Intravascular ultrasound assessment of remodelling and reference segment plaque burden in type-2 diabetic patients

Lisette Okkels Jensen1*, Per Thayssen1, Gary S. Mintz2, Michael Maeng3, Anders Junker1, Anders Galloe4, Evald Hoej Christiansen3, Soeren K.S. Hoffmann1, Knud Erik Pedersen1, Henrik Steen Hansen1, and Knud Noerregaard Hansen1

1Catheterization Laboratory, Department of Cardiology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark; 2Cardiovascular Research Foundation, New York, NY, USA; 3Department of Cardiology, Aarhus University Hospital, Skejby Hospital, Aarhus, Denmark; and 4Department of Cardiology, Gentofte Hospital, Gentofte, Denmark

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Aims Intravascular ultrasound (IVUS) assesses arterial remodelling by comparing the lesion external elastic membrane (EEM) with the reference segments; however, reference segments are rarely disease-free. The aim was to assess lesion and reference segment remodelling and plaque burden in patients with type-2 diabetes mellitus.

Methods and results We used pre-intervention IVUS to study 62 de novo lesions in 43 patients with type-2 diabetes mellitus. The lesion site was the image slice with the smallest lumen cross-sectional area (CSA). The proximal and distal reference segments were the most normal-looking segments within 5 mm proximal and distal to the lesion. Plaque burden was measured as plaque CSA/EEM CSA. The remodelling index was defined as lesion EEM CSA/mean reference EEM CSA. Reference segment plaque burden measured 0.54 ± 0.09. The majority of lesions (83.9%) had negative remodelling (lesion EEM, reference). Similarly, the slope of the regression line relating EEM to plaque CSA within the lesion was less than the reference substantiating negative remodelling. The reference segment plaque burden correlated inversely with the difference between IVUS lumen and quantitative coronary angiographic artery size [slope = −0.12 (95% CI −0.17 to −0.07); P < 0.001] in all patients with type-2 diabetes mellitus.

Conclusion Lesions in type-2 diabetic patients are different from previous reports in non-diabetics. Lesions in type-2 diabetics are characterized by a large reference segment plaque burden and negative lesion site remodelling. These IVUS findings may explain the angiographic appearance of small arteries in diabetic patients.

KEYWORDS Remodelling; Diabetes; Intravascular ultrasound; Reference vessel

Introduction

The term arterial remodelling refers to changes in vascular dimensions during the development of atherosclerosis. Remodelling can be either positive (when the vascular area increases as plaque develops) or negative (when the vascular area decreases as plaque develops).1 Intravascular ultrasound (IVUS) assesses arterial remodelling by comparing the lesion external elastic membrane (EEM) with the reference segments to generate a remodelling index (RI); however, reference segments are rarely disease-free, typically have a significant plaque burden, and, therefore, may also have undergone remodelling changes. Remodelling has been studied in vitro2 as well as in vivo using IVUS.3–9 Factors that have been shown to affect the RI include hypercholesterolaemia,10–12 diabetes,13 and the clinical presentation of coronary artery disease.8,14–16 The present study assesses lesion and reference segment remodelling and plaque burden in patients with type-2 diabetes mellitus.

Methods

Study population

From February 2005 to March 2006, 43 patients with type-2 diabetes mellitus and angiographically significant coronary stenoses in native coronary arteries were included. Use of IVUS before coronary intervention was at the operator's discretion, but no pre-dilation was allowed. The patients in the current analysis were from a study of 150 diabetic patients randomized to Cypher vs. Taxus stents. The including criteria for the randomized stent study were reference segment ≥ 2.0 mm and acceptance from the patient to have an 8 month IVUS follow up. Excluding criteria were vein grafts and intolerance to aspirin or clopidogrel. Pre-intervention IVUS was attempted in 43 patients in whom the treatment lesion was not
deemed too tight to perform pre-intervention imaging; it was successful in all the 43 patients. Severely calcific lesions and ostial lesions were not included in the study. All patients provided written, informed consent, and the local institutional review board (The Scientific Ethics Committee for the County of Aarhus, Denmark) approved the protocol (case no. 20040170).

