Factors in this group, or on untargeted preventive measures. Whatever the reason, this phenomenon must be monitored and fast changes in lifestyles (diet, smoking, physical activity) should be induced.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1-2).

References


Non-invasive assessment of endothelial shear stress and coronary stiffness using multislice computed tomography

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We present a methodology for a safe, accurate, direct and rapid assessment of coronary stiffness and endothelial shear stress (ESS) with the use of multislice computed tomography. We report a positive correlation between coronary stiffness and ESS, which is a novel finding adding a new perspective to the already known interplay between ESS and plaque progression. High-volume plaques are located in arterial regions with low ESS and are less stiff compared to low-volume plaques, while non-stenotic plaques have lower stiffness than stenotic ones. Also, this is the first study to show that normal regions in the immediate proximity to plaques (≤2 mm) are less stiff and have lower ESS compared to normal segments located elsewhere. Coronary stiffness may potentially be a novel surrogate marker to characterize atherosclerotic plaque progression and vulnerability.

ESS is a major factor affecting atherosclerosis [1,2] as it determines the individual progression rate of any lesion [3]. Its calculation typically requires a three-dimensional (3D) coronary artery reconstruction by fusing intravascular ultrasound and coronary angiography [3–7]. However, these are both invasive procedures and embrace specific patient risks [8]. Novel non-invasive methods for 3D coronary imaging as multislice computed tomography (MSCT) [9] warrant diminished risks of adverse events and may be more widely applicable.

In vascular physiology, stiffness reflects the rigidity of the arterial wall [10]. During atherosclerotic plaque growth, the coronaries sustain qualitative and quantitative changes which result in gradual wall stiffening [11]. Stiffness is an emerging independent risk factor for coronary disease [12,13], as it is proposed to interplay with local ESS accentuating flow conditions which favor atherosclerosis [2].

We non-invasively studied the effects of coronary stiffness on ESS and atherosclerosis in 10 subjects (9 males, mean age 60.6 ±
3.4 years) undergoing cardiac MSCT (128-slice, SIEMENS, SOMATOM Definition AS+) for evaluation of suspected coronary artery disease. Blood pressure was measured with an arm-band sphygmomanometer prior to MSCT. The examination took place in a single breath hold and the images were ECG-gated. All participants provided written informed consent.

The coronary arteries were 3D reconstructed with use of MIMICS® v13.1 (Materialise NV, Leuven, Belgium). The lumen was reconstructed in both systole and diastole based on the ECG, whereas the arterial wall was reconstructed only in diastole (Fig. 1).

A computational grid was applied in each vessel (Gambit®, Fluent Inc Products, Lebanon, NH, USA) and was subsequently imported to computational fluid dynamics software (Fluent®, Fluent Inc Products, Lebanon, NH, USA). ESS and wall pressure were estimated in diastole and systole (Fig. 2). Each artery was divided in 2 mm-long segments (Rhinoceros® v4.0 McNeel and Associates, Seattle, WA, USA) (Fig. 3). Mean ESS and mean wall pressure were calculated in each segment in both cardiac phases using Matlab® (The MathWorks Inc, Natick, MA, USA).

Segments were further classified as diseased (apparent atherosclerotic lesions or wall thickening) and non-diseased (controls), and also in low- and high-ESS groups, the cut-off being 1 Pascal (Pa) in diastole. Lumen area and wall volume were measured in each segment. We considered the wall volume to represent plaque. Using the median volume (14.08 mm³) as cut-off, the plaques were assigned to high- and low-volume groups.

Arterial remodeling was assessed by calculating % luminal stenosis (% Stenosis) and using the mean of cross-sectional areas at the beginning (Sproximal) and end (Sdistal) of each plaque as reference (Fig. 4).

\[
\% \text{Stenosis} = \frac{S_{\text{reference}} - S_{\text{lesion}}}{S_{\text{reference}}} = \frac{S_{\text{proximal}} + S_{\text{distal}} - 2 \times S_{\text{lesion}}}{S_{\text{proximal}} + S_{\text{distal}}}
\]

where \(S_{\text{reference}}\) is the reference area and \(S_{\text{lesion}}\) the minimum lumen area in cases where lesion area was smaller than \(S_{\text{reference}}\) or the maximum lumen area in the cases where lesion area was larger than \(S_{\text{reference}}\). As of this definition, negative values for \% Stenosis denote luminal dilatation. Stenotic was considered for plaques causing \% Stenosis ≥25% whereas non-stenotic for those with values <25% or with luminal dilatation.

Coronary stiffness was computed in each segment using the formula

\[
\text{Stiffness} = \frac{\Delta P \times \Delta V}{V}
\]

where \(\Delta P\) is the mean wall pressure change, \(\Delta V\) the volume change from diastole to systole, and \(V\) the systolic volume [10].

![Fig. 1. Three-dimensional left anterior descending artery reconstruction, where both wall and lumen are visible.](image1)

![Fig. 2. Wall pressure and endothelial shear stress in the left anterior descending artery, calculated using computational fluid dynamics. Values are in Pascals.](image2)

![Fig. 3. Division of an artery in 2 mm-long segments.](image3)
where lesion area was larger than $S_{\text{reference}}$.

were 320 segments identified, 108 diseased and 212 non-diseased (Tables 1 and 2).

