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Positive remodeling at 3 year follow up is associated with plaque free coronary wall segment at baseline: A serial IVUS study

Jolanda J. Wentzel [a, c, *], Frank J.H. Gijsen [a], Rose van der Giessen [a], Gaston Rodriguez -Granillo [b], Johan C.H. Schuurbiers [a], E. Regar [b], Pim J. de Feyter [b], Antonius F.W. van der Steen [a, c]

[a] Department of Biomedical Engineering, ErasmusMC, Rotterdam, The Netherlands
[b] Department of Interventional Cardiology, ErasmusMC, Rotterdam, The Netherlands
[c] The Interuniversity Cardiology Institute the Netherlands, Utrecht, The Netherlands

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ABSTRACT

Aims: At present it is unknown what limits the arterial remodeling process during atherosclerotic plaque formation. In healthy arteries remodeling is regulated by the shear stress induced response by the endothelium. As endothelium at the plaque site is assumed to be dysfunctional, we tested the hypothesis that plaque free wall (PFW) determines vascular remodeling during atherosclerotic plaque build-up.
Methods & results: 66 human coronary ROIs (38 patients) were studied at baseline and at 3 years follow up applying intravascular ultrasound (IVUS). From the IVUS images the lumen and external elastic membrane contours were delineated to assess wall thickness (WT), vessel area (VA), Plaque Area (PA) and plaque burden (PA/VA*100%). WT < 0.5 mm was defined as normal and determined the arc of the PFW (0–360°). Positive remodeling was defined as relative difference of VA over time >5%. At baseline, IVUS-PFW was inversely related to plaque burden ($p < 0.05$). Positive remodeling was most frequently observed in ROIs with IVUS-PFW > 180° (i.e. larger than half of the circumference) compared to PFW < 180° (55% vs. 12%, $p < 0.05$). Accordingly, plaques with IVUS-PFW > 180° at baseline had the largest change in VA (1.1 ± 2.1 vs. −0.4 ± 0.6 mm^2, $p < 0.05$) with an odds ratio of 9.2 to develop positive remodeling.
Conclusions: Our serial IVUS data show that IVUS-PFW is a determinant of vascular remodeling. ROIs with PFW > 180 at baseline had the highest probability to undergo positive remodeling.

1. Introduction

In the course of atherosclerotic plaque build-up in the vascular system, it is well known that positive vascular remodeling of the artery is responsible for preservation of the lumen area [1]. However, if the disease proceeds and becomes in an advanced stage, patients are confronted with lumen stenosis implying that positive remodeling is not always sufficient to compensate for the total plaque load. Glagov et al. were the first to show that the limited capacity of cross sections to remodel outwards was related to the plaque burden, this is the plaque area to vessel area ratio [1]. Plaques with a plaque burden exceeding 40% showed lumen narrowing, whereas vascular cross sections with smaller plaque burdens were still prevented from luminal stenosis.

Positive vascular remodeling was studied with respect to the local plaque composition. Plaques that showed positive remodeling were often asymmetric, had large plaque burden and were composed of lipids [2,3], inflammation [2–4] and matrix degrading enzymes [4,5]. Whereas plaques that showed negative remodeling were more concentric diseased [2,6], had smaller plaques and sometimes superficial calcium [6,7]. From pathology studies, positive remodeling was recognized as one of the characteristics of the vulnerable plaque phenotype [8] and large prospective patients studies confirmed this observation. Recently, it became clear that coronary arteries with a small lumen size and/or a large plaque burden and/or positive remodeling with low attenuation on CT had a high propensity to cause an acute coronary event [9–11,12].

* Corresponding author. Biomedical Engineering, Biomechanics Laboratory, EE2322, ErasmusMC, PO Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 (0) 10 7044044; fax: +31 (0) 10 7044720.
E-mail address: j.wentzel@erasmusmc.nl (J.J. Wentzel).

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Although plaque composition was associated with positive remodeling, until now it is not fully understood how positive vascular remodeling during atherosclerotic plaque build-up is controlled and why at a certain moment positive vascular remodeling is inadequate to prevent lumen narrowing. In normal arteries, remodeling is a homeostatic response to changes in the flow and circumferential stretch to restore normal shear stress and wall tension, respectively [13]. The endothelial cells are instrumental in the blood flow related vascular response because of a number of endothelium dependent pathways [14]. Since the endothelium covering atherosclerotic plaque is considered to be dysfunctional [15] and positive remodeled plaques are mostly eccentric [6], we hypothesize that the healthy wall segment of the artery regulates positive remodeling in atherosclerotic arteries. Eccentric plaques often grow in circumferential direction, thereby decreasing the arc of the vessel wall being free of plaque, which will hamper further enlargement of the vessel area and thus vascular remodeling. In this study, we investigated the relationship between vascular remodeling over a 3 year period and the size of the plaque free vessel wall using serial intravascular ultrasound measurements.

2. Methods

2.1. Study population/demographics

Patients underwent IVUS imaging as part of the PERSPECTIVE study, which is a sub-study of the EUROPA trial [16]. The PERSPECTIVE trial investigated the effect of long-term 3 years administration of perindopril on plaque progression in not infarct-related or treated coronary arteries as assessed by intravascular ultrasound [17]. After a run-in period of 4 weeks, in which all patients received perindopril, patients were randomly assigned perindopril 8 mg once daily, or matching placebo. We performed a post-hoc analysis on the placebo patients of this trial. The institutional medical ethical committee approved the study protocol, and all patients gave written informed consent to participate in this study.

2.2. Intravascular ultrasound image acquisition

Intravascular ultrasound (IVUS) images were acquired using a 30 or 40 MHz imaging catheter (UltraCross or Atlantis 2.9Fr, Boston Scientific). The IVUS catheter was positioned just distal to an anatomically identifiable landmark, including calcified spots and side branches. The position of the IVUS catheter before the pullback was documented by using x-ray angiography. An automatic pullback device was performed with a continuous speed of 0.5 mm/s until the ostium of the artery was reached. IVUS images were acquired after the administration of nitroglycerin to minimize the influence of vascular tone on the results. At 3 years follow up the measurements were repeated and an IVUS catheter with the same frequency as was used for the baseline imaging was positioned according to the anatomical landmarks to ensure visualization of the same region of interest.

