Plaque Structural Stress Estimations Improve Prediction of Future Major Adverse Cardiovascular Events After Intracoronary Imaging

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Background—Although plaque rupture is responsible for most myocardial infarctions, few high-risk plaques identified by intracoronary imaging actually result in future major adverse cardiovascular events (MACE). Nonimaging markers of individual plaque behavior are therefore required. Rupture occurs when plaque structural stress (PSS) exceeds material strength. We therefore assessed whether PSS could predict future MACE in high-risk nonculprit lesions identified on virtual-histology intracoronary ultrasound.

Methods and Results—Baseline nonculprit lesion features associated with MACE during long-term follow-up (median: 1115 days) were determined in 170 patients undergoing 3-vessel virtual-histology intravascular ultrasound. MACE was associated with plaque burden ≥70% (hazard ratio: 8.6; 95% confidence interval, 2.5–30.6; P=0.001) and minimal luminal area ≤4 mm² (hazard ratio: 6.6; 95% confidence interval, 2.1–20.1; P=0.036), although absolute event rates for high-risk lesions remained <10%. PSS derived from virtual-histology intravascular ultrasound was subsequently estimated in nonculprit lesions responsible for MACE (n=22) versus matched control lesions (n=22). PSS showed marked heterogeneity across and between similar lesions but was significantly increased in MACE lesions at high-risk regions, including plaque burden ≥70% (13.9±11.5 versus 10.2±4.7; P=0.001) and thin-cap fibroatheroma (14.0±8.9 versus 11.6±4.5; P=0.02). Furthermore, PSS improved the ability of virtual-histology intravascular ultrasound to predict MACE in plaques with plaque burden ≥70% (adjusted log-rank, P=0.003) and minimal luminal area ≤4 mm² (P=0.002). Plaques responsible for MACE had larger superficial calcium inclusions, which acted to increase PSS (P<0.05).

Conclusions—Baseline PSS is increased in plaques responsible for MACE and improves the ability of intracoronary imaging to predict events. Biomechanical modeling may complement plaque imaging for risk stratification of coronary nonculprit lesions. (Circ Cardiovasc Imaging. 2016;9:e004172. DOI: 10.1161/CIRCIMAGING.115.004172.)

Key Words: atherosclerosis ■ autopsy ■ coronary disease ■ myocardial infarction ■ prospective studies

Atherosclerosis is a multifocal disease, with myocardial infarction (MI) remaining a leading cause of morbidity and mortality. Around two thirds of all spontaneous thrombotic coronary events resulting in MI or sudden cardiac death are caused by rupture of an atheromatous plaque.1,2 Repeated cycles of subclinical rupture and repair also underlie rapid plaque growth,1 leading to luminal encroachment and symptoms of progressive angina. Morphologically, ruptured plaques exhibit large necrotic lipid cores, thin overlying fibrous caps, and evidence of microcalcification.4 The precursor lesion for rupture, termed a thin-cap fibroatheroma (TCFA), displays several of these compositional features.5 However, prospective studies have shown that future clinical event rates attributable to high-risk plaques were <10% for 3 years,6 highlighting that novel, non–imaging-based markers are required to improve plaque-based risk stratification.

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Plaque rupture occurs when the plaque structural stress (PSS) exceeds the material strength of the tissue.6 Autopsy studies have shown that PSS is increased after plaque rupture and that the location of peak PSS can accurately predict
rupture site. 7 8 Plaque composition can also affect PSS, with large lipid cores, thin fibrous caps, and superficial microcalcification, all acting to increase PSS. 9–11 Although direct in vivo measurement of PSS is currently impossible, it can be estimated using finite element analysis (FEA) based on coronary plaque imaging. The imaging modality must be able to display whole plaque architecture, while also discriminating between plaque tissue components. At present, virtual-histology intravascular ultrasound (VH-IVUS) remains one of the few imaging modalities that possesses these qualities, permitting reliable characterization of coronary plaques through automated analysis of ultrasound backscatter signal. 12

We recently developed a novel tool to calculate PSS derived from VH-IVUS data and showed that PSS levels were increased in coronary plaques in patients presenting with MI compared with stable angina. 11 On the basis of these results, we hypothesized that PSS may be increased in plaques responsible for major adverse cardiovascular events (MACE) and that integration of PSS with high-risk VH-IVUS characteristics could improve our ability to predict future plaque rupture. Here, we prospectively studied the ability of combined PSS/VH-IVUS to predict MACE in the Virtual Histology in Vulnerable Atherosclerosis (VIVA) study. 13 We show that: (1) short-term VH-IVUS imaging predictors of MACE are also associated with longer-term MACE, (2) PSS estimations from VH-IVUS and histology are significantly correlated, (3) baseline PSS varies markedly both between and within higher-risk plaques, (4) baseline PSS is significantly elevated in plaques responsible for MACE compared with matched control lesions, (5) PSS significantly improves the ability of VH-IVUS to predict MACE, and (6) subtle differences in plaque architecture increase PSS. Combining PSS calculations with plaque imaging data may significantly improve risk stratification of coronary plaques.

Methods

Patient Recruitment

The VIVA study design, including exclusion/inclusion criteria, has been described previously 11 (Methods section in the Data Supplement). Patients (n=170) undergoing percutaneous coronary intervention (PCI) with either stable angina or acute coronary syndrome were prospectively enrolled. VH-IVUS imaging was performed in the culprit vessel before PCI and in all 3 major coronary arteries after PCI. Exclusion criteria for VH-IVUS were any vessel with visual reference diameter <2.5 mm or with excessive tortuosity preventing catheter delivery. All data were obtained using 20 MHz Eagle-Eye Gold catheters (Volcano Corporation, Rancho Cordova, CA) after administration of glyceryl trinitrate, using a motorized pullback at 0.5 mm/s from the most distal safe position in the vessel. In total, 30372.2 mm of IVUS were included in the analysis (median: 177.2 [145.3–216.4] mm per patient). Nonculprit lesions (NCLs) were defined as any lesions imaged at baseline that did not undergo PCI. The study protocol was approved by the regional ethics committee (Ref: 07/Q0106/47), and all participants provided written informed consent.

