BASIC RESEARCH

Coronary artery remodelling is related to plaque composition

G A Rodriguez-Granillo, P W Serruys, H M Garcia-Garcia, J Aoki, M Valgimigli, C A G van Mieghem, E McFadden, P P T de Jaegere, P de Feyter

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See end of article for authors' affiliations

Correspondence to: Professor Patrick W Serruys, Thoraxcentre, Bd-406, Dr Molewaterplein 40, 3015-GD Rotterdam, Netherlands; p.w.j.c.serruys@erasmusmc.nl

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Objective: To assess the potential relation between plaque composition and vascular remodelling by using spectral analysis of intravascular ultrasound (IVUS) radiofrequency data.

Methods and results: 41 coronary vessels with non-significant (< 50% diameter stenosis by angiography), ⩽ 20 mm, non-ostial lesions located in non-culprit vessels underwent IVUS interrogation. IVUS radiofrequency data obtained with a 30 MHz catheter, were analysed with IVUS virtual histology software. A remodelling index (RI) was calculated and divided into three 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 had a significantly larger lipid core than lesions with RI 0.96–1.04 and RI ⩽ 0.95 (22.1 (6.3) *v* 15.1 (7.6) *v* 6.6 (6.9), $p < 0.0001$). A positive correlation between lipid core and RI ($r = 0.83$, $p < 0.0001$) and an inverse correlation between fibrous tissue and RI ($r = -0.45$, $p = 0.003$) were also significant. All of the positively remodelled lesions were thin cap fibroatheroma or fibroatheromatous lesions, whereas negatively remodelled lesions had a more stable phenotype, with 64% having pathological intimal thickening, 29% being fibrocalcific lesions, and only 7% fibroatheromatous lesions ($p < 0.0001$).

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

Glagov *et al*[1] described vascular remodelling as a compensatory enlargement of the coronary arteries in response to an increase in plaque area. This concept has further evolved into a dynamic theory whereby 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 concentrations, larger lipid cores, and pronounced medial thinning in positively remodelled vessels.[4 5 7]

Recently, retrospective pathological studies have identified morphological and compositional features characteristic of plaque rupture.[8 9] This has led to a new classification of coronary lesions that more comprehensively illustrates plaque progression.[9]

Grey 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 (VH)) has the potential to provide detailed quantitative information on plaque composition and has been validated in explanted human coronary segments.[11]

In this study, we sought to evaluate in vivo the relation between plaque composition and coronary artery remodelling by using ultrasound radiofrequency data analysis. In addition, we classified lesions with respect to their morphology and evaluated the potential relation between lesion type and coronary remodelling.[9]

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. Patients were excluded if they had diffusely diseased vessels or lacked a lesion occluding ⩾ 40% of the cross sectional area (CSA). Lesions located in proximal and mid segments of a coronary artery were included in the study.

Major exclusion criteria were coronary anatomy that precluded safe IVUS 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.[11] 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, fibrolipidic, lipid core, and calcified) were correlated with a specific spectrum of the radiofrequency signal.[11] These plaque components were assigned colour codes. Calcified, fibrous, fibrolipidic, and lipid core regions were labelled white, green, greenish yellow, and red, respectively.

IVUS-VH data were acquired after intracoronary administration of nitrates by means of a continuous pullback (0.5 mm/s) with a commercially available mechanical sector scanner (Ultracross 2.9 French, 30 MHz catheter; Boston Scientific, Santa Clara, California, USA) by a dedicated IVUS-VH console (Volcano Therapeutics, Rancho Cordova, California, USA). The IVUS-VH data were stored on a CD ROM and sent to the imaging core laboratory for offline analysis. IVUS B mode images were reconstructed from the radiofrequency data by customised software (IVUSLab, Volcano Therapeutics). Subsequently, contours of both the lumen and the media–adventitia interface were detected

Abbreviations: CSA, cross sectional area; IVUS, intravascular ultrasound; MLA, minimum lumen area; RI, remodelling index; VH, virtual histology

manually. To account for catheter to catheter variability the acquired radiofrequency data were normalised by 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 normalisation.[12 13] Compositional data of the minimum lumen area (MLA) were expressed as percentage of the plaque CSA corresponding to each plaque component.