2.3. Intravascular ultrasound analysis

The IntelliGate™ image-based gating method was retrospectively applied to the IVUS images selecting end-diastolic frames [18] for analysis.

In order to match the corresponding two pullbacks of each patient, we developed software (MATLAB, Mathworks Inc., USA), so that both the baseline and follow up IVUS images were visualized simultaneously side-by-side accounting for differences in longitudinal resolution due to differences in heart rate. This software allows for manual registration, based on anatomically landmarks, of the two stacks of IVUS images so as to obtain matched data sets. Only precisely matched cross sections were used for further analysis.

Quantitative IVUS analysis was performed using semi-automated contour detection software (Curad, version 3.1, Wijk bij Duurstede, The Netherlands). The contours of the lumen-leading edge interface and the lamina elastica externa were delineated and the following parameters were derived: lumen area (LA), vessel area (VA), plaque area (PA) = VA − LA, plaque burden = PA/VA*100%. The dimensions of the coronary arteries (lumen, wall and outerwall) within an ROI were averaged to represent the overall ROI response. Wall thickness was determined as the distance between lumen-leading edge interface and the lamina elastica externa. Plaque thickness >0.5 mm was considered as diseased. This cut-off value was based on earlier histological data [19] and IVUS study [20], that also used this criterion to discriminate between presence and absence of plaque. Plaque free wall (PFW) was defined as the arc of the vessel wall having a wall thickness<0.5 mm [19,20] expressed in degrees: PFW = 360° means totally healthy, PFW = 0° means disease with more than 0.5 mm wall thickness over the complete circumference. To determine the PFW on IVUS (IVUS-PFW), the circumference was subdivided into 32 equidistant angles and at each angle the wall thickness was evaluated.

For all parameters also the change over time was calculated such that baseline values were subtracted from the follow up values and expressed as ΔLA, ΔVA, ΔPA, ΔIVUS-PFW, Δplaque burden. The relative change in VA was defined as: ΔVA/VA baseline*100%. Positive remodeling was defined as the relative change in VA>5% and negative remodeling as relative change in VA < −5%, as also was used by the group of Pasterkamp [19]. Note that positive and negative remodeling are now defined as change in VA over time with respect to the baseline VA contrasting other studies, which use a reference cross section at a different location as reference.

Only cross sections in between side branches were used for the statistical analysis, except for the cross sections having more than 90° of calcium or for other reasons more than 90° of invisible lamina elastic externa at baseline or follow up.

2.4. Statistics

A region of interest (ROI) consists of all the cross sections in between two side branches. For each ROI the average of the geometrical parameters (LA, VA, PA, IVUS-PFW, plaque burden) was calculated, which represents the geometry of the ROI. Averaging the data for each ROI was performed because of 2 reasons: a) individual cross section within 0.5 mm might not be considered independent b) analyzing each individual cross section would unacceptably increase the power. Subsequently, the ROIs were stratified according to the vascular remodeling response over the 3 year period: positive remodeling (>5% relative ΔVA), no remodeling, negative remodeling (<−5% relative ΔVA) and differences between those 3 groups regarding baseline geometric parameters were investigated using ANOVA.

An X^2-test was used to study differences in frequency distribution of the vascular remodeling response among ROIs with a small or large IVUS-PFW (<180° and >180°), small or large plaque burden (<40% vs. >40%), originating from different vessel types, originating from patients with or without myocardial infarction.

A general linear model was used to study the differences in remodeling response among the ROIs with a small or large IVUS-PFW (<180° and >180°). This analysis was repeated to study the influence of plaque burden (<40%, >40%) on the 3 years remodeling response.

We built a logistic regression model to study the determinants of positive remodeling in the 3 year follow up period. The parameters included in the model were the IVUS-PFW and the ΔPA. The plaque growth was added to the model to correct for individual differences in plaque progression and thereby to highlight the role of PFW in the remodeling process. The model provided us with odds ratios for positive remodeling dependent on IVUS-PFW corrected for plaque growth. Therefore, the ROIs were divided into 2 groups based on the ΔPA (median of ΔPA = 0.18 mm^2, category 1: <0.18 mm^2, category 2 > 0.18 mm^2).

The sensitivity, specificity, positive predictive value and negative predictive value of IVUS-PFW for prediction of future positive remodeling was calculated. All statistical analysis were performed with SPSS 16.0 SPSS Inc., Chicago, IL, USA); $p < 0.05$ was considered significant.

3. Results

3.1. Patient information

A total of 58 coronary arteries of 58 patients were imaged at baseline and follow up. Because of technical reasons no data were available in 10 patients, 8 had poor image quality and 2 had not enough landmarks to match the baseline and follow up data, resulting in 38 analyzable patients with high quality, serial datasets. In these 38 patients 66 ROIs were distinguished, consisting of 1432 matched cross sections; this is on average 1.7 ± 0.7 ROIs per patient. The demographics are listed in Table 1. The average follow up time was 3.4 ± 0.5 years.

Table 1
Baseline patient characteristics ($n = 38$).

Age	54 ± 8
Male sex (*n*, %)	33 (87%)
Diabetes (*n*, %)	5 (13%)
Hypertension (*n*, %)	11 (29%)
Hypercholesterolemia (*n*, %)	31 (82%)
Smoking (*n*, %)	4 (11%)
Family History of CHD (*n*, %)	13 (34%)
Previous MI (*n*, %)	20 (53%)
Previous PTCA (*n*, %)	38 (100%)
Previous CABG (*n*, %)	0 (0%)
Heart rate	66 ± 6
Medications	
Lipid lowering therapy	31 (13%)
Platelet inhibitors	37 (97%)
β-blockade	23 (60%)
Calcium channel blockers	14 (37%)
Nitrates	5 (13%)

Hypercholesterolemia defined as cholesterol > 6.5 mmol/L or on lipid-lowering therapy. Hypertension: blood pressure> 160/95 mmHg or receiving antihypertensive treatment. All values are mean ± SD or (*n*, %).

3.2. Baseline geometric parameters

At baseline, the average LA, VA and PA area for the ROIs were respectively, 10.0 ± 4.0 mm^2, 15.8 ± 4.9 mm^2, 5.8 ± 2.4 mm^2. The average plaque burden was 37 ± 11%, while the average IVUS-PFW equaled 215 ± 79°. IVUS-PFW and plaque burden were significantly, inversely related to each other (IVUS-PFW = 430-5.7* plaque burden, $r = 0.85$, $p < 0.05$), implying that with increasing plaque burden the PFW decreases (Fig. 1).

