The influence of plaque orientation (pericardial or myocardial) on coronary arterial remodeling


Division of Cardiovascular Medicine, Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94305-5218, USA

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Abstract

Background: Many systemic, regional and lesion factors have been identified which may influence arterial remodeling, but little is known about the importance of extravascular resistance to vessel enlargement. As myocardial systolic splinting may significantly affect vessel expansion the effect of plaque orientation on arterial remodeling in eccentric coronary atherosclerotic lesions was examined. Methods: Using intravascular ultrasound imaging to obtain cross-sectional vessel area (VA), plaque area (PA) and lumen area (LA), remodeling in eccentric left anterior descending coronary artery lesions was compared which predominantly involved the pericardial or free arc (P, n = 25) and the myocardial side (M, n = 40) of the vessel wall. Normalized vessel area (NVA, VAlesion/VAreference) was compared as a continuous and categorical variable (positive > 1.05, intermediate 0.95–1.05, negative < 0.95) as well as remodeling index (RI, VAlesion – VAreference/PAlesion – PAreference). Results: The two groups were well matched for clinical and lesion characteristics known to affect remodeling. Reference segments areas were similar in the two groups; while lesion LA was also similar, in the pericardial group there was significantly greater lesion PA (P 12.78 ± 0.72, M 10.26 ± 0.50 mm², P < 0.05) and VA (P 15.71 ± 0.90, M 12.82 ± 0.57 mm², P < 0.05) demonstrating enhanced compensatory remodeling. Outward remodeling was significantly greater in P than in M by both NVA (P 1.03 ± 0.03, M 0.86 ± 0.03, P < 0.01) and RI (P 0.02 ± 0.07, M 1.10 ± 0.32, P < 0.01). Positive, intermediate and negative remodeling occurred in nine, nine and seven lesions in P and in four, ten and 26 lesions in M (P < 0.01). Conclusions: Remodeling compensates more for plaque growth in eccentric coronary lesions which are surrounded by the pericardium than those surrounded by the myocardium. Extravascular resistance appears to influence arterial remodeling. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Remodeling; Orientation; Support; Eccentric; Atherosclerosis

1. Introduction

Arterial remodeling, or change in cross-sectional vessel size, is an important morphological change occurring with the growth of atherosclerotic lesions. Compensatory remodeling, where the vessel expands with plaque enlargement, delays the onset of luminal stenosis with progressive atherosclerosis while constrictive remodeling, or reduction in vessel size, exacerbates stenosis. While large-scale post-mortem studies have found that remodeling response is more predictive of luminal stenosis than plaque size [1], little is known about the factors that influence the magnitude and direction of atherosclerotic remodeling.

In one of the first experimental descriptions of arterial remodeling, compensatory enlargement was associated with localized medial thinning underneath a developing plaque and ‘bulging’ of the plaque into the vessel wall, so that a circular lumen was maintained despite eccentric plaque distribution [2]. Similar morphological changes were subsequently observed in a human coronary intravascular ultrasound (IVUS) study [3], prompting these and other authors [4,5] to postulate that localized outward remodeling results from passive mechanical deformation of the vessel in response to atheroinflammatory weakening of the vessel wall.

The hypothesis of this study was that outward remodeling of arteries at sites of such weakness might be...
attenuated by external splinting, and specifically in coronary arteries, that the myocardium may provide sufficient splinting to that side of the vessel to affect remodeling whereas the pericardial side would be unrestricted. It was therefore investigated whether coronary plaque orientation in eccentric lesions (i.e. predominantly pericardial or myocardial) influences the pattern of vascular remodeling.

2. Methods

2.1. Patient population

The Stanford University Medical Center intravascular ultrasound (IVUS) core laboratory database was interrogated to find all preintervention IVUS studies of eccentric coronary lesions (eccentricity index > 3, using the index originally described by Mintz [6]). Lesions which were heavily calcified (> 90° arc of calcium) and those which involved a bifurcation or where a proximal reference segment was unavailable (ostial lesions) were excluded from the study. The study was limited to those lesions in the left anterior descending coronary artery for two reasons: extravascular landmarks (pericardium, anterior interventricular vein, and diagonal and septal branches) are sufficiently consistent for orientation, and the artery has myocardium and pericardium abutting approximately half of its circumference throughout its course. Clinical information recorded on these patients included age, sex, the presence or absence of atherosclerotic risk factors (smoking history, hypertension, hyperlipidemia, diabetes, family history), and clinical presentation (with or without an acute coronary syndrome).