Ex Vivo Validation

Permission to use autopsied human hearts for research was sought from relatives, with the study protocol approved by the regional ethics committee (07/H3036/123). At autopsy, the left anterior descending artery was identified and excised along with ≈40 mm of surrounding tissue to maintain structural integrity. 14 A guiding catheter was then sutured into the ostium of the artery, and side branches ligated. The specimen was fixed to an imaging rig, prewarmed (to 37 °C), and subsequently pressure perfused at a constant pressure of 100 mm Hg. Electrocardiographic signals were obtained through use of an automated generator, permitting capture of VH-IVUS data using 20 MHz Eagle-Eye Gold catheters (Volcano Corporation, Rancho Cordova, CA), again at a constant motorized pullback of 0.5 mm/s. Specimens were then fixed in formalin, after decalcification if necessary, with each plaque undergoing histological processing. Slides were digitally imported (NanoZoomer, Hamamatsu, Japan) and stored for subsequent analysis. Careful coregistration between VH-IVUS data and plaques was performed using measurements documented at time of imaging, with the assistance of fiduciary landmarks. 14 Matched histological and VH-IVUS plaques (n=48) were then included in the validation analysis.

Clinical End Points

MACE data were collected by telephone interview and clinic follow-up (median: 1115 days). MACE comprised events driven by presumed plaque rupture, defined as a composite of cardiac death, MI, unplanned revascularization, or hospitalization from progressive angina, according to the Braunwald Unstable Angina Classification. An independent review panel composed of 4 independent cardiologists adjudicated and categorized each clinical event. MACE occurring without angiographic follow-up (n=3) were classified as indeterminate and excluded from analysis. After adjudication and repeat angiography, MACE were linked to a plaque imaged at the index procedure either at a previously untreated site (NCLs) or an initially treated site (culprit lesion), consistent with previous reports. 8 Overall, 17 events (40.5%) were deemed to be attributable to a culprit lesion at baseline (restenotic) and were excluded from all NCL analysis. The study flow diagram is presented online (Figure I in the Data Supplement).

IVUS Analysis

Independent IVUS analysis was performed by Krakow Cardiovascular Research Institute core laboratory using Volcano Image Analysis Software 3.0.394 (Volcano Corporation). Luminal and external elastic membrane borders were manually corrected, allowing calculation of plaque burden (PB) and luminal area. Positive remodeling on IVUS was defined as a remodeling index of >1.05, being calculated as the external elastic membrane area at the minimal luminal area (MLA) divided by the mean external elastic membrane of the proximal and distal reference segments. ECG-gated radiofrequency data were recorded at the R-wave peak, permitting identification and quantification of individual plaque components, each displayed as separate colors: fibrous (dark green), fibrofatty (light green), necrotic core (red), and dense calcium (white). VH-defined plaque classification was performed with a plaque (PB>40%) classified as VH-TCFA if >10% confluent necrotic core was in contact with the lumen for 3 consecutive frames. 11 Full details of the VH-IVUS plaque classification scheme used are available online (Methods section and Figure II in the Data Supplement).

Biomechanical Analysis

NCLs responsible for MACE (n=22) were matched to control lesions based on plaque characteristics that are known to affect PSS, including luminal area, PB, necrotic core/dense calcium volume, and plaque classification. Predicted probabilities for every NCL were determined by logistic regression analysis, allowing propensity matching to be performed between plaques responsible for MACE and a control arm (n=22). After matching, these 2 plaque groups then underwent dynamic 2D FEA simulations, as described previously. 11 Vessel geometry and plaque architecture/composition were obtained at diastole (Figure 1A) and imported into dedicated analysis software (proprietary code, MATLAB R2012b, The MathWorks, Inc), allowing construction of 5120 segmented plaque models (Figure 1B). Nonuniform circumferential vessel shrinkage was applied to VH-IVUS images to create a zero-pressure configuration, as required for FEA. 11,15 Individual plaque components (n=100/43) were modeled...
as incompressible, piecewise homogeneous, nonlinear isotropic, and hyperelastic as described by the modified Mooney–Rivlin strain energy density function:

\[ W = c_1(l_1 − 3) + D_1 \left( \exp(D_2(l_1 − 3)) − 1 \right) + \kappa(J − 1) \]

where \( l_1 \) is the first invariant of the modified right Cauchy-Green tensor \( \mathbf{C} = J^{-\frac{1}{2}} \mathbf{F} \mathbf{F}^T \); \( J \) is the Jacobian of the deformation gradient tensor, \( C \); \( \kappa \) is the Lagrange multiplier; and \( c_1 \), \( D_1 \), and \( D_2 \) are material constants derived from previous experimental work\(^1\) and include arterial vessel wall, \( c_1 = 0.138 \) kPa, \( D_1 = 3.833 \) kPa, and \( D_2 = 18.803 \) kPa; fibrous tissue, \( c_1 = 0.186 \) kPa, \( D_1 = 5.769 \) kPa, and \( D_2 = 18.219 \); and necrotic core, \( c_1 = 0.046 \) kPa, \( D_1 = 4.885 \) kPa, and \( D_2 = 5.426 \). The motion of each plaque component was governed by kinetic equations as:

\[ \rho \dot{v}_i = \sigma_{ij,i} (i, j = 1, 2) \]