3.3. Vascular remodeling at 3 year follow up versus baseline geometric parameters

In total from the 66 ROIs, 11 ROI (17%) were negatively remodeled during the follow up period, 26 ROI (39%) did not remodel and 29 ROI (44%) underwent positive remodeling. Baseline geometric parameters for ROIs developing positive remodeling, no remodeling or negative remodeling during the follow up period are presented in Table 2. ROIs with positive remodeling in the follow up period had at baseline a smaller plaque burden and a smaller PA than segments that did not undergo positive remodeling (no remodeling or negative remodeling), whereas the LA and VA were the same. Furthermore, the PFW at baseline was larger (248 ± 61° vs. 168 ± 68°, $p < 0.001$) for the ROI's that experienced positive remodeling compared to the ROIs with negative remodeling. At follow up, ROIs that underwent positive remodeling resulted in a larger LA and a smaller IVUS-PFW than at baseline being still borderline significant from the other ROIs (Table 2).

3.4. Positive remodeling at 3 year follow up is associated with plaque free wall and plaque burden at baseline

To further study the involvement of IVUS-PFW in the vascular remodeling response at 3 year follow up, the ROIs were divided into 2 groups based on IVUS-PFW at baseline (<180°, >180°) and the remodeling response (ΔVA and the relative ΔVA) was plotted for both groups (Fig. 2A and B). For ROIs with IVUS-PFW>180° ($n = 49$) at baseline, the VA increased in the follow up period (1.1 ± 2.1 mm^2, 7.8 ± 14.3%, $p < 0.01$), contrasting ROIs with IVUS-PFW<180° ($n = 17$), in which no change in VA (−0.4 ± 1.7 mm^2, −2.1 ± 8.0%, p = ns) was observed. Accordingly, positive remodeling (relative ΔVA >5%) was most often observed for ROIs with IVUS-PFW>180° at baseline (55% vs. 12%, $p < 0.05$, X^2-test, Fig. 2C). If we analyzed the data per vessel type, we noticed that the remodeling response in the RCA differed from the LAD and LCX, showing positive remodeling in 90% of the ROIs with IVUS-PFW >180° while that was 46% and 50% for the LAD and LCX respectively ($p < 0.05$, X^2-test). The frequency with which positive remodeling was observed in the 3 year follow up period in ROIs with large IVUS-PFW (IVUS-PFW >180) at baseline did not differ for patients that had experienced a myocardial infarction in their history compared to the ones without a myocardial infarction (55% vs. 55%). However, for patients with a history of myocardial infarction positive remodeling was less exclusively associated with IVUS-PFW >180°, but was also seen in 29% of the ROIs with IVUS-PFW <180°.

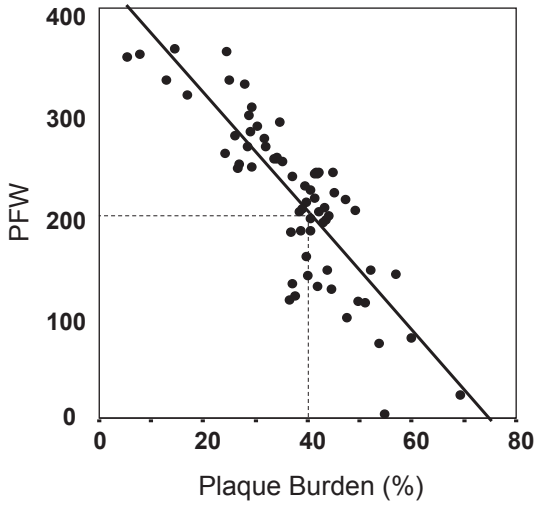

Fig. 1. Regression plot of PFW vs. plaque burden – Relationship between plaque free vessel wall (PFW, degrees) and plaque burden (%) at baseline. PFW equals 202° for plaque burden is 40%.

Table 2
Vascular remodeling at 3 year follow up versus geometric parameters.

Baseline	Negative remodeling $N = 11$	No remodeling $N = 26$	Positive remodeling $N = 29$	*P* value
Lumen area (mm^2)	10.3 ± 4.9	9.2 ± 2.6	10.5 ± 4.5	p = ns
Vessel area (mm^2)	17.6 ± 5.8	15.5 ± 4.3	15.4 ± 5.0	p = ns
Plaque area (mm^2)	7.3 ± 2.4[a]	6.3 ± 2.5	4.9 ± 1.9	$p < 0.001$
Plaque burden %	42.8 ± 12.7	40.3 ± 10.1[a]	32.7 ± 11.1	$p < 0.05$
PFW	168 ± 68[a]	198 ± 89	248 ± 61	$p < 0.001$
Follow up				
Lumen area (mm^2)	10.3 ± 4.9	9.2 ± 2.8[a]	12.2 ± 5.6	$P < 0.05$
Vessel area (mm^2)	15.8 ± 5.0	15.3 ± 4.3	17.8 ± 5.6	p = ns
Plaque area (mm^2)	6.8 ± 2.3	6.1 ± 2.7	5.6 ± 2.6	p = ns
Plaque burden %	44.6 ± 14.9[a]	38.9 ± 10.4	32.7 ± 14.0	$p < 0.05$
PFW	178 ± 78	201 ± 87	237 ± 81	$p = 0.095$

[a] Significant difference compared to positive remodeling group, All values are mean ± SD.

Fig. 3 depicts an example of a representative IVUS cross section from 2 different ROIs, one with a IVUS-PFW <180° and one with a IVUS-PFW >180° at baseline. The one with IVUS-PFW >180 showed positive remodeling at follow up, while the one with PFW <180°, no change in VA was observed. The odds ratio to develop positive remodeling for ROIs with IVUS-PFW >180° equaled 9.2 compared to ROIs with PFW <180° (Logistic regression analysis with IVUS-PFW >180° as determinant, $p < 0.05$).