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

Remodelling was assessed by means of the remodelling index (RI), expressed as the external elastic membrane CSA (MLA site) divided by the reference external elastic membrane CSA as previously described.[6 14 15].

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 MLA site was defined as:

$$vessel_{area}MLA - lumen_{area}MLA/vessel_{area}MLA \times 100.$$

In accordance with previously reported data, we classified lesions as pathological intimal thickening (mainly fibrotic–fibrolipidic tissue, with the lipid core constituting 0% to ⩽ = 3% of the CSA), fibrocalcific lesions (featuring mainly fibrotic plaques, with some calcification and a lipid core occupying between 3–10% 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. To classify lesions, these 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 µm, we assumed that the absence of fibrous tissue overlying a lipid core suggested a cap thickness of below 100–150 µm.[16]

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean (SD). We looked for correlations between the RI and both plaque components and percentage stenosis MLA by using Pearson correlation coefficients. Differences in means between groups were analysed by a two sided *t* test or by one way analysis of variance. We compared frequencies by means of the χ^2 test. A probability value of $p < 0.05$ indicated significance. Data were statistically analysed with SPSS software version 11.5 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Table 1 shows patient characteristics. Mean age was 55.9 (10.9). Most patients were men (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 six patients (14.6%).

Lesions with positive remodelling had significantly larger lipid core percentages than lesions with no remodelling or negative remodelling (22.1 (6.3)% *v* 15.1 (7.6)% *v* 6.6 (6.9)%, respectively, $p < 0.0001$). Negative remodelling lesions tended to have larger fibrous tissue percentages than lesions with no remodelling and positive remodelling (68.6 (13.7)% *v* 62.9 (9.5)% *v* 58.1 (12.9)%, $p = 0.13$). Table 2 shows these results.

Table 3 presents Pearson correlation coefficients between the RI and both plaque components and percentage stenosis MLA. The positive correlation between the lipid core and the RI was significant ($r = 0.83$, $p < 0.0001$) (fig 2). Moreover, fibrous tissue was inversely correlated with the RI ($r = -0.45$, $p = 0.003$) (fig 3). Lastly, the percentage stenosis of the MLA and the RI were non-significantly inversely related ($r = -0.27$, $p = 0.09$).

With regard to lesion type, thin cap fibroatheroma and fibroatheromatous lesions comprised 100% of the positively

Table 1 Baseline characteristics (n = 41)

Age (years)	55.9 (10.9)
Men	19 (83%)
Diabetes	3 (7.3%)
Hypertension*	12 (29.3%)
Current smoking	8 (19.5%)
Previous smoking	15 (36.6%)
Hypercholesterolaemia†	32 (78%)
Family history of coronary disease	19 (46.3%)
Previous myocardial infarction	6 (14.6%)
Artery	
Right coronary	19 (46.3%)
Left anterior descending	16 (39%)
Left circumflex	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%)

Data are mean (SD) or number (%).
*Blood pressure ⩾160/95 mm Hg or treatment for hypertension; †total cholesterol >5.57 mmol/l or treatment for hypercholesterolemia; ‡these patients were studied at scheduled follow up angiography.

Table 2 Geometrical and compositional data of the minimum lumen area (MLA) site

	Remodelling index			
	⩽0.95	0.96–1.04	⩾1.05	p Value
Number	29 (70.7%)	3 (7.3%)	9 (22%)	
Stenosis (%)	63.1 (7.5)	69.1 (8.6)	59.9 (9.9)	0.24
Calcific 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

Data are mean (SD).
Percentage stenosis of the MLA site is calculated as $vessel_{area}MLA - lumen_{area}MLA/vessel_{area}MLA \times 100$. Remodelling index (RI) is defined as MLA of the external elastic membrane (EEM) cross sectional area (CSA)/reference EEM CSA.