where \([\dot{v}_i]\) and \([\sigma_{ij}]\) are the displacement vector and stress tensor, respectively, \( \rho \) is density of each component, and \( t \) is time. The entire plaque model was then meshed using 9-node quadrilaterals (Figure 1C), generating \( \approx 40,000 \) nodes and \( \approx 100,000 \) elements per model. Both displacement and strain were assumed to be large. There was no relative movement at the interface of individual atherosclerotic components, and the relative energy tolerance was set to 0.005. Two adjacent points were fixed at the outer wall of the model to prevent rigid body movement. The loading conditions for each simulation were taken from coronary pressure recordings taken during VH-IVUS acquisition, with outer boundary pressure set at zero. FEA was performed using ADINA 8.6.1 (ADINA R&D, Inc., Watertown, MA). Because plaque rupture is thought to result from superficial plaque destabilization, PSS was calculated \( \pm 200 \) \( \mu \)m depth from the luminal contour, representing the axial resolution of VH-IVUS.\(^2\) Variation in PSS during one cardiac cycle was also calculated, being defined as:

\[ \text{Variation of PSS} = \max (PSS_i) - \min (PSS_i) \]

in which the subscript \( i \) is the \( i \)th integration node and the superscript \( t \) is time were computed. All PSS values presented refer to maximum principal stress normalized by coronary pressure (Figure 1D), creating a dimensionless index allowing comparisons between patients.\(^1\) Researchers performing simulations were blinded both to plaque classification and patient outcome. Intraclass correlation coefficients for PSS absolute agreement on identical VH-IVUS images were excellent for both intra- and interobserver variability (all \( > 0.97; P < 0.001 \)).

**Statistical Analysis**

Data were assessed for normality using the Shapiro–Wilks test. Normally distributed data are presented as mean (SD or SEM) and compared using an unpaired \( t \) test, with non-normal data as medians (Q1–Q3) and compared using a Mann–Whitney \( U \) test. Categorical variables were analyzed using \( \chi^2 \) or Fisher exact tests, where appropriate. Paired analyses were performed using either a paired \( t \) test or McNemar test, as appropriate. Cox proportional hazard regression models using a robust sandwich estimator to account for patient clustering were fitted to assess the effect of NCL on MACE. To assess predictive performance, the sensitivity, specificity, positive predictive value, and negative predictive value, with 95% confidence intervals, were calculated for plaque characteristics associated with MACE. Because plaques comprise several VH-IVUS frames, linear mixed-effect models were used to compare PSS values between patients and clinical outcomes. Receiver-operating characteristic curves were calculated by plotting sensitivity versus (1 specificity), allowing calculation of area under the curve. Integrated PSS and plaque imaging time-to-event data are presented as Kaplan–Meier estimates of cumulative hazard and compared using a clustering-adjusted log-rank method. Power calculations from pilot data suggested that 20 plaques per group were required to detect a 1.3 difference for PSS between MACE and non-MACE plaques (SD 1.7; \( \alpha=0.05; \beta=0.1 \)). All calculations were 2-tailed with \( P < 0.05 \) considered statistically significant. Statistical analyses were performed in SPSS 21.0.0 (SPSS, Inc, IBM Computing), R 2.10.1 (The R Foundation for Statistical Computing), and Stata MP 13.1 (StataCorp LP).

**Results**

**Baseline Patient Characteristics and MACE**

The VIVA study enrolled 170 patients with stable angina or ACS who were undergoing PCI for 3-vessel VH-IVUS imaging. Overall, 42 MACE occurred in 28 patients during a median of 1115 days (968–1537), which included 3 deaths, 6 MIs, 18 unplanned revascularization procedures, and 15 hospitalizations because of progressive angina. Patient demographics were similar among patients who did or did not sustain MACE, as presented in Table 1.

**Baseline NCL Characteristics**

Baseline IVUS plaque characteristics for the whole NCL lesion cohort (n=931 plaques) and those responsible for MACE are presented in Table 2. On gray-scale IVUS, MACE NCLs had smaller lumens (lower MLA and luminal volume; both \( P < 0.001 \)) and were larger (increased PB and plaque

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**Figure 1.** Calculation of plaque structural stress. (A), Virtual-histology intravascular ultrasound image identifying plaque components as white (dense calcium), red (necrotic core), green (fibrous), and light green (fibrofatty). (B and C), Segmented plaque model (B) complete with magnified image of fine mesh (C) demonstrating the basis for finite element analysis. (D) Final band plot of plaque structural stress (PSS) identifying regions of high stress within the plaque.
Plaque Stress and MACE

Table 1. Baseline Patient Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=170)</th>
<th>MACE (n=28)</th>
<th>Non-MACE (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3 (10.4)</td>
<td>61.9 (12.2)</td>
<td>62.4 (10.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>131 (77)</td>
<td>21 (75)</td>
<td>110 (78)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>87 (51)</td>
<td>14 (50)</td>
<td>73 (51)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>23 (14)</td>
<td>5 (18)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>35 (21)</td>
<td>3 (11)</td>
<td>32 (23)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>18 (11)</td>
<td>4 (14)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>ACS presentation, n (%)</td>
<td>70 (41)</td>
<td>9 (32)</td>
<td>61 (43)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.4 (3.8–5.3)</td>
<td>4.4 (3.5–5.6)</td>
<td>4.4 (3.9–5.3)</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.3 (1.7–2.7)</td>
<td>2.2 (1.4–2.8)</td>
<td>2.3 (1.8–2.7)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.1 (0.9–1.3)</td>
<td>1.1 (0.9–1.3)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>88.5 (19.9)</td>
<td>89.8 (19.5)</td>
<td>88.2 (20.1)</td>
</tr>
<tr>
<td>FRS, %</td>
<td>20.5 (12.6)</td>
<td>19.4 (12.2)</td>
<td>20.8 (12.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or median (25th–75th percentile), as appropriate. ACS indicates acute coronary syndrome; FRS, Framingham Risk Score for 10-y estimated risk of total cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

