Physiological predictors of acute coronary syndromes: emerging insights from the plaque to the vulnerable patient

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Word Count: 3841

Acknowledgement - Research support from the British Heart Foundation RE-13-5-30177 to CB and TF.

Abstract

In this review, we explore the evolving evidence linking physiological assessment of coronary artery disease with plaque progression and vulnerability. Reducing clinical events including acute coronary syndromes (ACS) remains the ultimate goal for diagnostic tests and we highlight evidence supporting their use as predictors of patients at risk of adverse clinical events. Historical and contemporary studies support synergy between lesion severity, ischemia, plaque vulnerability and patient prognosis. Ischemia contributes to clinical events through association with plaque burden, however we review the emerging concept that it signifies disturbed lesion hemodynamics with a role in atherothrombosis. Biomechanical pathophysiological forces including endothelial shear stress – the frictional force generated by blood flow on the vessel wall – are increasingly linked with atherogenesis, vulnerable plaque morphology in addition to platelet and leucocyte activation. We conclude by transitioning from the model of the vulnerable plaque to the concept of the 'vulnerable patient' looking more broadly at physiological contributors to Virchow's triad underpinning ACS.

Key Words

Coronary physiology, endothelial shear stress, plaque vulnerability, acute coronary syndromes, mechanisms of atherosclerosis

Abbreviations

ACS – Acute coronary syndrome
APS – Axial plaque stress
AMI – acute myocardial infarction
CFD – Computational fluid dynamics
CCTA - coronary computed tomography angiography
DS – diameter stenosis
ESS – Endothelial shear stress
FFR – Fractional flow reserve
MACE – Major adverse cardiac event
TCFA - Thin-cap fibroatheroma

Introduction

The fractional flow reserve (FFR) reflects the extent to which maximal myocardial flow is decreased due to the presence of an epicardial narrowing.(1,2) Revascularization decisions based on FFR improve prognosis in patients with coronary artery disease.(3,4) Moving beyond flow-limitation, the anatomical and physiological characteristics of a plaque implicate a role for physiological factors and biomechanical forces in the pathophysiology of plaque rupture.(5) Endothelial shear stress – the frictional force generated by blood flow on the vessel wall – is increasingly linked with atherogenesis and plaque vulnerability in addition to platelet and leucocyte activation.(6,7) While coronary physiologic indices such as FFR have been proposed for interrogation of the ischemic potential of stable coronary stenoses, lesion hemodynamics are associated with atherosclerotic plaque biology and vulnerability.(8)

Coronary physiologic data may be integrated with anatomical information from coronary angiography and intravascular imaging to provide novel insights into lesion pathobiology with potential to better inform the treatment of coronary disease. In this review, we will explore the evolving evidence linking physiological assessment of coronary artery disease with plaque progression and vulnerability.

1 - Ischemia based on anatomic evaluation (invasive coronary angiography)

Coronary angiography for detecting plaque and assessing vulnerability

Luminal changes demonstrable on coronary angiography have traditionally been used to determine whether a coronary stenosis is of hemodynamic significance i.e. associated with myocardial ischemia. However, x-ray angiography is merely a 'luminogram' and estimating physiological significance from diameter stenosis (DS) is fraught with many pitfalls: the ratio of the minimum luminal diameter to the adjacent normal segment ignores the facts that atherosclerosis is a diffuse disease and angiography alone is often unable to distinguish between normal and diseased segments.(9) The Glagov phenomenon of positive vessel remodeling may obfuscate plaque within the vessel wall without causing lumen encroachment. Histopathological studies show that luminal narrowing typically occurs late after the atheroma expands to around 45% plaque burden by cross-sectional area (the limit of external elastic media expansion).(10) Despite advances in quantitative coronary angiography (QCA) techniques, there are well recognized limitations of angiography in determining the hemodynamic significance of intermediate coronary lesions (40-70% DS).(11)

The relationship between lesion severity and vulnerability

Only a minority of early atherosclerotic plaques progress to high-risk thin-cap fibroatheroma (TCFA) which are thought to be the most common precursors to ruptured plaques.(12) Non-obstructive plaques are more prevalent than obstructive plaques, however the absolute risk of plaque rupture is higher with an obstructive lesion.(8,13) Contemporary angiographic studies support that at the

time of myocardial infarction the underlying lesion on angiography is usually severely stenotic (Mean DS 66+/-12%).(14) Post mortem data confirms the majority of lesions causing fatal infarction are obstructive when plaque burden is analyzed by histopathological cross-sectional area: more than 75% stenosis is seen in 70% of plaque ruptures.(15) It is likely that rapid, though usually asymptomatic progression and resultant stenosis/thrombosis occurs in the days-to-weeks preceding AMI such that acute total vessel occlusion typically develops at the site of an obstructive narrowing.

