Coronary Artery Remodelling is related to plaque composition

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ABSTRACT

Background: Arterial remodelling has been related to clinical presentation and positively remodelled plaques have previously shown typical features of plaque vulnerability.

Objective: To assess the potential relationship between plaque composition and vascular remodelling using spectral analysis of IVUS radiofrequency data.

Methods and Results: Forty-one coronary vessels with non-significant (<50 % diameter stenosis by angiography), ≤ 20 mm, non-ostial lesions located in non-culprit vessels underwent IVUS interrogation. Spectral analysis of intravascular ultrasound radiofrequency data, obtained with a 30 MHz catheter, was performed with IVUS-Virtual Histology™ software. Remodelling index (RI) was calculated and divided into 3 groups. Lesions with RI ≥ 1.05 were considered to have positive remodelling and lesions with RI ≤ 0.95 were considered to have negative remodelling. Lesions with RI ≥ 1.05 showed significantly larger lipid core than lesions with RI 0.96-104 and RI ≤ 0.95 respectively (22.1±6.3 vs 15.1±7.6 vs 6.6±6.9, p<0.0001). There was also a significant positive correlation between lipid core and RI (r=0.83, p=0.0001) and a statistically significant inverse correlation between fibrous tissue and RI (r=-0.45, p=0.003).

Thin-cap fibroatheroma (TCFA) and fibroatheromatous lesions comprised 100 % of the positively remodelled lesions, whereas negatively remodelled lesions presented a more stable phenotype, with 64 % of pathological intimal thickening, 29 % of fibrocalcific and only 7 % of fibroatheromatous lesions (p<0.0001)

Conclusions: In this study, in vivo plaque composition and morphology assessed using spectral analysis of IVUS radiofrequency data was related to coronary artery remodelling.
INTRODUCTION

Vascular remodelling was described by Glagov as a compensatory enlargement of the coronary arteries in response to an increase in plaque area\(^1\). This concept has further evolved to a dynamic theory where vessels may also shrink in response to plaque growth\(^2\). This remodelling modality has been related to a more stable phenotype and clinical presentation\(^3,6\), whereas several studies showed an increase in inflammatory marker levels, larger lipid cores and pronounced medial thinning in positive remodelled vessels\(^4,5,7\).

Recently, retrospective pathological studies have identified morphological and compositional features characteristic of plaque rupture \(^8,9\). This has lead to a new classification of coronary lesions that illustrates plaque progression in a more comprehensive manner \(^9\).

Gray-scale intravascular ultrasound (IVUS) is of limited value for identification of specific plaque components \(^10\). However, spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology) has demonstrated the potential to provide detailed quantitative information on plaque composition and has been validated in studies of explanted human coronary segments \(^11\).

In this study, we sought to evaluate \emph{in vivo} the relationship between plaque composition and coronary artery remodelling using ultrasound radiofrequency data analysis. In addition, we classified lesions with respect to its morphology \(^9\) and evaluated the potential relationship between lesion type and coronary remodelling.
METHODS

Patients

Forty-one consecutive patients were retrospectively selected after screening a 54 patient database where non-culprit, angiographically non-obstructive (<50 %), ≤ 20 mm, non ostial lesions were investigated with IVUS. Diffusely diseased vessels and the lack of the presence of a lesion occluding ≥ 40% of the cross sectional area precluded the inclusion in this study. Lesions located in proximal and mid segments of a coronary artery were included in the study.

Major exclusion criteria included coronary anatomy that precluded safe intravascular ultrasonographic examination of a suitable region of interest. Informed, written consent was obtained from all the patients.

IVUS-VH Acquisition and Analysis

Details regarding the validation of the technique, on explanted human coronary segments, have previously been reported. Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that classify plaque into four major components. In preliminary in vitro studies, four histological plaque components (fibrous, fibrolipid, lipid core and calcium) were correlated with a specific spectrum of the radiofrequency signal. These different plaque components were assigned colour codes. Calcified, fibrous, fibrolipidic and lipid core regions were labeled white, green, greenish-yellow and red respectively.