Intravascular ultrasound imaging protocol and analysis

Pre-intervention IVUS was performed after administration of 200 μg intracoronary nitroglycerin. The IVUS system (Galaxy, Boston Scientific, Fremont, CA, USA) utilized a 40 MHz, 2.6 Fr IVUS catheter (Atlantis-Pro). Image acquisition using automated transducer pull-back at 0.5 mm/s was performed from at least 10 mm distal to the lesion retrograde to the aorto-ostial junction. Offline analysis was performed with a commercially available program for computerized planimetry (EchoPlaque, INDEC System, Mountain View, CA, USA).

For each 1 mm of axial length, lumen and EEM cross-sectional areas (CSAs) were measured. The EEM was measured at the leading edge of the adventitia. Plaque and media (P&M) CSA was calculated as EEM CSA minus lumen CSA. Plaque burden was calculated as P&M CSA divided by EEM CSA. The lesion site was the image slice with the smallest lumen CSA. Volumes were calculated using Simpson’s rule.

The proximal and distal reference segments were the most normal-looking segments (largest lumen with smallest plaque burden) within 5 mm proximal and distal to the lesion (Figure 1). RI was defined as lesion EEM CSA divided by mean reference EEM CSA. Negative remodelling was defined as an RI < 0.95.

Table 1  Baseline clinical characteristics

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>41</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>62</td>
</tr>
<tr>
<td>Age, years</td>
<td>63.0 ± 10.0</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>35 (85.4)</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td>143.2 ± 20.1</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>74.9 ± 11.7</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>11 (26.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3 ± 4.1</td>
</tr>
<tr>
<td>Insulin treatment, n (%)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Oral anti-diabetic medica-</td>
<td>29 (70.7)</td>
</tr>
<tr>
<td>tion, n (%)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Clinical presentation, n (%)</td>
<td>34 (82.9)</td>
</tr>
<tr>
<td>ACS</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>HgbA1c, mmol/L</td>
<td>0.075 ± 0.012</td>
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<tr>
<td>Lipid profile, mmol/L</td>
<td></td>
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<tr>
<td>Total cholesterol</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.3 ± 0.3</td>
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<tr>
<td>HDL cholesterol</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Statin treatment, n (%)</td>
<td>30 (73.2)</td>
</tr>
</tbody>
</table>

Statistical analysis

Categorical data are presented as counts and percentages, and continuous data are expressed as mean ± SD.

The statistical analyses were performed by SAS 9.1 (Proc Mixed). In order to take the multiple vessels within a patient into account, subjects were specified as random factor, and the measurements at different positions within a vessel (lesion, proximal reference, and distal reference segments, respectively) were specified as the repeated effect with a compound symmetry covariance structure. Other covariance matrices were estimated by restricted maximum likelihood. According to Akaike’s information criteria, the compound symmetry model was chosen. An additional random effect of vessel within patient was estimated, but the corresponding variance component was either zero or close to and therefore eliminated. This
model was used to test whether there was a significant change in CSA (EEM, lumen, P&M, and plaque burden) measurements at the three different positions: lesion, proximal reference, and distal reference segments, respectively (position used as a fixed effect). The mixed model was used for the analysis of covariance (linear regression). For this purpose, the repeated measurements within a patient was used to estimate an unstructured covariance matrix. The estimate for the covariate is called a slope in the presentation and is reported together with a 95% CI.

For all the models used, the degree of freedom was estimated by the method of Satterthwaite, and a probability value of \( P < 0.05 \) (two-sided) was considered significant.

Results

Baseline characteristics

We studied 62 de novo lesions in 41 patients with type-2 diabetes mellitus. Clinical features at baseline are shown in Table 1. Eight patients were treated with insulin, 29 patients were treated with oral antidiabetic medication, and four patients were treated with insulin plus one or more oral antidiabetic medications. Seven patients had acute coronary syndrome (ACS) and 34 patients had stable angina pectoris.

Intravascular ultrasound measurements

IVUS measurements are shown in Table 2. Overall, EEM CSA and lumen CSA were significantly smaller at the lesion site compared with the reference segments, whereas P&M CSA and plaque burden were significantly larger at the lesion site compared with the reference segments.