Studies of non-invasive angiography using CCTA strongly support that the larger plaque size associates with lesion vulnerability.(16) Other high risk atherosclerotic plaque features on CCTA include positive vessel remodeling, low-attenuation plaques, 'napkin-ring' sign, and spotty calcification (17,18).

The PROSPECT study of the natural history of atherosclerosis using intravascular ultrasound (IVUS) is the single most important contemporary evidence and supports the notion that events are linked with lesion severity. Plaque burden ≥70% was the strongest predictor of future events (hazard ratio [HR]: 5.03; $p < 0.001$). Minimal luminal area (MLA) was also an important independent predictor.(13) Lesions with plaque burden ≥70% had event rates of almost 10% over a median follow up of 3.4 years. These may not always appear obstructive on conventional angiography in keeping with the Glagov phenomenon and the accepted limitations of angiography.(10) There was not a single event arising from a coronary artery segment with <40% plaque burden. Analysis of non-culprit lesions in PROSPECT that were responsible for future MACE showed that the majority of these plaques were non-obstructive on

baseline angiography (mean diameter stenosis (DS), 32.3±20.6%), but later at the subsequent event the angiographic severity in this subgroup had progressed to a mean DS of 65%. Importantly, the dominant driver of these events was progression of angina; the more robust clinical end-point of AMI in a non-culprit vessel occurred in less than 1% of patients. Taken together, the most likely model of vulnerable plaques is that of step-wise accelerated progression with subclinical plaque ruptures and increasing lumen encroachment, with a continuum of both obstructive and non-obstructive plaques underlying ACS.(19)

2 - Ischemia based on functional evaluation

The adverse prognostic impact of ischemia has been well established using various imaging modalities for non-invasive functional assessment. Myocardial ischemia identified on single-photon emission computed tomography (SPECT) is strongly predictive of major adverse cardiac events (MACE) in both symptomatic and asymptomatic individuals.(20,21) Comprehensive follow up data from almost 70,000 myocardial perfusion scans highlights the high rates of MACE with moderate to high risk ischemia on SPECT compared with low risk – up to 8.5% per annum versus 0.6%.(22) Studies using stress perfusion cardiac magnetic resonance (CMR) offer additional insights owing to superior spatial resolution and enhanced classification of inducible ischemia and myocardial scar. Out of 1,152 patients with angina followed up after stress perfusion CMR, those with inducible ischemia suffered MACE at 3.9%/year compared with only 1% in those with negative scans. On multivariate analysis, ischemia was the strongest independent predictor of cardiac death, nonfatal myocardial infarction, and stroke at mean follow up of 4.2 years (HR 3.21, 95% CI 2.06–5.00;

P<0.0001).(23) Furthermore recent CMR data suggests the presence of an 'ischemic threshold' whereby a burden of ≥1.5 ischemic segments was independently associated with nearly 9-fold increased risk of cardiac death, MI, or late coronary revascularization during a mean follow-up of 2.5 years.(24) Importantly, even when left ventricular function and myocardial scar burden were accounted for, this 'ischemic threshold' remained the strongest independent predictor of 'hard' clinical end-points - cardiac death and MI.

Ischemia may be a surrogate marker for anatomical plaque burden – indeed the COURAGE trial highlighted the intuitive interaction between ischemia on SPECT and anatomical disease burden on baseline angiography (p=0.03). Taken together, the COURAGE data showed anatomic disease burden to be a more consistent predictor of events compared with ischemia.(25),(26) Importantly, this study overlooked the fact that the degree of ischemia was determined before treatment. The influence of ischemia on outcome should be at least partly annulled following initiation of treatments aimed at alleviating its existence - thus it is unsurprising that plaque burden was more predictive of events. The COURAGE nuclear substudy did not show that ischemia was associated with risk of future events, however it was not powered to perform this non pre-specified analysis and may have been affected by selection bias.(27) Other contemporary cohorts have found ischemia on SPECT to be the strongest predictor of events, providing complementary additional information to the anatomical disease burden assessed by coronary artery calcium score.(28) Amongst patients with previous revascularization, the residual ischemic burden is the strongest independent predictor of future events, consistently identifying high-risk patients in groups with similar degrees of anatomical plaque burden.(29,30)