The stiffness of low-ESS segments was significantly smaller than that of high-ESS segments [median 57.8 IQR 36.4 to 93.4 mm Hg vs. median 83.1 IQR 38.5 to 166.2 mm Hg, $p<0.01$]. Non-stenotic plaques had also reduced stiffness compared to stenotic ones (median 50.2 IQR 32.7 to 90.9 mm Hg vs median 134.6 IQR 79.2 to 218.7 mm Hg, $p<0.001$). Atherosclerosis-free regions immediate (≤2 mm) and proximal to plaques (toward the ostium) tended to be less stiff (median 60.2 IQR 35.7 to 84.4 mm Hg vs median 81.2 IQR 51.5 to 143.3 mm Hg, $p=0.05$) and have lower ESS (median 0.85 IQR 0.60 to 1.44 Pa vs median 1.39 IQR 0.87 to 1.92 Pa, $p=0.06$) compared to the remaining normal segments.

These data show that atherosclerotic lesions with reduced wall stiffness have lower ESS (median 0.85 IQR 0.60 to 1.44 Pa vs median 1.39 IQR 0.87 to 1.92 Pa, $p=0.06$) compared to the remaining normal segments. High-volume plaques were prone to occur in low-ESS regions [odds ratio (OR) 2.29, 95% confidence intervals (CI) from 1.08 to 4.86, $p<0.05$] and were less stiff compared to low-volume plaques (median 52.5 IQR 36.9 to 101.9 mm Hg vs. median 83.1 IQR 38.5 to 166.2 mm Hg, $p<0.01$). Non-stenotic plaques had also reduced stiffness compared to stenotic ones (median 50.2 IQR 32.7 to 90.9 mm Hg vs median 134.6 IQR 79.2 to 218.7 mm Hg, $p<0.001$). Atherosclerosis-free regions immediate (≤2 mm) and proximal to plaques (toward the ostium) tended to be less stiff (median 60.2 IQR 35.7 to 84.4 mm Hg vs median 81.2 IQR 51.5 to 143.3 mm Hg, $p=0.05$) and have lower ESS (median 0.85 IQR 0.60 to 1.44 Pa vs median 1.39 IQR 0.87 to 1.92 Pa, $p=0.06$) compared to the remaining normal segments.

These data show that atherosclerotic lesions with reduced wall stiffness have lower ESS than areas with increased stiffness. Also, high-volume plaques are located in regions with lower ESS and are less stiff compared to low-volume plaques. Our study suggests that atheromatic lesions characterized by lower ESS and reduced stiffness accommodate high-volume plaques, where lipid-rich core likely prevails, but the lumen is preserved. On the other hand increased stiffness is noted in low-volume but stenotic plaques, where fibrous tissue and/or calcium are probably the major components.

Based on the above findings one could speculate that plaques with decreased stiffness are associated with certain features of vulnerability. High-volume plaques had a mean pathophysiologic basis with plaque vulnerability with extracellular matrix degradation being a common feature in both cases [14–16]. Vulnerable plaques are usually minimally stenotic and associated with expansive remodeling, characterized by a thin fibrous cap and a large necrotic lipid core, while low ESS has been found to be an independent predictor [1].

Normal segments proximal and contiguous to plaques tended to be less stiff and have lower ESS compared to the remaining normal segments, suggesting that regions close to plaques are susceptible to atherosclerosis. This concept may have potential implications in the optimal stent size selection in cases of percutaneous coronary intervention. This finding implies that in an earlier stage of atherosclerosis prior to intimal thickening, the coronary wall already exhibits structural changes reflected in decreased stiffness, and this may be the first marker of vascular pathology in these regions.

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Table 1
Study patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n)</th>
<th>Age (years)</th>
<th>Males</th>
<th>Body mass index (kg/m²)</th>
<th>Heart rate (bpm)</th>
<th>Medical history (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics/clinical characteristics</td>
<td>10</td>
<td>60.6 (43–77)</td>
<td>9</td>
<td>27.35 (24.6–38.2)</td>
<td>59 (44–77)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (10%)</td>
<td></td>
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<tr>
<td>Arrhythmia</td>
<td>2 (10%)</td>
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<tr>
<td>Aortic aneurysm</td>
<td>1 (10%)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>1 (10%)</td>
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<tr>
<td>Risk Factors for coronary artery disease</td>
<td>1 (10%)</td>
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<tr>
<td>Smoking</td>
<td>3 (30%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2 (20%)</td>
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<tr>
<td>Hypercholesterolemia (˃240 mg/dl)</td>
<td>7 (70%)</td>
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<td>Arterial hypertension</td>
<td>6 (60%)</td>
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<td>Positive family history</td>
<td>4 (40%)</td>
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<tr>
<td>Exercise (n)</td>
<td>4 (40%)</td>
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<tr>
<td>Walking</td>
<td>3 (30%)</td>
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<td>Teacher of martial arts</td>
<td>1 (10%)</td>
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<td>Medication (n)</td>
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<tr>
<td>Statins</td>
<td>5 (50%)</td>
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<td>e3-fatty acids</td>
<td>2 (20%)</td>
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<td>Calcium antagonists</td>
<td>3 (30%)</td>
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<td>Angiotensin converting enzyme inhibitors</td>
<td>3 (30%)</td>
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<td>Diuretics</td>
<td>4 (40%)</td>
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<tr>
<td>Angiotensin II receptor blockers</td>
<td>1 (10%)</td>
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Table 2
Characteristics of the investigated vessels and subsegments.

<table>
<thead>
<tr>
<th></th>
<th>Average length (mm)</th>
<th>Vessels</th>
<th>Subsegments</th>
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<tr>
<td></td>
<td>(mm)</td>
<td>Non-diseased</td>
<td>Diseased</td>
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<tr>
<td>LAD</td>
<td>75.01</td>
<td>1</td>
<td>5</td>
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<tr>
<td>RCA</td>
<td>84.60</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>73.92</td>
<td>3</td>
<td>7</td>
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</table>

References


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