Overall, RI was 0.85 ± 0.13. The majority of lesions (84%) had negative remodelling. There were seven patients with two lesions (in two vessels) and seven patients with three lesions (in three vessels). In 12 of these 14 patients, the same remodelling pattern was seen in the multiple lesions studied. Similarly, the slope of the regression line relating EEM to P&M CSA within the lesion [slope = 1.06 (95% CI 1.01–1.12); \( P < 0.001 \)] was less than the reference [slope = 1.17 (95% CI 0.97–1.36); \( P < 0.001 \)] (Figure 2), substantiating negative remodelling at the lesion site. The slope of the regression line relating RI to P&M CSA within the lesion was significant [slope = 0.020 (95% CI 0.012–0.027); \( P < 0.001 \)] but this was not the case when relating RI to the reference segment P&M CSA [slope = 0.009 (95% CI –0.003 to 0.021); \( P = 0.13 \)].

Lesion EEM CSA correlated significantly with mean reference EEM CSA [slope = 0.94 (95% CI 0.83–1.06); \( P < 0.001 \)], and lesion P&M CSA correlated significantly with mean reference P&M CSA [slope = 1.10 (95% CI 0.90–1.30); \( P < 0.001 \)] (Figure 3).

When insulin-treated diabetics (whether or not they were also being treated with an oral agent) were compared with non-insulin-treated diabetics, RI was similar (0.82 ± 0.13 vs. 0.86 ± 0.12, \( P = 0.25 \)). Metabolic control (HgbA1c level) was not related to RI (\( P = 0.34 \)). RI was also similar when ACS patients were compared with stable patients (0.89 ± 0.18 vs. 0.84 ± 0.11, \( P = 0.35 \)). RI was similar in patients treated with a statin compared with no-lipid-lowering treatment (0.82 ± 0.10 vs. 0.87 ± 0.11, \( P = 0.20 \)).

Plaque burden in reference segments

Reference segment plaque burden measured 0.54 ± 0.10 (Figure 4): 0.55 ± 0.11 for the proximal reference segment and 0.53 ± 0.11 for the distal reference segment. Eighteen

| Table 2 | Intravascular ultrasound measurements |
|---|---|---|---|---|
| Lesion | Proximal reference | Distal reference | \( P \) |
| EEM CSA, mm\(^2\) | 11.9 ± 3.9 | 14.4 ± 4.1 | 13.4 ± 3.8 | <0.001 |
| Lumen CSA, mm\(^2\) | 2.9 ± 0.8 | 6.5 ± 2.7 | 6.1 ± 1.9 | <0.001 |
| P&M CSA, mm\(^2\) | 9.0 ± 3.6 | 7.9 ± 2.8 | 7.3 ± 2.9 | <0.001 |
| Plaque burden | 0.74 ± 0.08 | 0.55 ± 0.11 | 0.33 ± 0.11 | <0.001 |

![Figure 2](http://eurheartj.oxfordjournals.org/)

Relation between lesion external elastic membrane cross-sectional area and plaque and media cross-sectional area, and the relation between reference external elastic membrane cross-sectional area and plaque and media cross-sectional area.
(44%) of the patients had a plaque burden of >60% in the reference segment. The reference plaque burden was not related to the pattern of remodelling [slope = 0.13 (95% CI −0.05 to 0.31); \( P = 0.14 \)]. When insulin-treated diabetics were compared with non-insulin-treated diabetics, reference segment plaque burden was similar (0.54 ± 0.09 vs. 0.54 ± 0.10, \( P = 0.74 \)). When ACS patients were compared with stable patients, reference segment plaque burden was similar (0.59 ± 0.10 vs. 0.53 ± 0.09, \( P = 0.13 \)).

### Intravascular ultrasound volume measurements and lipids

In each lesion, a 10 mm long segment of artery centred on the minimum lumen site was analysed, and volumes were calculated. EEM and P&M volumes correlated inversely with total cholesterol, LDL cholesterol, and HDL cholesterol (Table 3).

### Quantitative coronary angiography vs. intravascular ultrasound

The overall angiographic diameter stenosis measured 54.8 ± 10.6%; the reference diameter measured 2.6 ± 0.4 mm (proximal reference = 2.7 ± 0.4 mm and distal reference = 2.5 ± 0.4 mm); MLD measured 1.2 ± 0.4 mm.