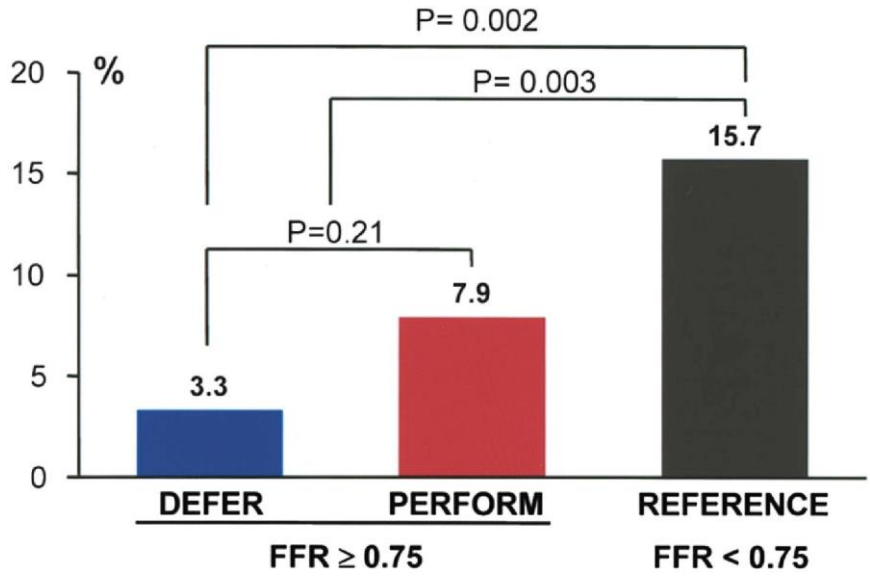
Lessons from FAME – is FFR a predictor of lesion vulnerability?

The FAME-II study (FFR versus Angiography for Multivessel Evaluation II) showed that patients with functionally significant lesions (FFR≤0.80) had superior outcomes with PCI and optimal medical therapy compared with optimal medical therapy alone.(3) Critics argue that urgent revascularizations were to be expected in this trial given that both patients and physicians were potentially aware of the significant lesions that were not stented. This may have lowered the threshold for urgent revascularization in patients with FFR-positive stenosis in the medical therapy group. Besides the fact that this phenomenon did not happen in the registry patients (also aware of the presence of untreated lesions), half of the urgent revascularizations occurred in the context of positive biomarkers or new ECG changes, while 80% occurred in patients with these findings or rest angina. A blinded and independent clinical event committee adjudicated all these events. In addition, it is very likely that the large number of unplanned revascularizations in patients randomized to medical therapy actually limited the number of "hard end-points" (death or myocardial infarctions). The two-year follow up data showed that after excluding the potentially more benign peri-procedural myocardial infarctions, the incidence of death or myocardial infarction was lower in the PCI group than in the medical-therapy group (4.6% vs. 8.0%, p=0.04).(3) There was a significantly lower incidence of revascularization procedures triggered by ECG changes or MI in the PCI group than in the medical-therapy group (3.4% versus 7.0%, p=0.01).

Equally, FAME and now 15-year follow-up data from the DEFER study highlight the negative predictive value of FFR: non-ischemic stenosis have an excellent prognosis on medical therapy with <1% annualized incidence of

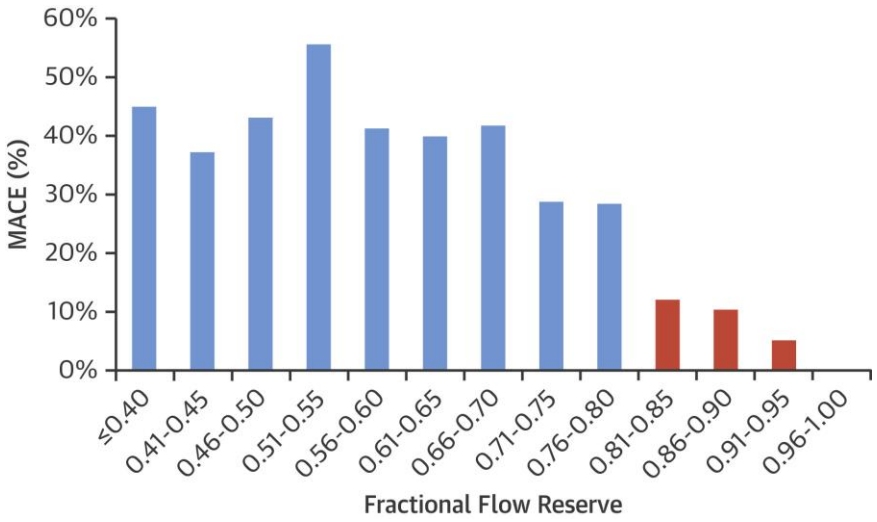
MI.(31) The study also reinforces the known adverse prognostic implications of ischemia: lower FFR values are associated with over double the rates of death/MI (Figure 1).(32)