As plaque burden was known to influence the vascular remodeling response, this analysis was repeated for the plaque burden. Therefore, the ROIs were subdivided based on plaque burden at baseline (plaque burden <40%, plaque burden >40%) and the remodeling response was plotted (Fig. 4). ROIs with plaque burden <40% ($n = 37$) at baseline showed an increase in VA (1.2 ± 2.4 mm^2, 8.4 ± 14.8%, $p < 0.01$) over the follow up period, while for ROIs with plaque burden >40% ($n = 29$) no significant VA change (0.1 ± 1.6 mm^2, 1.1 ± 10.7%) was observed (Fig. 4A and B). Correspondingly, ROIs with plaque burden<40% were more frequently positively remodeled (57%) compared to ROIs with plaque burden>40% (38%, $p < 0.01$, X^2-test) (Fig. 4C). The odds ratio to develop positive remodeling for segments with plaque burden<40% equaled 3.4 compared to segments with plaque burden>40% (logistic regression analysis, $p < 0.05$). If we analyzed the data per vessel type, we noticed that the remodeling response in the RCA differed from the LAD and LCX, showing positive remodeling in 89% of the ROIs with plaque burden <40% while that was 39% and 57% for the LAD and LCX respectively ($p < 0.05$, X^2-test). The frequency with which positive remodeling was observed in the 3 year follow up period in ROIs with small plaque burden (<40%) at baseline did not differ for patients that had experienced a myocardial infarction in their history compared to the ones without a myocardial infarction (57% vs. 56%).

3.5. Positive remodeling at 3 year follow up is associated with plaque free wall at baseline corrected for plaque growth

Because plaque accumulation is a known determinant of vascular remodeling, plaque accumulation itself might explain the presence or absence of vascular remodeling irrespective of the size of the IVUS-PFW. Therefore, the ROIs were also divided into 2 groups based on the ΔPA (median of ΔPA = 0.18 mm^2, category 1: <0.18 mm^2, category 2 > 0.18 mm^2). The average ΔPA for category 1 was −0.84 ± 0.72 mm^2, meaning that the plaque decreased over the follow up period ($p < 0.05$). Segments in category 2 showed an increase in plaque area with an average ΔPA of 1.18 ± 1.18 mm^2.

Fig. 5A and B shows that both IVUS-PFW and ΔPA significantly contributed to ΔVA (Fig. 5A, general linear model, $p < 0.05$ both parameters). ROIs that had plaque growth (category 2) resulted in the largest increase in VA for ROIs with IVUS-PFW >180° compared

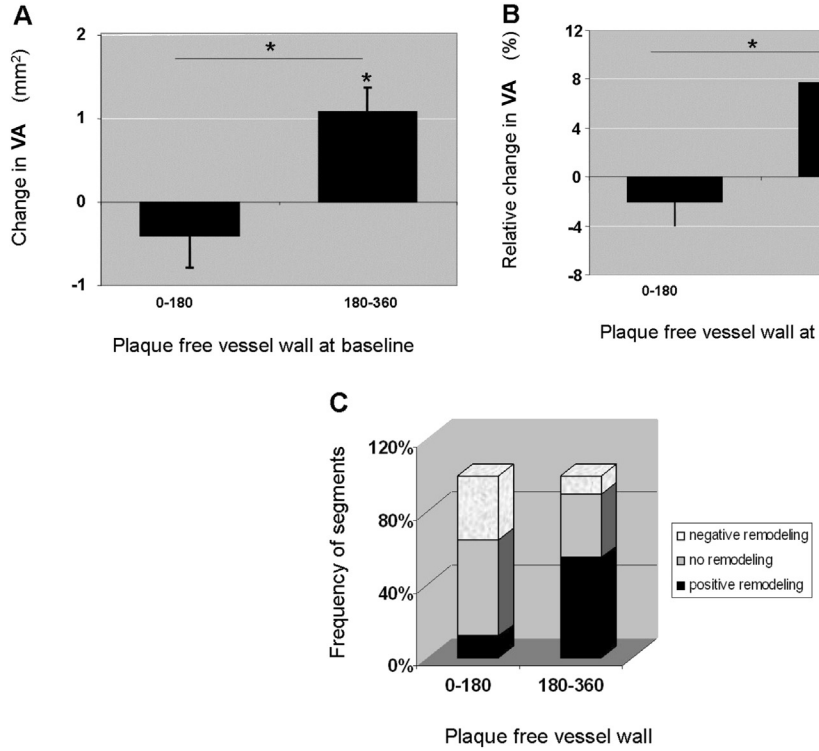

Fig. 2. Bar graph of remodeling vs. PFW- Bar graph illustrating A) the relationship between change in VA and plaque free vessel wall at baseline B) the relationship between the relative change in VA and plaque free vessel wall at baseline C) Frequency of segments with positive remodeling, no remodeling and negative remodeling dependent on PFW (<180°, >180°).

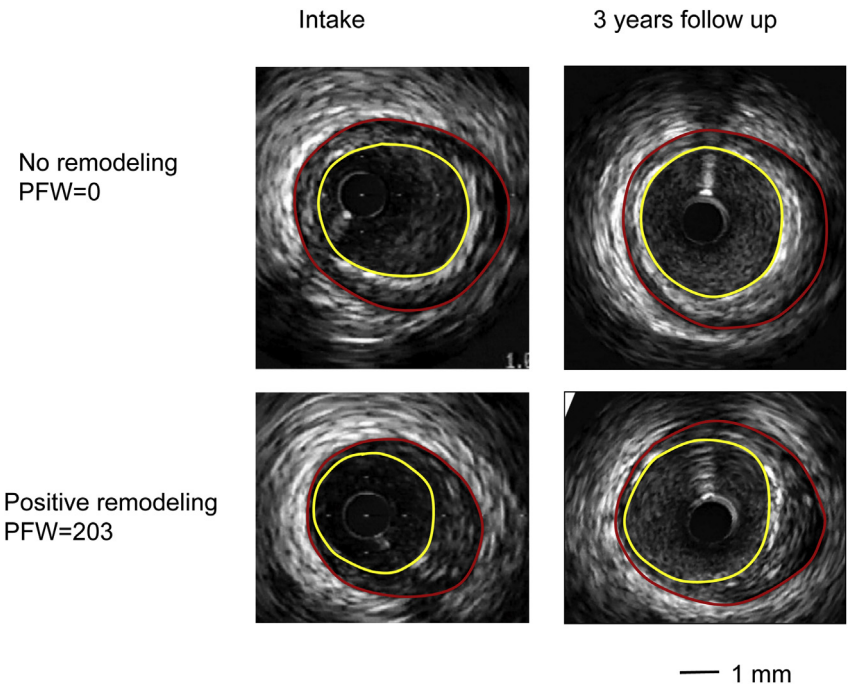

Fig. 3. Representative intravascular ultrasound cross section of 2 different segments: Upper panels: PFW = 0° at baseline and lower panels PFW = 203° at baseline (yellow = lumen; red = boundary at lamina elastica externa = vessel area). At follow up a different response is observed for the segment with PFW<180°: no remodeling (right, upper panel), while for the segment with PFW>180° positive remodeling was observed (right, lower panel).