volume; both P<0.001). Plaque composition, defined either by percentage VH-IVUS tissue type or classification, was not significantly different between groups. Plaque-level characteristics associated with long-term MACE on univariate analysis included PB≥70% (hazard ratio 8.6; 95% confidence interval, 2.5–30.6; P=0.001) and MLA≥4 mm2 (hazard ratio 6.6; 95% confidence interval, 2.1–20.1; P=0.001), whereas VH-TCFA was not statistically significant (hazard ratio 3.6; 95% confidence interval, 0.8–16.5; P=0.10). However, these higher risk regions had clearly different temporal relationships with MACE. MLA≥4 mm2 and PB≥70% were associated with MACE throughout the study period, whereas MACE attributable to VH-TCFA appeared only after ~600 days of follow-up (Figure 2). Absolute MACE rates for plaques exhibiting PB≥70%, MLA≥4 mm2, or VH-TCFA were 9.5%, 6.3%, and 3.3%, respectively, with positive predictive value of 9.6%, 6.8%, and 2.9%, respectively. Full details of predictive performance for each plaque characteristic are presented in Table I in the Data Supplement. Overall, 122 plaques (13.1%) exhibited all 3 high-risk VH features (PB≥70%+MLA≥4 mm2+VH-TCFA), with this combination increasing MACE to 10.7%.

**PSS Calculated by VH-IVUS and Histology Is Comparable**

Late follow-up of the VIVA cohort confirms results of previously published prospective studies. However, event rates of only ≈10% for the highest risk plaques indicate that additional markers are required to improve MACE prediction. We have previously found that PSS estimated from VH-IVUS is increased in patients presenting with ACS versus stable angina, suggesting that PSS may be increased in unstable lesions and might help predict future MACE.

To assess whether VH-IVUS can identify plaques with high PSS, we first estimated PSS in 48 plaques imaged at autopsy by VH-IVUS and compared these with coregistered histology specimens (Figure III in the Data Supplement), including 16 (33%) classified as fibroatheromas. PSS values derived from histology were located superficially in 81.3% plaques, consistent with a role for PSS in superficial plaque rupture. Although histology-derived PSS was higher than VH-IVUS–derived PSS (mean: 1.67 [1.24–2.21] versus 1.34 [1.01–1.69]; P<0.001 and 95th centile: 4.84 [3.42–6.26] versus 3.53 [3.10–4.02]; P<0.001), PSS derived from VH-IVUS showed a moderate and positive correlation with PSS derived from histology (mean: r=0.57; P<0.001 and 95th centile: PSS r=0.41; P=0.004; Figure IV in the Data Supplement). In addition, there was no significant difference in either mean (1.16 [0.77–1.48] versus 1.00 [0.84–1.31]; P=0.92) or 95th centile PSS (3.62 [2.48–4.50] versus 3.58 [3.01–3.91]; P=0.93) between PSS derived from VH-IVUS or histology in fibroatheromas, maintaining the positive correlation (r=0.56; P=0.02). Thus, PSS derived from VH-IVUS provides reliable estimates of stress experienced by coronary plaques in vivo.

**PSS Is Increased in MACE Lesions**

We next examined PSS in NCL plaques responsible for MACE (n=22) compared with control (non-MACE) plaques (n=22). Plaques were matched based on their VH-IVUS composition and classification as shown in Table 2. PSS was determined throughout whole plaques and within discrete, predefined, higher-risk regions (eg, PB≥70%). There were marked differences in PSS in higher-risk regions between plaques, and PSS varied markedly even within a higher-risk region of the same plaque (Figure 3). These findings indicate that PSS is determined by differences in plaque composition and geometry even within the same lesion and does not just reflect plaque size or lumen area. Despite this heterogeneity, PSS was significantly increased in MACE plaques compared with non-MACE controls at specific high-risk regions, including PB≥70% (mean±SEM 13.9±0.66 versus 10.2±0.24; P<0.001) and in VH-TCFA (14.0±2.28 versus 11.6±0.12; P=0.02; Table 3). In contrast, PSS was similar at MLA≥4 mm2 sites or within other plaque regions (both P>0.05).

**PSS Significantly Improves Prediction of MACE**

These findings suggest that PSS is not just a surrogate for geometric features of a plaque and might discriminate between NCLs that do or do not cause MACE, for example, those higher risk regions that also have high PSS. To assess whether PSS improves the ability to predict MACE when combined with VH-IVUS, we performed a lesion-based analysis in 10% of the NCL population (96 plaques). Using a separate developmental cohort (n=20), PSS was calculated for each high-risk plaque region defined by VH-IVUS (PB≥70%, MLA≥4 mm2, and VH-TCFA), and receiver-operating characteristic analysis performed to determine cutoff points for PSS to predict MACE (Figure V in the Data Supplement). Time-to-event curves, adjusted for the presence of multiple plaques within a patient, confirmed that PSS markedly increased the ability of VH-IVUS to predict MACE in plaques with PB≥70% (P=0.003) and MLA≥4 mm2 (P=0.002; Figure 4). A similar pattern, albeit not statistically significant (P=0.22), was observed for plaques classified as VH-TCFA.
Table 2. Baseline Gray-Scale and Virtual-Histology Intravascular Ultrasound Characteristics for Nonculprit Lesions