Figure 1 - Adverse prognostic implications of ischemia - Cardiac death and acute myocardial infarction rate in the 3 groups of the DEFER study after a follow-up of 5 years. (Reprinted from Pijls et al(32) with permission of the publisher. Copyright © 2007, Elsevier).



Moreover, the outcome in the FAME 2 registry group (FFR>0.8) at two years was identical to that observed in the PCI group. Further comprehensive evidence for the relationship between physiological lesion severity measured by the FFR and clinical outcomes was demonstrated in a large meta-analysis.(33) Johnson et al used study-level and raw patient-level data from all published studies of FFR with prospective clinical follow up for MACE, elegantly plotting risk of MACE using cox modelling as a function of FFR modulated by therapeutic choice (medical therapy/revascularization). Barbato et al recently provided further analysis from the FAME-2 study showing the natural history of events according to FFR in patients who did not undergo revascularisation . They showed a step-up increase in the rates of MACE by decreasing FFR values (Figure 2).(34)

Figure 2 - MACE rates at 2 years in FAME 2 patients randomized to medical therapy. (Reprinted from Barbato et al(34) with permission of the publisher. Copyright © 2016, Elsevier).



These findings are consistent with the hypothesis that FFR assists in the prediction of plaque behaviour: the ischemic potential of a lesion may be a surrogate marker of plaque vulnerability with its attendant risk of rupture. It is

important to note that a lower absolute value of FFR corresponds with a higher risk of events, however risk stratification using this approach does not necessarily detect which ischemia producing lesion will drive events. Prospective studies have shown that up to half of future MACE relates to non-target vessels, but a large proportion of the future MACE is attributable to the lesion's FFR. Stenting these hemodynamically significant vulnerable lesions may prevent future coronary events.(33)

How ischemia affects plaque vulnerability and propensity to ACS

There are two main reasons for why an ischemia-producing lesion is more likely to cause ACS than a non-ischemia-producing lesion. First, an obstructive stenosis that limits blood flow is more likely to become occlusive leading to an acute MI as the burden of plaque increases (plaque progression). Second, the increasing stenosis severity leads to changes in flow dynamics and wall shear stress which in turn increase the likelihood of plaque rupture.(8) Versteeg *et al.* demonstrated that the responses and expression of monocyte toll-like receptors 2 and 4, which are thought to be related to plaque vulnerability, are significantly greater in patients with an FFR <0.75 compared with patients with an FFR of >0.80.(35)

Recent data has shown that the fibrous cap thickness (FCT) of intermediate grade lipid-rich plaques correlates with the physiological significance of the lesion (FFR<0.8).(36) A positive FFR is strongly predictive of a thin-capped fibroatheroma (<80 microns). Histopathological studies suggest that vulnerable plaques are those with a cap thickness of <65 microns, more recent in-vivo OCT data supports the FFR-predicted critical cap thickness value of <80 microns.(37)