to the ROIs with IVUS-PFW <180°. Because plaque growth itself was not related to IVUS-PFW at baseline (Fig. 5C, p = NS), the differences in response of the VA (Fig. 5A) must be attributable to differences in IVUS-PFW at baseline. Fig. 5D depicts the percentage segments that undergo positive remodeling dependent on IVUS-PFW and ΔPA. This figure illustrates that the majority of the segments (68%) with plaque increase > 0.18 mm^2 and a IVUS-PFW >180° will result in positive remodeling which differs significantly from the segments

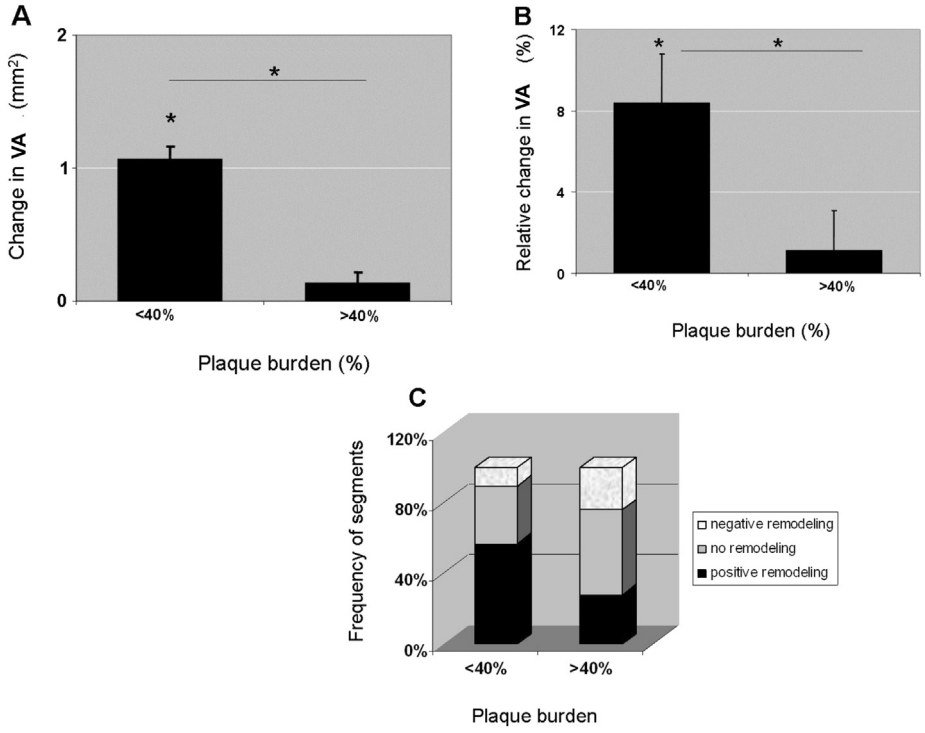

Fig. 4. Bar graph of remodeling vs. plaque burden – Bar graph illustrating A) the relationship between change in VA and plaque burden at baseline B) the relationship between the relative change in VA and plaque burden at baseline C) Frequency of segments with positive remodeling, no remodeling and negative remodeling dependent on plaque burden (<40%, >40%).

with IVUS-PFW <180° and plaque decrease (category 2) (0%). The odds ratio for developing positive remodeling corrected for ΔPA is 7.5 for segments with IVUS-PFW >180° compared to segments with IVUS-PFW <180°.

3.6. Predictive value of PFW

To further investigate IVUS-PFW >180° as predictor for positive remodeling over a 3 years period, we calculated the sensitivity, specificity, positive predictive value and negative predictive value being 0.93, 0.43, 0.55, 0.88 respectively (Fig. 6). This means that 93% of the ROIs that underwent positive remodeling had a IVUS-PFW >180° at baseline and 55% of the ROIs that had IVUS-PFW >180° at baseline resulted in positive remodeling. Obviously, positive remodeling is only needed if plaque growth is present, so we also studied the combination of IVUS-PFW >180° and plaque growth in the follow up period (ΔPA > 0.18 mm^2) as determinants for positive remodeling. The combined measure resulted in a sensitivity, specificity, positive predictive value and negative predictive value for positive remodeling of 0.65, 0.76, 0.68, 0.74 respectively.

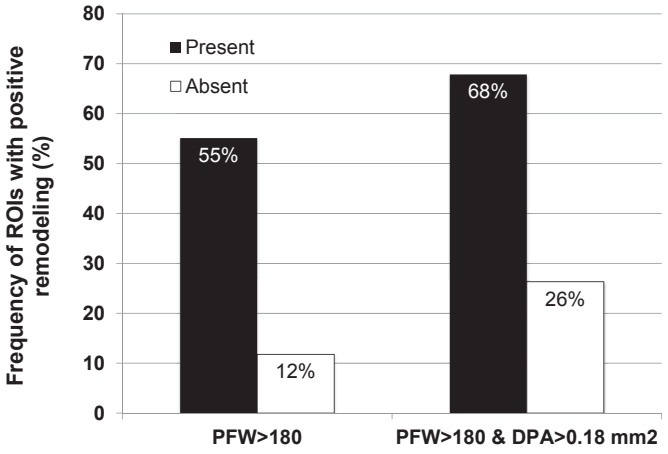

Fig. 6. Frequency of ROIs with positive remodeling (%) if at baseline the PFW>180° (left part) or PFW>180 + ΔPA>0.18 mm^2 (right part) is present (black bars).

4. Discussion

We described the relationship between plaque free vessel wall at baseline and changes in vessel area *over a 3 year time period* using intravascular ultrasound. For the studied cohort of patients, positive remodeling at 3 years follow up was associated with PFW at baseline also after correction for plaque growth. For segments with IVUS-PFW >180° the odds ratio to develop positive remodeling in the follow up period was 9.2 compared to PFW <180°, which still was 7.5 when adjusting for the effects of plaque accumulation.

