arteries and atherosclerosis progression can be further enhanced through the integration of OCT and CFD.
reconstructions have recently been validated against IVUS and quan-
titative coronary angiography-based models for ESS calculations. Additional methodological improvements correcting for length 
and rotational mismatch between angiography and OCT images 
have allowed incorporation of side branches reconstructed from 
quantitative coronary angiography to generate patient-specific cor-
onary trees suitable for CFD analysis (Figure 4).

Complementary intravascular techniques such as near infrared 
spectroscopy (NIRS) have also significantly broadened the spec-
trum of information available on plaque composition. Although 
NIRS cannot be used directly for image-based CFD, the informa-
tion it provides can be combined with invasive and non-invasive 
imaging to reconstruct 3D computational models suitable for CFD analysis. For instance, a hybrid NIRS-IVUS and multislice 
CT-based reconstruction has been used to map ESS in an in vivo human coronary artery, illustrating the potential of hybrid and 
multi-modality imaging to serve as the basis for future CFD and 
FEA analyses.

Other modelling strategies include reconstruction of longer cor-
onary segments with multiple bifurcations to better understand the 
role of downstream lesions and side branch geometry on upstream 
and main branch flow. Investigators from our group have recently 
examined ESS distribution in a population-based phantom model 
of three successive bifurcation lesions (Figure 5). This work has 
implicated downstream lesions in generating significant flow recircu-
lation and potentiating exposure to low ESS in upstream regions, a 
potentially pathologic flow pattern that would not be detected by 
CFD simulations of solitary lesions or bifurcations. Such modelling 
of multiple successive lesions may improve the accuracy and speci-
cificity of ESS to detect high-risk plaques.

**Computational fluid dynamic methodology**

Computational fluid dynamic simulations have become more realis-
tic due to advances in methodology afforded by continued increases 
in computational power. Although pulsatile flow simulations utilizing 
patient-specific reconstructions and boundary conditions are 
already routine, most CFD simulations still assume rigid, static 
vessels. Given natural vessel elasticity and cardiac motion, however, 
the effects and relevance of arterial compliance, vessel bending, 
and cardiac contraction are also being actively investigated using 
FEA and FSI methods. Other ongoing improvements are likely 
to include techniques to measure and incorporate additional
patient-specific boundary conditions such as microvascular resistance and collateral flow, and improved understanding and modelling of whole blood rheology.

More rigorous interpretation of CFD data generated through existing methods may be another way to improve the predictive capacity of computational analyses. For instance, techniques such as cross-sectional sector analysis may significantly enhance the spatial resolution of ESS distribution in regions of complex flow. Another alternative is the use of complementary haemodynamic parameters such as oscillatory shear index, relative residence time, wall shear stress gradient, stress phase angle, and LDL accumulation algorithms. These measures have also shown early potential in their predictive capacity, but their clinical applicability and relevance remain experimentally unconfirmed.

As a modelling technique, CFD also relies on simplifying assumptions such as specifying blood as a Newtonian fluid with constant viscosity. Due to its solid and liquid phases, however, blood exhibits non-Newtonian properties such as shear-thinning, the apparent thinning of blood at high shear rates. While the Newtonian assumption is generally acceptable in healthy segments of larger arteries, it may not be as accurate in the setting of complex flow patterns arising near diseased bifurcations and distal to stenoses. A hypothesis-generating CFD simulation comparing the Newtonian and non-Newtonian models of blood rheology demonstrates similarity in the overall distribution of flow disturbances between the two models; however, pockets of flow recirculation are more focused in the non-Newtonian model (Figure 6). While this model requires further computational and clinical validation, these observations have been reflected by previous studies. The clinical relevance and necessity of modelling non-Newtonian behaviour remain debated, but this preliminary work suggests that incorporating shear-thinning behaviour in some circumstances may improve the specificity of ESS. Of note, this model may also be relevant in the study of platelet activation and thrombosis, the mechanisms of which rely on the formation of a shear-dependent plasma-rich cell-free layer near the arterial wall as a result of non-Newtonian rheology.

Even with inevitable improvements in imaging and CFD methods, given the complexity of atherosclerosis it is possible that ESS has a fundamentally limited capacity to specifically predict future culprit lesions. Another approach to elucidate new markers of future culprit lesions has been to examine the mechanisms of plaque rupture in order to identify features unique to such plaques.
Tissue stress and plaque rupture

Once a plaque has developed vulnerable features due to a combination of systemic factors and local haemodynamics, the chance of cap rupture hinges on the balance between disruptive mechanical forces and plaque stability.\(^\text{14,15,89,114}\) Stability of the plaque, its ultimate tensile strength, depends on the widely varying biomechanical properties of its component tissues: the fibrous cap, lipid core, cellular components, calcifications, and layers of the vessel wall.\(^\text{15,28,29,32,114,115}\) (Figure 7). Great differences in the material properties of adjacent tissues generate stress concentrations, or weak points, within the atherosclerotic plaque and vessel wall. Disruptive forces may arise from an acute rise in blood pressure, which elevates both shear stress and circumferential strain, but may also exacerbate axial plaque deformation induced by the increased pressure gradient across a stenosis.\(^\text{25,26,116}\) The overall average estimated plaque rupture threshold is \(\approx 300\) kPa, but the actual value associated with rupture may be considerably higher.\(^\text{15}\)