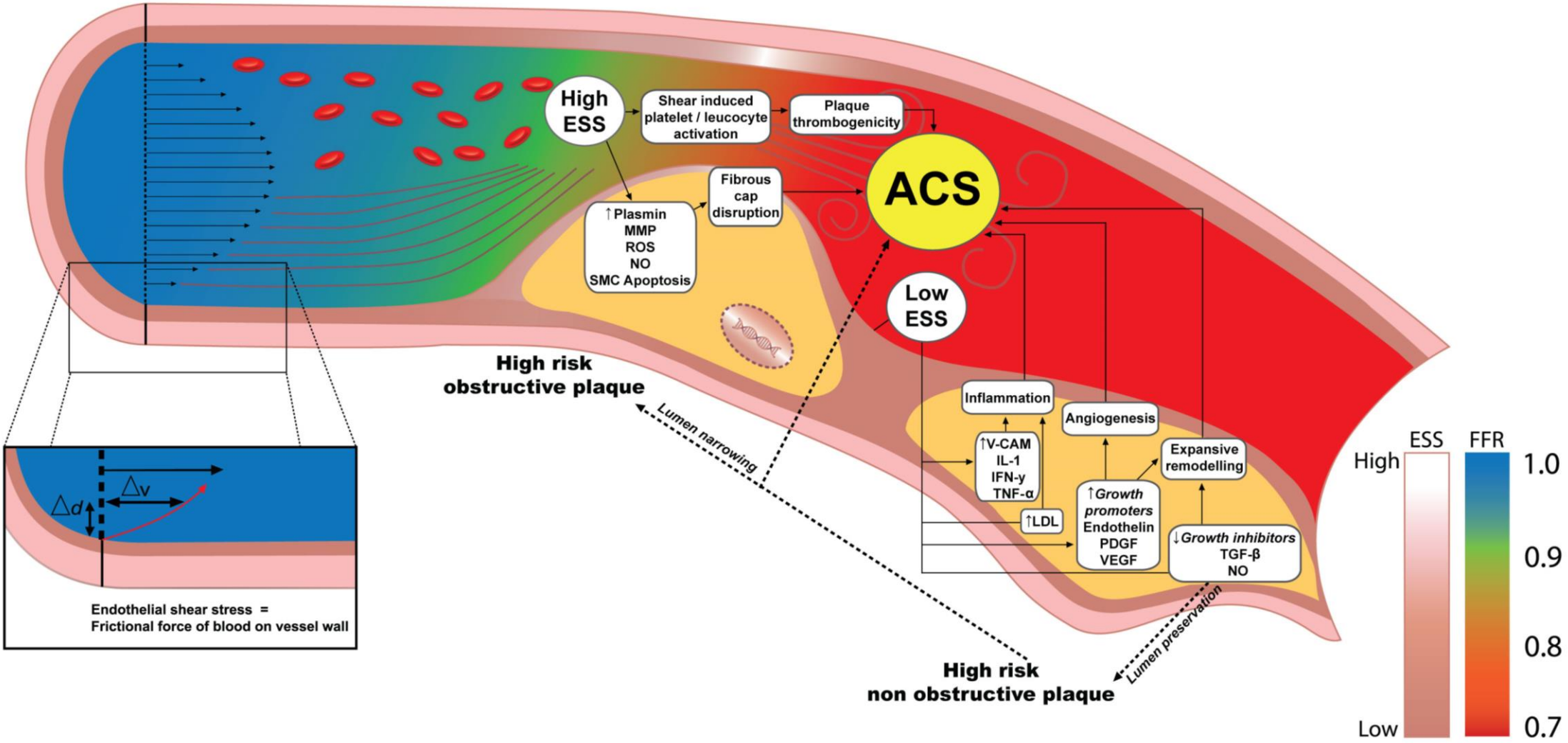
Importantly, rupture of these thin caps overlying vulnerable plaques is the cause of 75% of ACS.(38) There is a wealth of evidence supporting the role of more severe (and likely ischemia producing lesions) to be more dangerous. ROMICAT-II showed stenosis severity on CCTA to be the strongest predictor of ACS in acute chest pain.(39) Multivariate analysis from a cohort of over 3000 patients undergoing CCTA showed that whilst non obstructive plaques were almost 4 times more prevalent than obstructive ones, stenotic lesions were stronger predictors of ACS (HR: 3.2: 95% CI: 2.11–5.00; $p<0.0001$).(40) In ACS patients studied with IVUS & OCT severely stenotic areas had TCFA with more features of plaque vulnerability.(41) Pathology studies have shown that plaques are constantly rupturing and healing and when this happens over a non-severely obstructing lesion it is more likely to be silent.(42) Ruptured TCFA with thrombus formation superimposed on a severe stenosis is more likely to limit the coronary blood flow (and lead to clinical events) than the same event superimposed on a non-severe stenosis.