4.1. Vascular remodeling versus plaque free wall

Glagov et al. showed in 1987 for the first time that positive vascular remodeling prevents lumen narrowing during atherosclerotic plaque build-up [1] and many researchers showed the

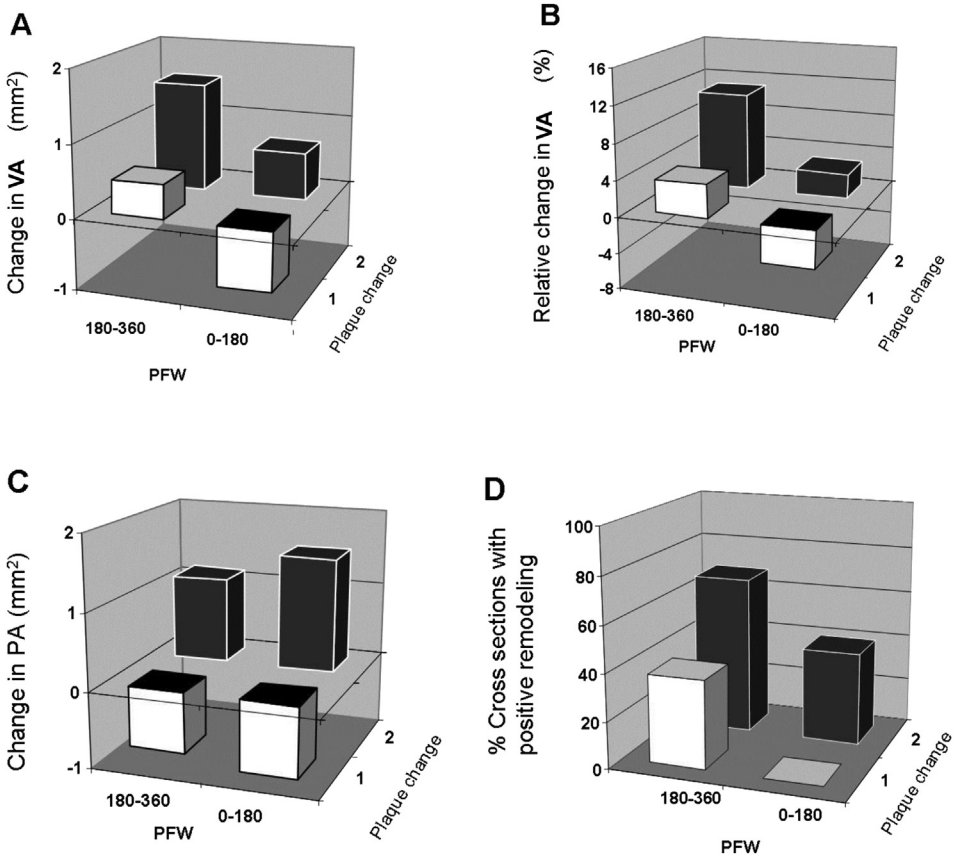

Fig. 5. Bar graph of remodeling vs. PFW and plaque growth – Bar graph illustrating A) the relationship between change in VA, plaque change (category 1: <0.18 mm^2 and category 2: >0.18 mm^2) and PFW at baseline B) the relationship between the relative change in VA, plaque change and PFW at baseline C) Frequency of segments with positive remodeling, no remodeling and negative remodeling dependent on plaque change and PFW.

validity of his observation [21–23]. However, until now no explanation was found for the observation that at a certain moment during the atherosclerotic process lumen narrowing start to occur, which is associated with inadequate positive vascular remodeling. Glagov [1] showed that lumen narrowing started to occur for plaques with plaque burden exceeding 40%.

As to find a reason for inadequate positive remodeling for plaques exceeding plaque burden of 40%, knowledge on factors involved in vascular remodeling is of utmost importance. Glagov mentioned 2 possible mechanisms for vascular remodeling during plaque growth [1]. The first mechanism which was proposed to explain vascular remodeling during plaque growth was the notion that the segment opposite of the plaque, free of disease, could respond to changes in the local shear stress. At the plaque free site it is anticipated that the endothelium is still functional contrasting the plaque site where the endothelium is dysfunctional. With increasing plaque burden focal lumen narrowing theoretically increase the shear stress and trigger vascular adaptation of the PFW. Because of plaque growth the circumference of the vessel wall would be fully occupied, which could prevent further enlargement of the vessel area by eliminating the segment that reacts to increased flow velocity. Indeed, in mice with atherosclerotic plaques exposed to flow increase, MMP expression was upregulated at the plaque free part, implying remodeling at that side of the wall (personal communication with dr. S. Lehoux). This implies that the plaque free vessel wall would be responsible for the capacity of the artery to react to changes in shear stress and thus would control the lumen in the vascular remodeling process. Varnava et al. also mentioned this possibility after showing that positively remodeled arteries had a larger arc free of disease [2]. Although we showed that the changes in vessel area over a 3 year period were related to the extent of the plaque free vessel wall at baseline (Fig. 2), we cannot confirm the involvement of the PFW in maintaining the lumen size (Table 2). Positively remodeled vessels showed an increase in lumen area. However, our study was limited by the use of medication, especially statins that aim at plaque regression and improvement of endothelial function. Whether that is the reason for the observed local plaque regression and/or lumen increase in these patients needs to be further studied.

Our data contradict the results obtained in human autopsy material [19], were no relationship between PFW and vascular remodeling was found. However, that data were obtained at one moment in time and quantification of vascular remodeling was based on a reference cross section supposedly representing the geometry before remodeling, which is shown to be disputable [24].

In addition, we found a strong inverse relationship between the relative plaque burden and IVUS-PFW (Fig. 1, $r = 0.85$). This means that plaques with increasing plaque burden are confronted with a smaller PFW, such that plaques with plaque burden larger than 40% have IVUS-PFW smaller than 202°. This might explain the observation of Glagov et al. that plaques with a plaque burden >40% did not adequately remodel resulting in lumen narrowing, as those plaques with plaque burden>40% were confounded by the presence of a small IVUS-PFW. If IVUS-PFW >202 was used to predict positive remodeling in the follow up period the positive predictive value was 0.63, which increased to 0.78 if also plaque growth was taken into consideration. This means that ROIs with a large IVUS-PFW at baseline (larger than 202°) that have plaque growth (ΔPA >0.18 mm^2) will undergo positive remodeling in 78% of the cases. Obviously, cardiologists would not know on forehand if the disease would further progress in a particular patient, but it shows the importance of the IVUS-PFW.