IVUS-VH data was acquired after intracoronary administration of nitrates using a continuous pullback (0.5 mm per second) with a commercially available mechanical
sector scanner (Ultracross™ 2.9F 30 MHz catheter, Boston Scientific, Santa Clara, CA), by a dedicated IVUS-VH console (Volcano Therapeutics, Rancho Cordova, CA). The IVUS VH data were stored on a CD-ROM and sent to the imaging core lab for offline analysis. IVUS B-mode images were reconstructed from the RF data by customized software (IVUSLab, Volcano Therapeutics, Rancho Cordova, CA). Subsequently, manual contour detection of both the lumen and the media-adventitia interface was performed. To account for catheter-to-catheter variability the acquired RF data was normalized using a technique known as “Blind Deconvolution”. Blind deconvolution is an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus enabling automated data normalization. Compositional data of the minimal lumen area (MLA) were expressed as percentage of the plaque cross sectional area (CSA) corresponding to each plaque component.

The MLA site and a reference ≤ 10 mm proximal to the lesion were selected. There were no major side-branches between MLA and reference sites.

Remodelling was assessed using the remodelling index (RI), expressed as the EEM CSA (MLA site) / EEM CSA (reference’s) as previously described, where EEM refers to the external elastic membrane.

We defined positive remodelling as RI ≥ 1.05 and negative remodelling as RI ≤ 0.95. Values in between were considered neutral (no remodelling). Percentage stenosis of the minimal luminal area (MLA) site was defined as:

\[
\text{Vessel}_{\text{area,MLA}} - \text{Lumen}_{\text{area,MLA}} / \text{Vessel}_{\text{area,MLA}}, \times 100.
\]

In accordance with previously reported data, we classified lesions into pathological intimal thickening (mainly fibrotic-fibrolipidic tissue, with lipid core comprising from
0% to \leq 3\% of the CSA), fibrocalcific lesions (featuring mainly fibrotic plaques, with some calcium and a lipid core occupying between 3\% and 10\% of the CSA), fibrous cap atheroma [lipid-rich (>10\% CSA) plaques with overlying fibrous tissue] and thin-cap fibroatheroma [lipid-rich (>10\% CSA) plaques with no overlying fibrous tissue]. Figure 1 depicts examples of this classification. In order to classify lesions as such, the above criteria had to be met in the MLA site plus the immediate distal and proximal cross-sections. Since the axial resolution of this technique is between 100-150 \text{ um}, we assumed that the absence of fibrous tissue overlying a lipid core suggested a cap thickness of below 100-150 \text{ um}^{16}.

**Statistical Analysis**

Discrete variables are presented as counts and percentages. Continuous variables are presented as means \pm SD. We looked for correlations between RI and both plaque components and percentage stenosis MLA using Pearson correlation coefficients. Differences in means among groups were analyzed by a two-sided t-test or by one-way analysis of variance. We compared frequencies with the \chi^2 test. A p value of less than 0.05 indicated statistical significance. Statistical analyses were performed with use of SPSS software version 11.5.
RESULTS

Patient characteristics are shown in table 1. Mean age was 55.9±10.9, most patients were male (83%) with a low prevalence of diabetes (7.3%). The study vessel was the right coronary artery in 19 patients (46.3%), the left anterior descending in 16 patients (39.0%) and the left circumflex in 6 patients (14.6%). Lesions with positive remodelling presented significantly larger lipid core percentages than lesions with no remodelling or negative remodelling (22.1±6.3 vs 15.1±7.6 vs 6.6±6.9 %, p<0.0001).

Negative remodelling lesions tend to show larger fibrous tissue percentages than lesions with no remodelling and positive remodelling (68.6±13.7 vs 62.9±9.5 vs 58.1±12.9 %, p=0.13). These results are shown in table 2.

Pearson correlation coefficients between RI and both plaque components and percentage stenosis MLA are presented in table 3. There was a significant positive correlation between lipid core and the RI (r= 0.83, p<0.0001, figure 2). Moreover, fibrous tissue was inversely correlated to the RI (r= -0.45, p=0.003, figure 3). Finally, there was a non-significant inverse relationship between the percentage stenosis MLA and the RI (r=-0.27, p=0.09).

With regards to the type of lesion, thin-cap fibroatheroma (TCFA) and fibroatheromatous lesions comprised 100% of the positive remodelled lesions, whereas negative remodelling lesions presented a more stable phenotype, with 64% of pathological intimal thickening, 29 % of fibrocalcific and only 7 % of fibroatheromatous lesions (Figure 4, p<0.0001)
Discussion.