<table>
<thead>
<tr>
<th></th>
<th>All NCL (n=931)</th>
<th>MACE NCL (n=22)</th>
<th>Non-MACE NCL (n=909)</th>
<th>PSS NCL Controls (n=22)</th>
<th>P Value (MACE NCL vs Non-MACE NCL)</th>
<th>P Value (MACE NCL vs PSS NCL Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gray-scale IVUS</strong></td>
<td></td>
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<tr>
<td>MLA, mm²</td>
<td>5.62 (3.58–8.58)</td>
<td>3.00 (2.20–3.79)</td>
<td>5.70 (3.62–8.61)</td>
<td>3.16 (2.30–4.21)</td>
<td>&lt;0.001</td>
<td>0.50</td>
</tr>
<tr>
<td>MLA≥4 mm², %</td>
<td>27.0</td>
<td>77.3</td>
<td>27.6</td>
<td>81.8</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Luminal volume, mm³</td>
<td>53.1 (24.6–125.5)</td>
<td>93.0 (75.0–250)</td>
<td>51.9 (24.5–124.7)</td>
<td>124.0 (68.0–301.0)</td>
<td>&lt;0.001</td>
<td>0.93</td>
</tr>
<tr>
<td>Plaque volume, mm³</td>
<td>50.9 (21.1–129.5)</td>
<td>187.0 (107.5–344.5)</td>
<td>50.1 (20.9–126.4)</td>
<td>216.0 (96.0–359.0)</td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>48.1 (44.2–53.4)</td>
<td>58.0 (56.0–61.0)</td>
<td>48.0 (44.1–53.2)</td>
<td>57.7 (52.5–61.1)</td>
<td>&lt;0.001</td>
<td>0.50</td>
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<tr>
<td>PB ≥70%, %</td>
<td>20.2</td>
<td>81.8</td>
<td>18.7</td>
<td>86.4</td>
<td>&lt;0.001</td>
<td>0.77</td>
</tr>
<tr>
<td>RI &gt;1.05, %</td>
<td>27.3</td>
<td>63.6</td>
<td>26.5</td>
<td>68.2</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Virtual-histology IVUS</strong></td>
<td></td>
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<tr>
<td>Fibrous tissue volume, mm³</td>
<td>15.4 (6.0–44.3)</td>
<td>63.6 (35.9–111.1)</td>
<td>18.3 (6.6–50.0)</td>
<td>80.2 (30.4–111.9)</td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>Fibrofatty tissue volume, mm³</td>
<td>2.9 (0.9–9.5)</td>
<td>13.6 (7.5–39.1)</td>
<td>3.3 (1.0–10.7)</td>
<td>14.7 (4.9–26.2)</td>
<td>&lt;0.001</td>
<td>0.90</td>
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<td>Necrotic core volume, mm³</td>
<td>5.3 (1.8–17.3)</td>
<td>19.6 (10.4–39.1)</td>
<td>5.8 (1.9–19.8)</td>
<td>29.4 (10.6–60.0)</td>
<td>0.001</td>
<td>0.85</td>
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<tr>
<td>Dense calcium volume, mm³</td>
<td>2.0 (0.5–6.7)</td>
<td>5.5 (2.1–17.3)</td>
<td>2.1 (0.5–7.6)</td>
<td>14.1 (3.6–26.4)</td>
<td>0.003</td>
<td>0.55</td>
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<tr>
<td>Fibrous tissue, %</td>
<td>58.9 (50.0–66.5)</td>
<td>53.4 (45.5–63.8)</td>
<td>59.0 (50.4–66.4)</td>
<td>55.8 (47.9–63.6)</td>
<td>0.31</td>
<td>0.87</td>
</tr>
<tr>
<td>Fibrofatty tissue, %</td>
<td>10.0 (6.0–16.6)</td>
<td>12.0 (7.1–23.2)</td>
<td>10.3 (6.2–16.6)</td>
<td>12.4 (8.9–19.4)</td>
<td>0.16</td>
<td>0.79</td>
</tr>
<tr>
<td>Necrotic core, %</td>
<td>20.9 (14.6–27.1)</td>
<td>18.3 (12.5–27.4)</td>
<td>20.7 (14.6–26.9)</td>
<td>20.5 (14.0–26.1)</td>
<td>0.42</td>
<td>0.98</td>
</tr>
<tr>
<td>Dense calcium, %</td>
<td>7.2 (3.5–13.1)</td>
<td>7.0 (2.1–16.9)</td>
<td>7.1 (3.4–12.9)</td>
<td>7.0 (4.7–14.4)</td>
<td>0.40</td>
<td>0.61</td>
</tr>
<tr>
<td>VH classification, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.74</td>
</tr>
<tr>
<td>TCFA</td>
<td>60.3</td>
<td>72.7</td>
<td>60.0</td>
<td>77.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ThCFA</td>
<td>15.7</td>
<td>13.6</td>
<td>15.7</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fca</td>
<td>9.9</td>
<td>9.1</td>
<td>9.9</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIT</td>
<td>14.2</td>
<td>4.5</td>
<td>14.4</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data were compared using linear mixed-effect models to account for clustering of plaques within patients. Matched data were compared using paired t test or McNemar test, as appropriate. Data are presented as median (25th–75th percentiles). FCa indicates fibrocalcific; MACE, major adverse cardiovascular events; MLA, minimal luminal area; NCL, nonculprit lesion; PB, plaque burden; PIT, pathological intimal thickening; PSS, plaque structural stress; PSS NCL controls, plaque structural stress nonculprit lesion control group; RI, remodeling index; TCFA, thin-cap fibroatheroma; and ThCFA, thick-cap fibroatheroma.

Influence of Plaque Composition on PSS

Our biomechanical analysis shows a difference in PSS values between lesions responsible for MACE versus control plaques. Because plaques were matched for higher risk features (PB, MLA, and VH-T DFA), other features that increase PSS must be responsible. We therefore studied the subplaque architecture within these regions to determine the microstructural differences that may be responsible, focusing on features that increase risk of rupture, including necrotic core and microcalcification (Figure 5). Mean or maximal component necrotic core areas were similar within PB≥70% or VH-T DFA regions in MACE versus non-MACE plaques (Table II in the Data Supplement). However, MACE plaques exhibited larger superficial dense calcium inclusions in both PB≥70% (0.16±0.47 versus 0.13±0.31 mm²; P=0.047) and VH-T DFA (0.28±0.57 versus 0.20±0.41 mm²; P=0.049).