3 – Biomechanical pathophysiological forces including endothelial shear stress

Blood flow within a conduit artery exerts three distinct types of biomechanical strain on the vessel: axial, circumferential, and shear stress. Stress is a reflection of force normalized per unit area (Newtons per square meter or Pascals or dynes per square centimeter; 1 N/m^2 = 1 Pa =10 dyn/cm^2). Endothelial shear stress (ESS) is the most studied of these forces and appears to be the most fundamental and robust predictor of atherosclerotic initiation and development.(43) ESS is the tangential force exerted on the vessel wall attributable to the friction of blood flow on the endothelial surface (Figure 3 – central illustration). These endothelial cells

are incredibly sensitive to ESS and regulate vascular function in health and disease through mechanotransduction. Axial plaque stress (APS) is a longitudinal mechanical force applied along the length of plaque resulting from arterial blood pressure and stretching with phasic cardiac motion. APS occurs at force 10^3-10^5 times greater than ESS and thus may be the biomechanical factor more causally related to plaque rupture. Challenges with in-vivo estimation may partly explain a relative paucity of research into its contribution to atherosclerotic plaque pathophysiology compared to ESS. Computerised modelling demonstrates that lesions with similar angiographic and hemodynamic severity can have hugely variable levels of axial plaque stress potentially accounting for differences in vulnerability relating to lesion geometry of the upstream or downstream shoulder (radial gradient). (44)

Figure 3: Central Illustration - Ischemic and physiological factors contributing to plaque vulnerability



How is ESS estimated in vivo?

The derivation of ESS depends on computational fluid dynamics (CFD) - incorporating flow data (often obtained from invasive Doppler wire) into 3D computerised models of coronary arteries. These reconstructions may be created from biplane or 3D coronary angiography and even integrated with intravascular imaging for more accurate vascular profiling.(45) CFD has recently been combined with coronary computed tomography angiography (CCTA) facilitating a non-invasive way of estimating shear stress.(46,47) 'Virtual FFR' (FFR-CT) can be obtained from 3D coronary reconstructions from CCTA using CFD modelling and have been shown to reduce cost and unnecessary invasive procedures in patients with stable angina.(48)

How does shear relate to plaque biology and vulnerability?

Caro et al first described the pathological role of low and oscillatory ESS, forming the hypothesis which is now the consensus mechanism for the initiation of atherosclerosis.(6,49,50) Coronary arteries with undisturbed flow and physiological ESS facilitate endothelial cell expression of atheroprotective genes and the suppression of pro-atherogenic genes leading to coronary plaque quiescence and stability. However in areas of disturbed low flow with low ESS, atheroprotective genes are down-regulated and pro-atherogenic genes up-regulated resulting in acceleration of atherogenesis.(43,51) Mechanoreceptors on the endothelial cell surface respond to low ESS stimuli leading to mechano-sensitive gene expression promoting atherosclerosis.(51) Reviewing the details nature of these mechanisms is outside the scope of this review, however there are a number of complex molecular and cellular signaling pathways outlined in the central illustration (Figure 3).

Thombotic milieu: emerging relationship between shear stress and platelet activation

Platelet aggregation is a physiological prerequisite at sites of arterial injury to arrest bleeding allowing for arterial repair. Nevertheless, an exaggerated platelet response at the site of a stenotic vulnerable plaque can lead to acute coronary syndrome. Platelets preferentially adhere to the low shear stress zones (typically located at the downstream face) forming thrombi as a consequence of disturbed blood flow hemodynamics.(52) Yong et al showed in humans that coronary artery stenosis severity correlates with shear stress and markers of platelet activation. (7) Shear appears to be a critical determinant of platelet activation and thus an important determinant of plaque vulnerability and propensity to acute coronary syndrome.

Relationship between shear stress, plaque progression and rupture

Depending on the plaque shape, a stenosis results in a concomitant spread of ESS with relatively low ESS occurring in the upstream shoulder of the plaque, high ESS at the most stenotic site of the plaque, and low oscillatory ESS at the downstream shoulder.(6,53) A sustained low ESS environment drives excessive inflammation, lipid accumulation and matrix degradation leading to fragility and a propensity to rupture. These sites demonstrate augmented mRNA expression with increased expression of matrix-degrading proteases thereby shifting plaque progression towards atheroma with a thin fibrous cap.(54) Positive (expansive) remodeling maintains luminal patency at the expense of perpetuating a low ESS environment locally, allowing ongoing lipid accumulation and inflammation and enhancing the plaque's vulnerable characteristics.(55) In-vivo human studies

using CT derived coronary artery reconstructions highlights lower average wall shear stress to be a sensitive predictor of plaque location.(56) More recently OCT vascular profiling after ACS showed coronary regions exposed to low ESS are associated with larger lipid burdens, thinner fibrous caps and a higher prevalence of TCFA.(57) Low ESS was associated with increased plaque burden on longitudinal follow up. In contrast, high ESS at the site of maximal stenosis may increase the strain and erosion of the fibrous cap with increased thrombogenicity and the potential for plaque destabilization.(58,59) In-vivo imaging of culprit arteries using IVUS supports a role of high ESS in fibrous cap rupture.(60)