Recently, the relationship between vascular remodelling and plaque composition was assessed using Intravascular ultrasound (IVUS)\textsuperscript{17-20}. This catheter-based diagnostic tool provides an accurate tomographic view of the coronary arteries and has shown a high correlation with histology samples in \textit{in-vitro} validation studies \textsuperscript{21-23}. Nevertheless, accurate plaque characterization with visual interpretation of gray-scale IVUS, particularly of lipid rich plaques, remains an unresolved issue \textsuperscript{22}. On the contrary, spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology) has demonstrated potential to provide detailed quantitative information on plaque composition and has been validated in studies of explanted human coronary segments \textsuperscript{11}.

The results of this study confirm \textit{in vivo} the relationship between plaque composition and coronary remodelling. Lipid core size was significantly larger in coronary lesions that demonstrated positive remodelling than in those that experienced vessel shrinkage. Furthermore, the fibrotic burden of the plaque was significantly and inversely correlated to the remodelling index.

Finally, positive remodelled lesions presented a higher risk phenotype, with 56 % of them being classified as TCFA, the lesion type with the highest likelihood of rupture \textsuperscript{24}. On the contrary, negative remodelling was associated with a more stable phenotype, with 64 % of pathological intimal thickening lesions and no evidence of TCFA. Fibrocalcific lesions, a potential hallmark of the end stage of the process of atheromatous plaque rupture and/or erosion with healing and calcification \textsuperscript{9}, were found in 29 % of negative remodelled lesions.
Overall, this findings support the importance of the histological composition of atherosclerotic plaque as a major contributor to its fate as described by Davies et al, who showed that plaques with $\geq 40\%$ of lipid core harbour a higher risk of undergoing rupture and subsequent thrombosis. The lipid core is a source of metalloproteinases, a group of proteolytic enzymes that have an important function in vascular remodelling mechanisms and whose most frequent location are foam-cell accumulation areas and shoulder regions.

Conversely, negative remodelled vessels showed predominantly fibrotic plaques. In addition, in line with previously reported data, lesions with negative remodelling were related to higher degree of stenosis. The findings of this study are consistent with previous pathological findings in sudden death patients. However, such post-mortem studies do not have implications in the natural history of high-risk plaques and thus in the clinical outcome of patients. On the contrary, we strongly believe that the identification of these high-risk plaques in vivo could provide more insights into the prognosis and natural history of such lesions and into the effect of conventional and emerging anti-atherosclerotic pharmacologic interventions.
Limitations

Since this was a cross sectional study and atherosclerosis is usually a diffuse disease, finding a fully non-diseased reference is not guaranteed. Therefore, we cannot rule out the early presence of remodelling in the reference site. In addition, this is a pilot study that needs further confirmation in a larger population. Moreover, lesion type classification performed by this technique lacks the accuracy of histopathology, since resolution is inferior. Nevertheless, a significant relationship was found using this arbitrary classification. Although histopathology remains the gold standard, this technique has the potential to provide real time accurate information regarding tissue characterization and plaque morphology.

Conclusions

In this small clinical study, in vivo plaque composition and morphology assessed using spectral analysis of IVUS radiofrequency data was related to coronary artery remodelling, supporting the role of plaque composition in the mechanisms of vessel remodelling. Lipid core size was significantly larger in coronary lesions that undergo positive remodelling than in those that experience vessel shrinkage. Furthermore, the fibrotic burden of the plaque was significantly and inversely correlated to the remodelling index. The findings of this study are consistent with previous pathological findings. However, post-mortem studies do not have potential to provide prospective information about the natural history of high-risk plaques. On the contrary, we strongly believe that the identification of these high-risk plaques in vivo could provide more insights into the prognosis and natural history of such lesions and into the effect of conventional and emerging anti-atherosclerotic pharmacologic interventions.
REFERENCES


### Table 1  Baseline characteristics (n: 41)

| Characteristic                                      | n (%)|  
|-----------------------------------------------------|------|---
| Age (yrs±SD)                                        | 55.9±10.9 |---
| Male sex                                            | 19 (83) |---
| Diabetes                                            | 3 (7.3)  |---
| Hypertension                                        | 12 (29.3)|---
| Current smoking                                     | 8 (19.5)|---
| Previous smoking                                    | 15 (36.6)|---
| Hypercholesterolemia                                | 32 (78) |---
| Family history of coronary disease                  | 19 (46.3)|---
| Previous myocardial infarction                      | 6 (14.6)|---
| **Clinical Presentation**                           |      |---
| No angina **                                        | 11 (26.8)|---
| Stable angina                                       | 14 (34.1)|---
| Unstable angina                                     | 6 (14.6)|---
| Myocardial infarction                               | 10 (24.4)|---

Vessel:
- Right coronary artery: 19 (46.3)
- Left anterior descending: 16 (39)
- Left circumflex: 6 (14.6)
Blood pressure ≥ 160/95 mmHg or treatment for hypertension, † total cholesterol >215 mg/dl or treatment for hypercholesterolemia. ** These patients were studied at scheduled follow-up angiography.
Table 2  Geometrical and compositional data of the minimal lumen area site.