In short, the precise site and circumstance of plaque rupture may be defined by where and when the heterogeneous distribution of tensile strength is overcome by the heterogeneous distribution of haemodynamic forces within the vessel over the cardiac cycle. The intuitive nature of this concept belies the actual complexity of plaque rupture in vivo, as illustrated by several observations. First, not all ruptures are acutely symptomatic. In fact, asymptomatic plaque rupture and fibrotic healing appear to be a relatively common occurrence contributing to silent plaque progression.\(^\text{33,117,118}\) Similarly, although TCFAs are most commonly responsible for symptomatic plaque rupture, most TCFAs do not lead to symptomatic rupture.\(^\text{10}\) Morphologic characteristics such as thin fibrous caps, large lipid cores, plaque burden, remodelling, and thrombus are associated with symptomatic plaque rupture\(^\text{117}\) but these late features cannot completely explain the incomplete penetration of symptomatic rupture in TCFAs. Second, plaque rupture occurring at rest localizes to the estimated site of maximum tissue stress only \(\approx 60\%\) of the time\(^\text{15}\) and most often correlates with rupture at the proximal plaque shoulder.\(^\text{14,33,80,119}\) That nearly 40\% of plaque rupture at rest occurs in midcap regions of high but sub-maximal stress implies tensile strength is not homogeneously distributed through the fibrous cap. Third, physical exertion tends to shift the plaque rupture site from the shoulder to the midcap. Approximately 75\% of exertion-related plaque rupture is characterized by midcap rupture, where shear stress is predicted to be highest.\(^\text{119}\) This observation has at least two implications: (i) the relative contribution of

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**Figure 7** Virtual histology- intravascular ultrasound demonstrates lesions consistent with thin-cap fibroatheroma in two different patients (A and C). Finite element analysis demonstrates that these two identically classified plaques manifest considerable differences in plaque stress (B and D), suggesting that these patients may have different risk for plaque rupture (from Teng et al.\(^\text{20}\)).
shear and circumferential stress to plaque rupture changes with exertion such that high ESS may become the predominant destabilizing force; (ii) the shoulder and midcap regions may have different susceptibility to shear and circumferential stress due to underlying tissue heterogeneity. These observations confirm that additional factors must account for the wide variety in presentation and morphology of plaque rupture. The elucidation of these factors may identify novel markers of plaque vulnerability, presenting another possible approach to earlier and more specific detection of future culprit lesions.

**Novel markers of plaque vulnerability**

**Microcalcification**

Microcalcifications as small as 1 μm are apparent in histologic specimens of even early atheroma, becoming larger and more numerous as disease progresses. Recent computational FEA studies based on ex vivo micro-computed tomography demonstrate that fibrous cap microcalcifications between 5 and 65 μm can amplify plaque tensile stress by up to 5-fold depending on their clustering, spatial orientation, degree of curvature, and length/diameter aspect ratio. Further analysis suggests that such microcalcifications may act as a nidus for plaque rupture initiation. These ex vivo studies represent an important step forward in understanding the mechanics of plaque rupture, but accurate in vivo imaging and computational studies will be necessary to first make a definitive link between microcalcifications and plaque rupture, and then to detect microcalcifications in a clinical setting. Currently, clinically available imaging modalities cannot reliably identify microcalcifications < 65 μm, but two techniques in development have demonstrated potential.

Micro-OCT, an invasive modality with a resolution of 1–2 μm, has been able to image both fibrous cap microcalcifications and cholesterol crystals. This technology is currently limited to ex vivo application but its further development may lead to in vivo imaging of individual microcalcifications. Another emerging technique is positron emission tomography and X-ray computed tomography (PET-CT) utilizing 18F-sodium fluoride (18F-NaF) tracer. Early evidence suggests this non-invasive modality may be able to identify areas of active vascular microcalcification with high specificity. Larger prospective studies will be critical in determining the clinical significance and role of 18F-NaF PET-CT in early and specific detection of vulnerable plaques.

**Cholesterol crystallization**

As a primary component of lipid-rich plaques, free cholesterol may reach concentrations high enough to crystallize. In vitro and postmortem histopathologic studies demonstrate an association between cholesterol crystals and inflammation, puncture of fibrous membranes, increased plaque size, disruption, and thrombus and coronary plaque rupture. While recent in vivo studies have associated cholesterol crystals with obstructive coronary lesions and other advanced morphologic features in patients with stable coronary disease, cholesterol crystals have not been causally linked to clinical events. Serial OCT-based CFD and FSI studies may be used to examine whether cholesterol crystallization within the intact fibrous cap contributes to increased ESS, intra-plaque and fibrous cap stress, and rupture in a process that may be analogous to the mechanism whereby acute intra-plaque hemorrhage is proposed to precipitate rupture.