Prospective in-vivo studies of atherosclerosis have only limited accuracy in predicting future events based on anatomical plaque characteristics alone.(13,61,62) The PREDICTION study is the largest prospective observational study of wall shear stress and morphology on clinical outcome allowing insights into the natural history of coronary atherosclerosis. A combination of low local ESS, large plaque burden, and a large necrotic core gave a positive predictive value of 53% for identifying coronary lesions leading to cardiac events. Low ESS was an independent predictor of worsening luminal obstruction both in the natural history of CAD and in the development of clinically relevant lesions treated with PCI.(63)

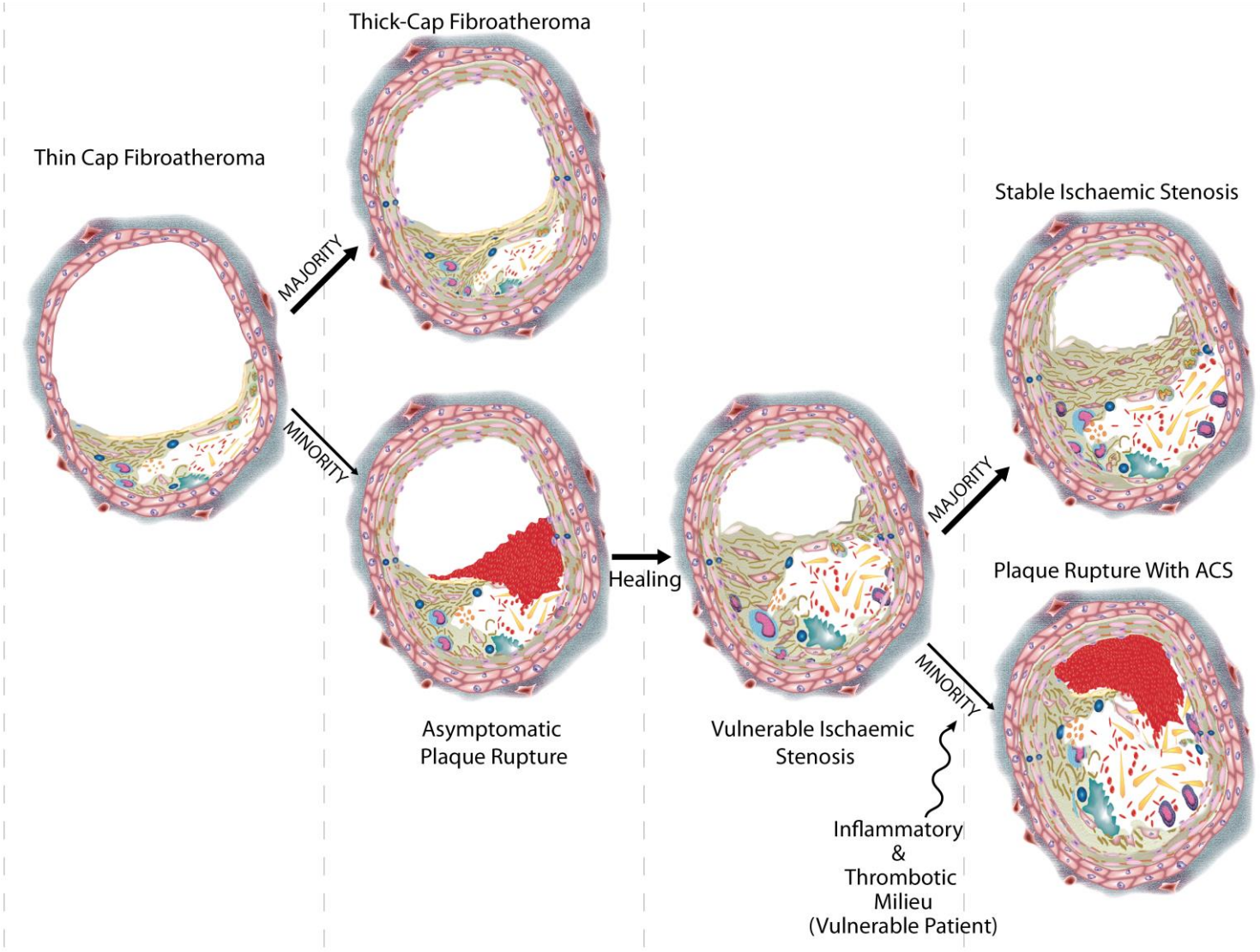
In summary, low ESS is a pathophysiological parameter important in localization of plaque burden and also correlates with features of vulnerability. High ESS may occur concurrently at the 'neck' of a stenosis increasing in magnitude with progressive lumen encroachment. This enhances local thrombogenicity and triggers molecular pathways implicated in fibrous cap disruption increasing the