Discussion

Atherosclerosis plaques are typically demonstrable at different stages of development throughout the coronary tree. Consequently, NCLs greatly outnumber culprit lesions in patients undergoing PCI and underlie the majority of subsequent MACE. Although VH-IVUS can identify NCLs at higher risk of causing future events, the low event rates observed in prospective studies suggest that factors additional to plaque composition determine rupture. PSS is a proposed driver of rupture that integrates plaque anatomy and composition with physical forces that plaques experience but has been largely neglected in clinical studies. We therefore examined whether PSS could discriminate those NCL that generate future MACE from those that do not and could therefore guide therapies to prevent plaque rupture.

There are several important and novel features in this study that complement and enhance our understanding of coronary
plaque behavior. First, we confirm previous observations that lesions with $\text{MLA} \leq 4 \text{ mm}^2$ and $\text{PB} \geq 70\%$ on IVUS are associated with long-term MACE. Second, PSS values derived from VH-IVUS and histology correlate well, suggesting that VH-IVUS–derived PSS is biologically meaningful and of potential clinical use. Third, plaques responsible for MACE have increased PSS values in higher-risk regions compared with matched controls, most marked at $\text{PB} \geq 70\%$. Fourth, PSS is not homogenous across higher risk regions and does not track with features such as PB or MLA. Fifth, calculation of PSS has potential to improve the ability of VH-IVUS to predict MACE.

Finally, increased PSS is associated with plaque microarchitecture, particularly larger superficial calcium inclusions.

Although we observed an association between baseline VH-IVUS plaque features and long-term clinical events, absolute rates were low, suggesting that although intracoronary imaging may identify the substrate for rupture, morphology alone is insufficient to identify plaques at highest risk of MACE. In contrast, mechanical forces have been hypothesized as determinants of plaque rupture,6 and factors that increase PSS, including hypertension, strenuous exercise, or emotional stimuli, also increase risk of cardiovascular events.20,21

Figure 2. Time-to-event curves for major adverse cardiovascular event (MACE) rates according to baseline plaque characteristics. (A–C), Kaplan–Meier curves for MACE rates in nonculprit lesions based on virtual-histology (VH) intravascular ultrasound features including plaque burden (PB) $\geq 70\%$ (A), minimal luminal area (MLA) $\leq 4 \text{ mm}^2$ (B), thin-cap fibroatheroma (VH-TCFA) (C). Factors compared using adjusted log-rank test.

Figure 3. Longitudinal profiles of plaque burden and structural stress. (A and B), Relationship between longitudinal plaque burden (PB) and plaque structural stress (PSS) within 2 coronary plaques. The plaque responsible for a major adverse cardiovascular event (MACE; A) displays increased PSS associated with high PB, whereas the non-MACE plaque (B) exhibits low PSS despite PB being high.
However, PSS has been largely overlooked or excluded from clinical studies, most likely because of limitations in imaging resolution and concerns that values obtained may be incorrect. Our study is the first to show that PSS estimates from VH-IVUS are highly reproducible and correlate positively with values derived from histology. More importantly, our study suggests that plaques exposed to high structural stresses in vivo can be identified correctly.

Our most important finding is that lesions resulting in MACE had significantly higher baseline PSS at specific plaque regions (e.g., PB ≥70%) compared with matched controls. Although previous studies showed increased PSS in plaques responsible for MI or sudden cardiac death, this is the first report showing that increased coronary PSS may occur before clinical events in higher-risk lesions. Plaque rupture results from failure of the fibrous cap, indicating that factors acting directly on the cap or within the superficial plaque are more likely to promote rupture. Indeed, we find that superficial (but not deep) PSS is associated with MACE. Recent trials have shown that NCL intervention can improve outcomes, although treatment was based on angiographic stenosis, which may miss high-risk lesions or overtreat low-risk lesions. In contrast, integration of PSS with VH-IVUS improved our ability to predict future MACE by 2- to 3-fold, suggesting that PSS may represent a novel and complementary parameter to plaque imaging in predicting future NCL events. This incremental gain in predictive accuracy could identify patients with a high burden of high-stress plaques and direct more intense pharmacotherapy or possibly even protective intervention.

PSS estimation assimilates several variables critical to plaque stability, including architecture, tissue material properties, luminal geometry, and patient hemodynamics. Although changes to these factors can alter PSS, the microstructural differences responsible for MACE were unknown. Indeed, PSS appears independent of other higher risk features because increasing PB or reducing luminal area does not increase PSS. In contrast, we find that PSS varies markedly both between and within higher-risk plaques. Furthermore, MACE lesions had increased areas of superficial calcification that can act as stress amplifiers depending on size, orientation, and relative location to one another. Thus, plaque microstructure influences PSS, and the overall risk of rupture for each lesion may be influenced by small changes in plaque composition. Established plaque classification algorithms rely on summary statistics to describe anticipated behavior of individual lesions, but this dilutes the overall effect of discrete, subtle changes in plaque structure that increase risk of rupture. In contrast, estimation of PSS at specific higher-risk plaque regions may represent an objective method to quantify these microstructural differences and determine risk of rupture.