The second mechanism, which was proposed to explain vascular remodeling during plaque growth, was the outward bulging of the plaque due to enzymatic degradation of the underlying media [1] caused by local inflammation [2,3]. However, this mechanism would not explain the limited vascular remodeling for plaques exceeding a certain thickness or plaque burden. Bentzon studied this mechanism in the aortic root of atherosclerotic mice [21]. They showed that with plaque growth the media was degraded behind the plaque, providing evidence for this theory. However, translation of these data to human coronary arteries is not so straightforward, as the anatomy of the aortic root differs considerably and has a much complexer hemodynamic environment. Other studies in coronary arteries of atherosclerotic pigs by the group of Peter Stone showed that low shear stress induced inflammation potentially stimulates expression of matrix degrading enzymes that are involved in excessive remodeling leading to plaque vulnerability [4,5]. On the other hand, plaque components may also lead to plaque retraction leading to negative remodeling as for instance a maturing plaque may show a reduction in lipid content, an increase in fibrosis, calcification and apoptosis [7]. Our study did not allow studying outward bulging or retraction as possible mechanism of vascular remodeling, as for that purpose an external reference structure is needed to check which part of the vessel wall had grown or retracted.

Although it cannot be ruled out that outward bulging or retraction contributed to the vessel dimensions of the vessel wall, vascular remodeling was independently related to IVUS-PFW, also after correction for plaque growth. Therefore it can be envisioned that both mechanisms work hand in hand: plaque composition is involved in plaque bulging or contraction and the PFW determines the final vessel area by growth of the plaque free part.

4.2. Vascular remodeling versus plaque burden at MLA

Our results are different from Hartman [23] and Schartl [25], who found no significant difference in vascular remodeling over a 12 months period between ROIs with plaque burden smaller and larger than 40%. They included in their study per ROI only the cross section with minimal lumen area (MLA), which is in contrast to our study that used the average of the ROI. The MLA is, per definition, the most diseased part of the ROI and therefore only a smaller range in disease is studied than if the average of the ROI was taken. If we, similar to Hartman et al. [23], selected per ROI the MLA cross sections, the plaque burden (<40% and >40%) did also not differentiate between the absolute increase in VA (1.7 ± 1.7 mm^2, 0.7 ± 2.2 mm^2, $p = 0.07$) and relative increase in VA ($11.8 \pm 13.7\%$ $5.8 \pm 15.5\%$, $p = 0.15$). Interestingly, if the MLA cross sections were divided into 2 groups based on PFW (<180°, >180°), a significant difference was observed in absolute and relative VA increase between the cross sections with IVUS-PFW >180° and IVUS-PFW <180° (IVUS-PFW <180°: 0.59 ± 1.98 mm^2, IVUS-PFW >180°:1.65 ± 2.12 mm^2, $p = 0.05$ and IVUS-PFW <180°: $4.6 \pm 14.2\%$, IVUS-PFW >180°: $12.8 \pm 15.6\%$, $p = 0.04$).

The change in vessel area per year that we found over the 3 year follow up period (0.3 mm^2/year), was lower than observed by Hartman (0.7–1.1 mm^2/year) and Sipahi et al. 0.7–1 mm^2/year [23,26,27], who studied patients with a 18 months time interval. If we performed the analysis at the cross section with MLA only, we obtained a maximal growth rate of the vessel area of 0.5 mm^2/year. Whether the remaining discrepancy in results can be attributed to the differences in follow up time needs to be investigated.

5. Limitations

As with the most long-term serial IVUS studies, the current paper included a relatively small number of patients. Of the 58 patients, only 38 could be used for this study, which resulted in 66

segments. Although the number was relatively small, significant differences between the studied groups were found.

Although the ROIs that we studied had a large range of plaque burdens, in general, the average in plaque burden was quite low (32–40%), implying early disease. We cannot exclude that in later phases of the disease the functionality of the endothelium of the plaque fee part is diminished and thereby overestimating the role of the PFW.

We showed the positive remodeling response to be dependent on the arc free of disease (IVUS-PFW), also if corrected for plaque growth. Although this finding does confirm our hypothesis on the contribution of healthy endothelium to this vascular remodeling response, we did not measure the local functionality of the endothelium and thereby cannot exclude that the functionality of the healthy part was diminished compared to patients free of disease, which might explain absence of positive remodeling at some locations. Future studies could benefit from endothelial function measurements, as factor to be included in the prediction model.

Other confounding factors potentially modulating the remodeling response include the presence of certain plaque components such as matrix degrading enzymes, inflammation [4]. However, because of the application of IVUS our study set up did not allow to include those factors in the prediction of vascular remodeling.

Another limitation of our study was that we could not study cross sections with more than 90° calcium. IVUS cannot visualize the vessel wall behind local calcium and therefore the vessel contour could not be properly delineated at those locations. An earlier study on the influence of calcium suggested a limited remodeling response in the presence of calcium, but could thereby not be investigated [7].

The angle defining the IVUS-PFW was based on the local wall thickness, such that a wall thickness smaller than 0.5 mm was considered as normal. Although this value was based on histological data of coronary segments [22] and used by others before [19,20,28], it could potentially influence the outcome of the study. Therefore, we checked whether adjustment of this value to 0.4 or 0.6 mm would change the conclusion of our study essentially. Obviously, the number of segments having a IVUS-PFW >180° changed, but the absolute and relative change in VA were still significant different for the segments with IVUS-PFW smaller and larger than 180°, including correction for plaque change.

6. Clinical relevance

Plaque rupture has been shown to be most frequently observed in vessels that underwent positive remodeling and therefore positive remodeling serves as one of the characteristics of the vulnerable plaque phenotype. However, large clinical trials on the natural history of plaques showed that not the remodeling status, but plaque burden >70% and lumen area <5 mm^2 resulted in a high hazard ratio (around 5–7) for future cardiovascular events [10,11]. In that study the positively remodeled vessels had the highest plaque burden, next to the negative remodeled vessels that showed the lowest lumen areas, being both predictive for coronary events [29]. So knowledge on determinants of positive remodeling, like PFW has potential to indirectly aid in the estimation of cardiovascular risk.