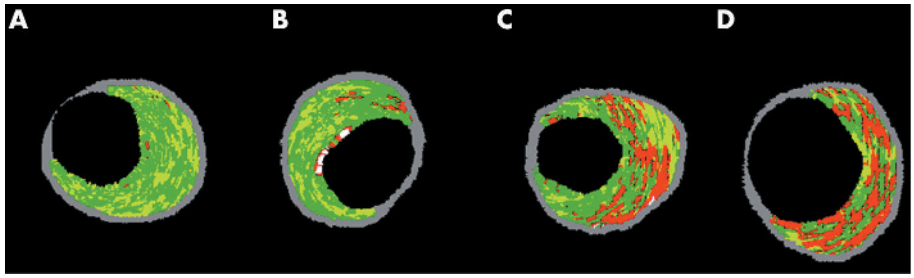

Figure 1 Minimum lumen area (MLA) sites depicting the progression of atherosclerotic disease. The plaque components were assigned colour codes. Calcified, fibrous, fibrolipidic, and lipid core regions were labelled white, green, greenish yellow, and red, respectively. MLA sites feature (A) pathological intimal thickening and (B) fibrocalcific, (C) fibroatheromatous, and (D) thin cap fibroatheromatous lesions.

Table 3 Relations between remodelling index (RI), percentage stenosis of the MLA, and plaque composition of the MLA site

	RI	p Value
Lipid core CSA (%)	0.83	<0.0001
Fibrous CSA (%)	−0.45	0.003
Percentage stenosis MLA	−0.27	0.09
Calcific CSA (%)	0.12	0.47
Fibrolipidic CSA (%)	−0.17	0.28

Data are Pearson correlation coefficients.

remodelled lesions, whereas negative remodelling lesions had a more stable phenotype: 64% had pathological intimal thickening, 29% were fibrocalcific, and only 7% were fibroatheromatous lesions ($p < 0.0001$) (fig 4).

DISCUSSION

Recently, the relation between vascular remodelling and plaque composition was assessed by IVUS.[17–20] This catheter based diagnostic tool provides an accurate tomographic view of the coronary arteries and in vitro validation studies have shown a high correlation with histological samples.[21–23] Nevertheless, accurate plaque characterisation with visual interpretation of grey scale IVUS, particularly of lipid rich plaques, remains unresolved.[22] On the contrary, spectral analysis of IVUS radiofrequency data (IVUS-VH) has the potential to provide detailed quantitative information on plaque composition and has been validated in studies of explanted human coronary segments.[11]

The results of the present study confirm in vivo the relation between plaque composition and coronary remodelling. Lipid core size was significantly larger in positively remodelled coronary lesions than in those with vessel shrinkage. Furthermore, the fibrotic burden of the plaque was significantly and inversely correlated with the RI.

Lastly, positively remodelled lesions had a higher risk phenotype, with 56% of them being classified as thin cap fibroatheroma, the lesion type most likely to rupture.[24] On the contrary, negative remodelling was associated with a more stable phenotype: 64% had pathological intimal thickening and no evidence of thin cap fibroatheroma. Fibrocalcific lesions, a potential hallmark of the end stage of atheromatous plaque rupture or erosion with healing and calcification, were found in 29% of negatively remodelled lesions.[9]

Overall, these findings support the importance of the histological composition of atherosclerotic plaque as a major contributor to its fate as described by Davies *et al*,[8] who showed that plaques with a large lipid core harbour a higher risk of 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 common locations are foam cell accumulation areas and shoulder regions.[25 26]

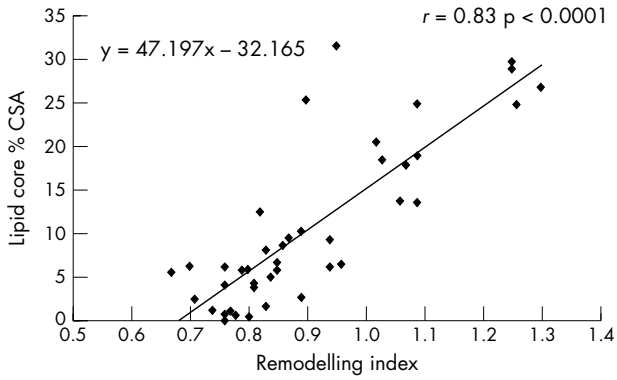

Figure 2 Linear regression plot showing positive correlation between lipid core and remodelling. CSA, cross sectional area. Remodelling index is defined as MLA of the external elastic membrane (EEM) CSA/reference EEM CSA.