<table>
<thead>
<tr>
<th>Remodelling index:</th>
<th>≤0.95</th>
<th>0.96-1.04</th>
<th>≥1.05</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%):</td>
<td>29 (70.7)</td>
<td>3 (7.3)</td>
<td>9 (22)</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD

| Percentage stenosis | 63.1±7.5 | 69.1±8.6 | 59.9±9.9 | 0.24    |
| Calcium CSA (%)     | 1.38±2.7 | 2.07±3.2 | 1.67±1.6 | 0.88    |
| Fibrous CSA (%)     | 68.6±13.7 | 62.9±9.5 | 58.1±12.9 | 0.13    |
| Fibrolipidic CSA (%)| 23.5±9.9 | 19.9±6.9 | 18.1±12.6 | 0.39    |
| Lipid core CSA (%)  | 6.6±6.9 | 15.1±7.6 | 22.1±6.3 | <0.0001 |

CSA refers to cross sectional area. Percentage stenosis of the minimal luminal area (MLA) site refers to \( \text{Vessel}_{\text{area}} \text{MLA} - \text{Lumen}_{\text{area}} \text{MLA} / \text{Vessel}_{\text{area}} \text{MLA}, \times 100 \). Remodelling index is defined as MLA EEM CSA / reference EEM CSA. EEM refers to external elastic membrane.
Table 3  Relationships between remodelling index, percentage stenosis of the minimal lumen area (MLA), and plaque composition of MLA site.

<table>
<thead>
<tr>
<th>Plaque Composition</th>
<th>Remodelling index</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid core CSA (%)</td>
<td>0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrous CSA (%)</td>
<td>-0.45</td>
<td>0.003</td>
</tr>
<tr>
<td>Percentage stenosis MLA</td>
<td>-0.27</td>
<td>0.09</td>
</tr>
<tr>
<td>Calcium CSA (%)</td>
<td>0.12</td>
<td>0.47</td>
</tr>
<tr>
<td>Fibrolipidic CSA (%)</td>
<td>-0.17</td>
<td>0.28</td>
</tr>
</tbody>
</table>

The values in the table are the Pearson correlation coefficients. CSA refers to cross sectional area. Percentage stenosis of the minimal luminal area (MLA) site refers to \( \frac{\text{Vessel}_{\text{area}}_{\text{MLA}} - \text{Lumen}_{\text{area}}_{\text{MLA}}}{\text{Vessel}_{\text{area}}_{\text{MLA}}} \times 100 \). Remodelling index is defined as \( \frac{\text{MLA EEM CSA}}{\text{reference EEM CSA}} \). EEM refers to external elastic membrane.
Legends:

Figure 1  Minimal lumen area (MLA) sites depicting the progression of the atherosclerotic disease. The different plaque components were assigned colour codes. Calcified, fibrous, fibrolipidic and lipid core regions were labeled white, green, greenish-yellow and red respectively. From left to right panels a, b, c and d show MLA sites featuring pathological intimal thickening, fibrocalcific, fibroatheromatous and thin-cap fibroatheromatous lesions.

Figure 2  Linear regression plot showing positive correlation between lipid core and remodelling. CSA refers to cross sectional area. Remodelling index is defined as MLA EEM CSA / reference EEM CSA. EEM refers to external elastic membrane.

Figure 3  Linear regression plot showing an inverse relationship between fibrous tissue and remodelling. CSA refers to cross sectional area. Percentage stenosis of the minimal luminal area (MLA) site refers to $\frac{Vessel_{area, MLA} - Lumen_{area, MLA}}{Vessel_{area, MLA}} \times 100$. Remodelling index is defined as MLA EEM CSA / reference EEM CSA. EEM refers to external elastic membrane.
Figure 4  Bar graphs illustrating the frequency on the different lesion types according to the remodelling modalities. Positive remodelled lesions showed 100 % of high risk plaques (56 % of thin-cap fibroatheroma and 44 % of fibroatheroma lesions). Negative remodeled lesions presented a more stable phenotype, with 93 % of low risk lesions and only 7 % of fibroatheromatous lesions.
Figure 1.
Figure 2
Figure 3
Figure 4