Besides our data on the association of PFW and future positive remodeling, PFW can also be instrumental in estimating the plaque burden. Fig. 1 shows a clear inverse relationship between PFW and plaque burden. Since, not all intravascular imaging modalities, including OCT, can visualize the outer boundaries of the vessel wall, they might benefit from knowledge on the relationship between PFW and plaque burden to be used in risk prediction. Other studies are needed to affirm the involvement of PFW in vulnerable plaque formation in the follow up period and clinical presentation.

7. Conclusion

This paper is the first to show that plaque free wall is associated with vascular remodeling during atherosclerotic plaque formation in a follow up period of 3 years. Furthermore, as we showed that IVUS-PFW is inversely related to the plaque burden, PFW could also serve in the estimation of plaque burden to be used in risk prediction.

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References

[1] Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316(22):1371–5.
[2] Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. Circulation 2002;105(8):939–43.
[3] Pasterkamp G, Schoneveld AH, van der Wal AC, Haudenschild CC, Clarijs RJ, Becker AE, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol 1998;32(3):655–62.
[4] Chatzizisis YS, Jonas M, Beigel R, Coskun AU, Baker AB, Stone BV, et al. Attenuation of inflammation and expansive remodeling by Valsartan alone or in combination with Simvastatin in high-risk coronary atherosclerotic plaques. Atherosclerosis 2009;203(2):387–94.
[5] Chatzizisis YS, Baker AB, Sukhova GK, Koskinas KC, Papafaklis MI, Beigel R, et al. Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps in pigs. Circulation 2011;123(6):621–30.
[6] von Birgelen C, Mintz GS, de Vrey EA, Kimura T, Popma JJ, Airiian SG, et al. Atherosclerotic coronary lesions with inadequate compensatory enlargement have smaller plaque and vessel volumes: observations with three dimensional intravascular ultrasound in vivo. Heart 1998;79(2):137–42.
[7] Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. Circulation 1997;95(7):1791–8.
[8] Schaar JA, Muller JE, Falk E, Virmani R, Fuster V, Serruys PW, et al. Terminology for high-risk and vulnerable coronary artery plaques. Eur Heart J 2004;25(12):1077–82.
[9] Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50(4):319–26.
[10] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364(3):226–35.
[11] Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in vulnerable atherosclerosis) Study. JACC Cardiovasc Imaging 2011;4(8):894–901.
[12] Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the prediction Study. Circulation 2012;126(2):172–81.
[13] Langille BL. Arterial remodeling: relation to hemodynamics. Can J Physiol Pharmacol 1996;74(7):834–41.
[14] Lehoux S, Castier Y, Tedgui A. Molecular mechanisms of the vascular responses to haemodynamic forces. J Intern Med 2006;259(4):381–92.
[15] Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315(17):1046–51.
[16] Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362(9386):782–8.
[17] Rodriguez-Granillo GA, Vos J, Bruining N, Garcia-Garcia HM, de Winter S, Ligthart JM, et al. Long-term effect of perindopril on coronary atherosclerosis progression (from the perindopril's prospective effect on coronary atherosclerosis by angiography and intravascular ultrasound evaluation [PERSPECTIVE] study). Am J Cardiol 2007;100(2):159–63.
[18] De Winter SA, Hamers R, Degertekin M, Tanabe K, Lemos PA, Serruys PW, et al. Retrospective image-based gating of intracoronary ultrasound images for

improved quantitative analysis: the intelligate method. Catheter Cardiovasc Interv 2004;61(1):84–94.
[19] Clarijs JA, Pasterkamp G, Schoneveld AH, van Leeuwen TG, Hillen B, Borst C. Compensatory enlargement in coronary and femoral arteries is related to neither the extent of plaque-free vessel wall nor lesion eccentricity. A post-mortem study. Arterioscler Thromb Vasc Biol 1997;17(11):2617–21.
[20] Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation 2001;103(22):2705–10.
[21] Bentzon JF, Pasterkamp G, Falk E. Expansive remodeling is a response of the plaque-related vessel wall in aortic roots of apoE-deficient mice: an experiment of nature. Arterioscler Thromb Vasc Biol 2003;23(2):257–62.
[22] Pasterkamp G, Borst C, Post MJ, Mali WP, Wensing PJ, Gussenhoven EJ, et al. Atherosclerotic arterial remodeling in the superficial femoral artery. Individual variation in local compensatory enlargement response. Circulation 1996;93(10):1818–25.
[23] Hartmann M, von Birgelen C, Mintz GS, Verhorst PM, Erbel R. Relation between baseline plaque burden and subsequent remodelling of atherosclerotic left main coronary arteries: a serial intravascular ultrasound study with long-term (> or =12 months) follow-up. Eur Heart J 2006;27(15):1778–84.
[24] Hong MK, Mintz GS, Lee CW, Kim YH, Lee JW, Song JM, et al. Intravascular ultrasound assessment of patterns of arterial remodeling in the absence of significant reference segment plaque burden in patients with coronary artery disease. J Am Coll Cardiol 2003;42(5):806–10.
[25] Schartl M, Bocksch W, Fateh-Moghadam S. Effects of lipid-lowering therapy on coronary artery remodeling. Coron Artery Dis 2004;15:45–51.
[26] Sipahi I, Tuzcu EM, Moon K-W, Nicholls S, Schoenhagen P, Zhitnik J, et al. Does the extent and direction of arterial remodeling predict subsequent progression of coronary atherosclerosis? A serial intravascular ultrasound study. Heart 2007.
[27] Sipahi I, Tuzcu EM, Schoenhagen P, Nicholls SJ, Crowe T, Kapadia S, et al. Static and serial assessments of coronary arterial remodeling are discordant: an intravascular ultrasound analysis from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. Am Heart J 2006;152:544–50.
[28] Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. Circulation 2001;103:604–16.
[29] Inaba Mintz GS, Farhat NZ, Fajadet J, Dudek D, Marzocchi A, Templin B, et al. Impact of positive and negative lesion site remodeling on clinical outcomes: insights from prospect. JACC Cardiovasc Imaging 2014 Jan;7(1):70–8.