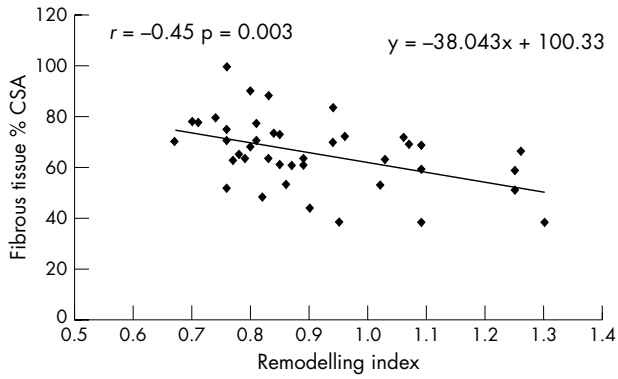

Figure 3 Linear regression plot showing an inverse relation between fibrous tissue and remodelling.

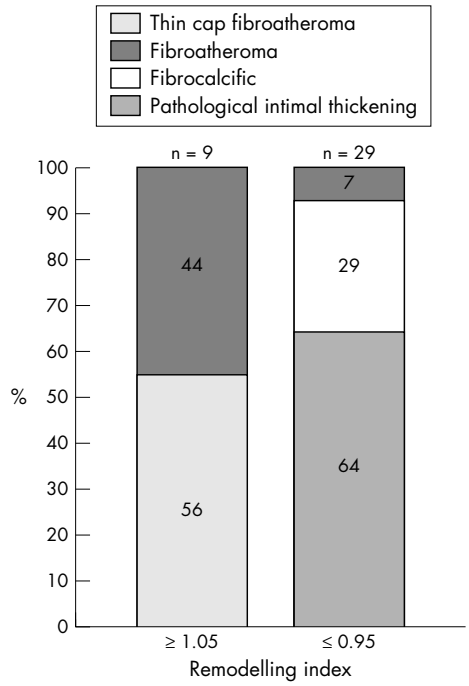

Figure 4 Bar graphs illustrating the lesion type frequencies according to remodelling modality. All of the high risk plaques had positive remodelling (56% were thin cap fibroatheroma and 44% fibroatheromatous lesions). Negatively remodelled lesions had a more stable phenotype, with 93% being low risk lesions and only 7% fibroatheromatous lesions.

Conversely, negatively remodelled vessels consisted predominantly of fibrotic plaques. In addition, in line with previously reported data, negatively remodelled lesions had a higher degree of stenosis.[2 17 27] The findings of this study are consistent with previous pathological findings in patients after sudden death.[5] However, such postmortem 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 may provide more insights into the prognosis and natural history of such lesions and into the

effect of conventional and emerging anti-atherosclerotic pharmacological interventions.

Limitations

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

Conclusions

In this small clinical study, in vivo plaque composition and morphology assessed by spectral analysis of IVUS radiofrequency data were related to coronary artery remodelling, supporting the role of plaque composition in the mechanisms of vessel remodelling. Lipid core size was significantly larger in positively remodelled coronary lesions than in those with vessel shrinkage. Furthermore, the fibrotic burden of the plaque was significantly and inversely correlated with the RI. The findings of this study are consistent with previous pathological findings. However, postmortem studies do not have the 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 may provide more insights into the prognosis and natural history of such lesions and into the effect of conventional and emerging anti-atherosclerotic pharmacological interventions.

Authors' affiliations

G A Rodriguez-Granillo, P W Serruys, H M Garcia-Garcia, J Aoki, M Valgimigli, C A G van Mieghem, E McFadden, P P T de Jaegere, P de Feyter, Thoraxcentre, Erasmus Medical Centre, Rotterdam, the Netherlands

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All authors have approved the final manuscript, which has not been published and is not under consideration elsewhere.

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