Our study has some limitations. First, although consistent with other studies, MACE numbers were relatively low; however, low MACE rates identified by imaging alone are the major

Table 3. Plaque Structural Stress in Lesions Responsible for Major Adverse Cardiovascular Events and Controls

<table>
<thead>
<tr>
<th></th>
<th>PSS MACE (n=22)</th>
<th>Non-MACE (n=22)</th>
<th>P Value</th>
<th>Variation of PSS MACE (n=22)</th>
<th>Non-MACE (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB ≥70%</td>
<td>13.9±0.66</td>
<td>10.2±0.24</td>
<td>&lt;0.001</td>
<td>17.9±0.89</td>
<td>12.6±0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLA≤4 mm²</td>
<td>13.3±0.35</td>
<td>10.7±0.20</td>
<td>0.06</td>
<td>16.9±0.44</td>
<td>13.3±0.27</td>
<td>0.14</td>
</tr>
<tr>
<td>VH-TCFA</td>
<td>14.0±0.28</td>
<td>11.6±0.12</td>
<td>0.02</td>
<td>17.1±0.35</td>
<td>14.2±0.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Other plaque regions</td>
<td>12.4±0.14</td>
<td>12.1±0.18</td>
<td>0.11</td>
<td>15.4±0.19</td>
<td>14.7±0.24</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Comparisons between groups are performed using linear mixed-effects models. Data are presented as mean±SEM. MACE indicates major adverse cardiovascular events; MLA, minimal luminal area; PB, plaque burden; PSS, plaque structural stress; and VH-TCFA, virtual-histology thin-cap fibroatheroma.
driver for additional modalities to predict risk. Second, proportional hazards models were all performed at a lesion-level, and the regression estimates presented apply to individual plaques and not patients. Third, other pathological processes may result in rapid plaque growth and MI, including plaque erosions and calcified nodules, and the role of PSS in these processes is unknown. Fourth, the overall calculation of PSS relies on accurate identification of plaque morphology, and debate continues regarding the accuracy of VH-IVUS. However, independent ex vivo validation has confirmed that VH-IVUS–defined plaque classification is reliable,14 the biological importance of VH-IVUS–defined plaque subtypes has been validated in prospective studies,5,13,24 and VH-IVUS–derived PSS correlated with histology-derived PSS.

Conclusions

We show that atherosclerotic plaques resulting in MACE show increased PSS compared with matched controls, and PSS estimates markedly improve the ability of VH-IVUS to predict MACE. Our results suggest that biomechanical modeling may complement plaque imaging risk stratification for coronary NCLs.

Acknowledgments

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Coronary plaque rupture underlies the majority of myocardial infarctions, with repeated cycles of subclinical rupture and repair driving rapid plaque growth. Although ruptured plaques have typical morphological features that can be reliably identified by intracoronary imaging, prospective studies have consistently shown low future major adverse cardiovascular event (MACE) rates attributable to such lesions. Thus, novel strategies to improve plaque risk stratification are urgently required. Plaque structural stress (PSS) is known to be higher in patients presenting with myocardial infarction, with elevated levels thought to promote rupture. In this study, baseline nonculprit plaque features were determined in 170 patients undergoing 3-vessel virtual-histology intravascular ultrasound imaging. MACE was associated with lesions that had plaque burden ≥70% and minimal luminal area ≤4 mm². However, absolute event rates for the highest-risk lesions identified by virtual-histology intravascular ultrasound remained <10%. However, PSS was increased at specific plaque regions in plaques responsible for MACE versus matched controls, including plaque burden ≥70% and thin-cap fibroatheroma. Furthermore, PSS improved the ability of virtual-histology intravascular ultrasound to predict MACE in plaques with plaque burden ≥70% and minimal luminal area ≤4 mm². Finally, we show that plaques responsible for MACE had larger superficial calcium inclusions, which acted to increase PSS. Our results suggest that integration of PSS with existing plaque imaging may improve our ability to identify those plaques at highest risk of rupture and subsequent adverse clinical events.
Plaque Structural Stress Estimations Improve Prediction of Future Major Adverse Cardiovascular Events After Intracoronary Imaging
Adam J. Brown, Zhongzhao Teng, Patrick A. Calvert, Nikil K. Rajani, Orla Hennessy, Nitesh Nerlekar, Daniel R. Obaid, Charis Costopoulos, Yuan Huang, Stephen P. Hoole, Martin Goddard, Nick E.J. West, Jonathan H. Gillard and Martin R. Bennett

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Supplemental Material

SUPPLEMENTAL METHODS

Patient recruitment

Full details of the VIVA study have been previously published. In brief, patients undergoing percutaneous coronary intervention (PCI) for either stable angina pectoris or following an acute coronary syndrome were enrolled. All patients provided informed written consent prior to recruitment. The study inclusion criteria were age >18 years, left ventricular ejection fractions >30%, at least one de novo culprit lesion of >40% stenosis in at least one coronary artery as determined by invasive cardiac catheterization, target vessel diameter >2.5mm and serum creatinine <150mmol/l. Exclusion criteria were prior revascularization, coronary anatomy unsuitable for 3-vessel VH-IVUS imaging and, in the ACS cohort, active inflammatory conditions or any form of surgery <3 months prior to enrolment.

Plaques were classified as culprit in stable patients if they were implicated by additional functional testing such as myocardial perfusion scintigraphy, stress echocardiography or stress cardiac magnetic resonance imaging. Within ACS populations, a culprit lesion was adjudicated on the basis of angiographic/IVUS appearance (e.g. presence of visible rupture or overlying thrombus) and if their arterial territory was implicated by changes on the electrocardiogram (ST-segment deviation or T-wave inversion).