By IVUS, the reference lumen diameter was 2.81 ± 0.42 mm and the reference EEM diameter was 4.18 ± 0.56 mm. The plaque burden in the reference segment correlated inversely with the difference between IVUS lumen and QCA artery size [slope = −0.12 (95% CI −0.17 to −0.07); \( P < 0.001 \)] in all patients with type-2 diabetes mellitus (Figure 5). Angiographic reference diameter did not correlate with IVUS plaque burdens, neither in insulin-treated nor in non-insulin-treated patients.

### Discussion

In the current study, lesions in type-2 diabetic patients differed from those in non-diabetics reported previously. Type-2 diabetics had a larger reference segment plaque burden and a high frequency (83%) of negative lesion site remodelling, with 90% of the lesions having an EEM CSA less than the reference. The remodelling pattern was similar in diabetic patients with ACS vs. stable angina pectoris. Again, this is in contrast with studies in non-diabetics (or studies containing a limited number of diabetic patients), which showed that positive remodelling is more frequently observed in culprit lesions of patients with ACS and/or ruptured plaques, whereas negative remodelling classification is more commonly observed in target lesions of patients with chronic stable angina.14,17–19 The analysis in the present study applies only to angiographically stenotic lesions in diabetics, not to angiographically occult (or insignificant) lesions.

### Remodelling in diabetics vs. non-diabetics

Most studies have shown a high frequency of negative remodelling in diabetics, but the exact frequency varied from
study to study and may have depended on the patient population and the definitions used. The present study demonstrated that the slope of the regression line relating EEM to P&M CSA within the lesion was less than the reference substantiating negative remodelling. Moreover, when other definitions of remodelling were used, 80% of lesions in this diabetic population still had negative remodelling.

The slope of the line relating the change in arterial dimensions to the change in plaque mass over time is the direct measure of remodelling. A slope >1.0 would indicate positive remodelling with overcompensation (resulting in net lumen increase). A slope of 1.0 would indicate perfect positive remodelling, in which the increase in plaque was exactly balanced by the increase in EEM CSA, leading to no lumen change. A slope <1.0 (or reduction in EEM CSA) would indicate negative remodelling. However, serial studies necessary to 'directly' measure remodelling are rare. Instead, indirect evidence of coronary artery remodelling is obtained using an index obtained at a single time point, comparing the lesion site with the reference segment EEM CSA. Positive remodelling refers to a lesion EEM CSA greater than the reference, whereas negative remodelling refers to a lesion EEM CSA less than the reference.

Reference segments
In two-thirds of the patients, the reference segment plaque burden measured >50%. This is in accordance with a previous study in which the average plaque burden in angiographically normal reference segments was 50% and in which diabetes was an independent clinical predictor of reference segment plaque burden. This larger plaque burden in diabetics is one potential explanation for the smaller angiographic vessel sizes typically seen in these patients. Another explanation is that the reference segments may not outwardly remodel as much in diabetics compared with non-diabetics; therefore, the same plaque accumulation would have a greater impact on reference lumen dimensions. Since arterial remodelling with compensatory EEM enlargement develops to preserve the lumen, the EEM size by IVUS may be significantly greater than the lumen size by angiography. In the present study, although the QCA–IVUS reference lumen dimension differences correlated with reference plaque burden, the absolute QCA reference lumen diameter did not; this supports an important contribution of a reduced outward remodelling to smaller reference lumen dimensions in diabetics.

Limitations
We did not have serial IVUS studies; instead, we compared the lesion with the reference to assess remodelling. The number of patients was too small to do meaningful subset (i.e. insulin-treated vs. non-insulin-treated patient) analysis. The aim of the present study was to describe remodelling and plaque burden in diabetic patients. Although these findings were discussed in comparison with the well-documented findings in non-diabetics patients in the literature, we did not have a matched cohort of non-diabetic patients. As in other remodelling studies using IVUS, heavily calcified lesions were excluded when calcium shadowing was >180°, precluding measurement of EEM dimensions. Similarly, as in other remodelling studies using IVUS, ostial lesions were excluded because of the lack of a proximal reference segment and because ostial lesions are typically negatively remodelled even in non-diabetics.

Conclusion
The present IVUS study demonstrates that lesions in type-2 diabetics are characterized by a large reference segment plaque burden and mostly negative lesion site remodelling. These IVUS findings may help to explain the angiographic appearance of small arteries in diabetic patients.

Conflict of interest: none declared.
References