probability of clinical manifestation as ACS.

Future directions: natural history of plaques, inflammation and plaque vulnerability

The pathobiology of atherosclerotic lesions is a dynamic process (Figure 4).

Figure 4: Contemporary premise on the natural history of coronary plaques: drivers towards ACS include local features of plaque vulnerability combined with systemic inflammatory factors and thrombotic milieu in the vulnerable patient



TCFA are common and can be found in the majority of patients presenting with ACS.(37,64) Nevertheless, the risk of an individual TCFA causing ACS is small and the nature history of these lesions varies from an indolent course, transforming into more stable plaque types(65) or alternatively progressive luminal obstruction may occur in step-wise fashion following asymptomatic rupture.(66,67) In-vivo and pathological studies support the concept that plaque ruptures are more likely to be symptomatic if they occur at the site of a severe stenosis with resultant thrombus potentiating abrupt vessel occlusion.(15,68)

The translation of a 'vulnerable plaque' to a 'vulnerable patient' involves all 3 components of Virchow's triad: altered coagulation/thrombosis, endothelial dysfunction and hemodynamic factors. This concept of the 'vulnerable patient' is key; efforts to treat the entire diffuse atherosclerotic process medically is paramount.(69) Intravascular imaging techniques allow for detailed lesion characterization but have not been proven to reduce events by directing percutaneous treatment (e.g. PCI). This reflects the dynamic nature of intracoronary plaques and low specificity of intravascular imaging in predicting lesion-specific future MACE. FFR is currently the most robust tool in identifying lesions with ischemic potential (often correlating with markers of plaque vulnerability) allowing targeted intervention in symptomatic patients with the aim of reducing future MACE.

Conclusion

Plaque vulnerability may result from the hemodynamic perturbations and altered biomechanical forces which associate with the functional significance of a coronary artery stenosis (and downstream ischemia). There is interplay and synergy between the

degree of luminal obstruction, ischemia, shear stress, activation of blood cells and subsequent vascular remodeling. Plaque vulnerability is determined by more than anatomy: coronary physiology is a predictor of plaque behavior and complements information from angiography identifying high-risk lesions and guiding revascularization to optimize patient outcomes. Future refinements in the use of coronary physiology may prove useful in the identification and treatment of both the vulnerable plaque and vulnerable patient.

Acknowledgements

None

Conflict of Interest Disclosures

None

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Figure Legends

Figure 1: Adverse prognostic implications of ischemia - Cardiac death and acute myocardial infarction rate in the 3 groups of the DEFER study after a follow-up of 5 years. (Reprinted from Pijls et al(32) with permission of the publisher. Copyright © 2007, Elsevier).

Figure 2: MACE rates at 2 years in FAME 2 patients randomized to medical therapy - This figure illustrates the rate of major adverse cardiovascular events (MACE) at 2 years of follow-up by 0.05 strata of fractional flow reserve (FFR) values. There is a step-up increase in the rates of MACE by decreasing FFR values. This increase is steeper below an FFR of 0.80 and plateaus below an FFR of 0.60. (Reprinted from Barbato et al(34) with permission of the publisher. Copyright © 2016, Elsevier).

Figure 3: Ischemic and physiological factors contributing to plaque vulnerability. This schematic demonstrates the links between coronary physiology, haemodynamic sheer forces and pathophysiology of plaque vulnerability.
MMP = matrix metalloproteinase; ROS = reactive oxygen species; NO = nitric oxide; SMC = smooth muscle cell; VCAM = vascular cell adhesion molecule; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; LDL = low-density lipoprotein cholesterol; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.

Figure 4: Contemporary premise on the natural history of coronary plaques: drivers towards ACS include local features of plaque vulnerability combined with systemic inflammatory factors and thrombotic milieu in the vulnerable patient