VH-IVUS plaque classification

A plaque was defined as a lesion with >40% plaque burden (PB) over three consecutive VH-IVUS frames. A fibroatheroma (VH-FA) was defined as a plaque with >10% confluent necrotic core over three consecutive frames. If the confluent necrotic core remained in contact...
with the lumen for these frames, then it was classified as a thin-cap fibroatheroma (VH-TCFA). Any VH-FA not meeting VH-TCFA criteria was classified as a thick-cap fibroatheroma (VH-ThCFA). A fibrocalcific plaque (VH-FCa) contained $\leq 10\%$ confluent necrotic core, but $>10\%$ confluent dense calcium. Any plaques not meeting criteria for a fibroatheroma or VH-FCa were classified as pathological intimal thickening (VH-PIT). Examples of VH-defined plaque classification can be found in Supplemental Figure 1.
Supplemental Table 1. Predictive performance of plaque characteristics

Performance of baseline non-culprit lesion plaque characteristics to predict major adverse cardiovascular events.

*MLA*, minimal luminal area; *NPV*, negative predictive value; *PB*, plaque burden; *PPV*, positive predictive value; *TCFA*, thin-cap fibroatheroma; *VH*, virtual-histology

Data presented include 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>PB≥70%</th>
<th>MLA≤4mm²</th>
<th>VH-TCFA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity, %</strong></td>
<td>81.8 (60.0-94.0)</td>
<td>77.3 (54.2-91.3)</td>
<td>72.7 (49.6-88.4)</td>
</tr>
<tr>
<td><strong>Specificity, %</strong></td>
<td>81.3 (78.6-83.7)</td>
<td>74.3 (71.3-77.0)</td>
<td>40.0 (36.9-43.3)</td>
</tr>
<tr>
<td><strong>PPV, %</strong></td>
<td>9.6 (5.9-14.9)</td>
<td>6.8 (4.1-10.8)</td>
<td>2.9 (1.7-4.7)</td>
</tr>
<tr>
<td><strong>NPV, %</strong></td>
<td>99.5 (98.5-99.8)</td>
<td>99.3 (98.2-99.7)</td>
<td>98.4 (96.3-99.3)</td>
</tr>
<tr>
<td></td>
<td>PB≥70%</td>
<td>VH-TCFA</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>MACE†</td>
<td>Non-MACE‡</td>
<td>MACE*</td>
</tr>
<tr>
<td>Mean NC Area, mm²</td>
<td>1.29 (1.22)</td>
<td>1.15 (0.76)</td>
<td>0.98 (0.95)</td>
</tr>
<tr>
<td>Maximal NC Component Area, mm²</td>
<td>0.50 (0.54)</td>
<td>0.46 (0.44)</td>
<td>0.41 (0.46)</td>
</tr>
<tr>
<td>Mean DC Area, mm²</td>
<td>0.88 (1.06)</td>
<td>0.74 (0.99)</td>
<td>0.88 (1.82)</td>
</tr>
<tr>
<td>Maximal DC Component Area, mm²</td>
<td>0.51 (0.77)</td>
<td>0.44 (0.80)</td>
<td>0.58 (1.67)</td>
</tr>
</tbody>
</table>

**Superficial plaque region**

|                      | MACE†           | Non-MACE‡       | MACE*    | Non-MACE# | † vs. ‡ | * vs. # |
| Mean NC Area, mm²    | 0.05 (0.23)     | 0.04 (0.15)     | 0.09 (0.26) | 0.08 (0.22) | 0.05 | 0.10 |
| Maximal NC Component Area, mm² | 0.04 (0.22) | 0.04 (0.14) | 0.08 (0.23) | 0.07 (0.19) | 0.08 | 0.29 |
| Mean DC Area, mm²    | 0.19 (0.55)     | 0.17 (0.39)     | 0.38 (0.77) | 0.26 (0.54) | 0.05 | 0.07 |
| Maximal DC Component Area, mm² | 0.16 (0.47) | 0.13 (0.31) | 0.28 (0.57) | 0.20 (0.41) | 0.04 | 0.04 |

**Supplemental Table 2. Plaque composition in regions associated with MACE**

Plaque component areas in regions that are associated with future major adverse cardiovascular events.

*DC, dense calcium; MACE, major adverse cardiovascular events; NC, necrotic core; TCFA, thin-cap fibroatheroma*
Supplemental Figure 1. Study flow diagram

Flow diagram illustrating major adverse cardiovascular event (MACE) numbers.

*VH-IVUS, virtual-histology intravascular ultrasound*
Supplemental Figure 2. Illustrative examples of plaque classification by virtual-histology intravascular ultrasound

Examples of coronary plaques classified by virtual-histology intravascular ultrasound as pathological intimal thickening (A), fibrocalcific plaque (B), thick-cap fibroatheroma (C) and thin-cap fibroatheroma (D).
Supplemental Figure 3. Plaque stress derived from histology and virtual histology intravascular ultrasound

An illustrative example of a fibroatheroma seen on histology (A), with subsequent segmented image (B) and Band plot (C) illustrating plaque structural stress (PSS). Co-registered virtual-histology intravascular ultrasound (VH-IVUS) of the same fibroatheroma (D), again undergoing segmentation (E) and calculation of PSS (F). Note the similar locations of PSS between the images.
Supplemental Figure 4. Correlations between histological and VH-IVUS-derived plaque stress values

Correlation between histological and virtual histology intravascular ultrasound (VH-IVUS) -derived plaque structural stress values in both non-atherosclerotic vessel (A) and in advanced fibroatheromata (B).

Variables are correlated using Spearman's rank correlation coefficient (rho) for non-normally distributed data.
Supplemental Figure 5. Receiver operating curves for plaque structural stress to predict major adverse cardiovascular events

Receiver operating curves (ROC) for mean PSS values to predict major adverse cardiovascular events in the developmental plaque cohort (n=20) where plaque burden (PB)≥70% (A), minimal luminal area (MLA)≤4mm² (B) and in virtual-histology thin-cap fibroatheroma (VH-TCFA)(C).
Supplemental References