**Axial plaque deformation**

The increased shear and circumferential tissue stress that accompany a rise in blood pressure are most commonly thought to trigger disruption of vulnerable plaques. However, fluid dynamic principles suggest axial plaque deformation as another potential source of acute strain. As described by the Bernoulli principle, a flow obstruction generates a negative pressure gradient that increases with higher proximal pressure and worsening stenosis. Large negative pressures distally may lead to plaque deformation and increased axial tensile stress. Plaque deformation has been observed by ultrasound in symptomatic carotid plaques and has been previously suggested as a contributor to coronary plaque rupture, but it remains unclear whether axial deformation occurs in non-obstructive and asymptomatic coronary plaques to be a detectable, early, and clinically relevant marker of future vulnerable plaques.

**Plaque geometry**

Lesion geometry also influences ESS distribution and the pressure gradient across a stenosis. Steep outlet geometry, for instance, is predicted to create a larger zone of distal flow recirculation, increasing both distal exposure to low ESS and the negative pressure gradient across the lesion compared with a shallow outlet geometry. In theory, steep outlet geometry may increase proximal tissue stress and the risk of fibrous cap disruption. A previous study has demonstrated geometric features such as plaque symmetry and steep outflow angle measured by quantitative coronary angiography are independently associated with risk for acute myocardial infarction within 12 months. A combination of stenosis symmetry index and maximal outflow angle >68% and 27°, respectively, identify intermediate lesions (40–70% diameter of stenosis) that become culprit lesions within 3 years with a sensitivity, specificity, and negative predictive values of 33, 85, 49, and 76%, respectively.

The mechanism for this observation remains unclear, but it may be related to multi-faceted exacerbation of hemodynamic disturbances and tissue stresses in the setting of propensity for thrombosis. Given the availability of high-resolution intracoronary imaging and computational methods, plaque geometry deserves reconsideration. If corroborated, plaque geometric features may add to the specificity of detecting vulnerable plaques that will become clinically relevant.

**Limitations of computational modelling**

Computational modelling of vascular shear and tissue stress in the research setting has undoubtedly advanced our understanding of atherosclerosis, but large long-term prospective studies will be necessary to establish prognostic relevance, clinical benefit, practicality, and cost-effectiveness. Several hurdles remain if these methods are to impact the clinical realm.

First, at the current stage computational modelling is not a trivial point-and-click endeavour. Accurate modelling requires the expertise of trained engineers to reconstruct models from medical imaging, run theoretically validated simulations, extract and present the clinically relevant data. Although the development of
sophisticated automated workflows is expected to improve the accessibility of these methods in the research setting, considerable advances will be needed before routine clinical implementation. Second, computational modelling is currently hindered by processing and computational times that often preclude clinically actionable real-time information, but this appears to be changing with continued increases in computational power and availability. The study of Kelly-Arnold et al. for instance, is particularly notable in that it required 1 h of computational time. These two limitations relate to the third: although developments in computational methodology will continue to improve the realism of simulations as previously discussed, the incremental utility of these advances must be carefully weighed against computational expense. Critically, does increased complexity improve the prognostic accuracy and clinical relevance of modelling, or does it unrealistically increase the computing power, time, and expertise required? An optimal balance must be maintained to achieve clinical applicability of computational methods. Fourth, perhaps the greatest limitation of computational modelling to detect future culprit lesions is its current reliance on invasive imaging. Despite significantly superior resolution, invasive imaging carries procedural risk and economic cost. Additionally, invasive imaging is only applicable to patients undergoing angiography for highly suspected or known coronary disease—at best, secondary prevention. Although non-invasive coronary CT-based CFD is already used for non-invasive measurement of FFR, the ability of coronary CT, F-NaF PET-CT, and other non-invasive modalities to detect early markers of future culprit lesions remains unclear. Improved non-invasive plaque imaging and computational characterization will be necessary for truly pre-emptive detection and primary prevention of clinically significant vulnerable plaque rupture.

Conclusions

Along with experimental and clinical studies, advances in computational methods and coronary imaging have contributed to a deeper understanding of plaque initiation, evolution, and rupture. While several sensitive morphologic and haemodynamic characteristics of vulnerable plaques have been identified, these features remain non-specific for lesions progressing to clinical relevance. Novel markers of plaque vulnerability will be necessary to prospectively identify those patients at highest risk for cardiovascular morbidity and mortality. High-resolution image-based computational stress analyses will likely play a significant role in identifying both currently known and novel markers, thereby improving detection of future culprit lesions.

Acknowledgements

The authors acknowledge Dr Eric Poon and Prof Andrew Ooi for their assistance with the computational simulations presented in this review, and Mr Darrel Yee for assistance with figures.

Funding

This work has been partially supported by the Australian Research Council through ARC Linkage Project LP120100233. This research was also supported by the Victorian Life Sciences Computation Initiative (VLSCI grant number VR0210) on its Peak Computing Facility at the University of Melbourne, an initiative of the Victorian Government, Australia.

Conflict of interest: none declared.

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