2.2. IVUS imaging and measurements

Images were obtained after intracoronary administration of 200 µg nitroglycerin using a 30MHz IVUS imaging catheter (2.9–3.5 F Microview, CVIS/Boston Scientific) with slow manual pullback. Images were recorded on super VHS tape for off-line analysis of vessel areas using a commercially available image analysis system (Tape Measure, Indec, Capitola, CA). Vessel area (VA, area within the external elastic lamina) and lumen area (LA) were measured from end-diastolic frames. Plaque area (PA, plaque + media) was then calculated as the difference between VA and LA. Lesion site was defined as the site with the smallest LA while proximal reference site was defined as the site within the same segment in which PA was smallest.

Plaque orientation was assessed using extravascular landmarks as previously described[7] [8] by three independent observers blinded to the IVUS measurements (examples are shown in Fig. 1). Lesions were classified by the orientation of the majority of the plaque. When plaque was equally distributed between the pericardial and myocardial sides of the vessel (lateral orientation) the case was excluded from the analysis. In cases of disagreement, combined assessment of the tapes was made until agreement could be reached, or the case was excluded from analysis.

Two commonly used measures of remodeling were used:

Fig. 1. Orientation of eccentric plaques using IVUS landmarks. In the left anterior descending coronary artery the location of the pericardium is frequently directly apparent. Panel A shows an eccentric plaque on the pericardial or free side of the vessel wall while Panel B shows a predominantly myocardial eccentric lesion (P, pericardial space; L, lumen; M, myocardium).
unpaired variables in the two groups were compared with an

9

Age 63.4

Sex (M:

F) 22

Smoker 14 (56)

Hyper tension 12 (48)

Diabetes 8 (32)

Hyperlipidemia 10 (40)

Family Hx 9 (36)

Prior anterior MI 5 (20)

ACS 5 (20)

LAD segment 11/2/2

Calcification 9 (36)

9

* All comparisons between the two groups P > 0.30.

Table 1
Patient and lesion characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pericardial (n = 25)</th>
<th>Myocardial (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.0 ± 1.7</td>
<td>63.4 ± 1.4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>22/3</td>
<td>31/9</td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (56)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (48)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (32)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (40)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Family Hx</td>
<td>9 (36)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Prior anterior MI</td>
<td>5 (20)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>ACS</td>
<td>5 (20)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>LAD segment (prox/mid/distal)</td>
<td>11/2/2</td>
<td>14/25/6</td>
</tr>
<tr>
<td>Calcification</td>
<td>9 (36)</td>
<td>13 (38)</td>
</tr>
</tbody>
</table>

* All mean ± S.E.M.

* P < 0.01 vs. pericardial.

1. Normalized vessel area (NVA) — \( \frac{VA_{lesion}}{VA_{reference}} \)

Remodeling was also categorized by this measure as positive (NVA > 1.05) intermediate (0.95 < NVA < 1.05) or negative (NVA < 0.95) as previously described [1].

2. Remodeling index — \( \frac{(VA_{lesion} - VA_{reference})}{(PA_{lesion} - PA_{reference})} \)

While the former is a more frequently used measure of remodeling, it may be misleading when two groups of lesions are compared with different proportions of the vessel occupied by plaque, as remodeling has been shown to be proportional to plaque burden. Therefore, plaque areas adjusted for vessel size (normalized plaque area, NPA, \( \frac{PA_{lesion}}{VA_{reference}} \)) were compared, and as plaque burden was significantly different between the two groups, the latter methodology was employed to confirm the results.

2.3. Statistics

All data are presented as mean ± S.E.M. Continuous variables in the two groups were compared with an unpaired t-test or rank sum test depending on whether the data were normally distributed. Categorical variables were compared by \( \chi^2 \) testing or Fisher’s exact test where appropriate. Multivariate analysis (multiple linear regression) was used to determine the effect of plaque orientation on NVA and RI when differences in clinical characteristics and position within the vessel were accounted for. Independent variables were entered in the order of the strength of their association with the dependent variable on univariate analysis. \( P \) value < 0.05 was considered statistically significant.

3. Results

3.1. Patient and lesion characteristics

From 584 de novo atherosclerotic lesions in the database, 234 were in the LAD, of which 122 had eccentricity index > 3. Seventy-seven of these lesions were suitable for inclusion in the study (not bifurcational, ostial or heavily calcified). Of these, eleven were excluded due to lateral orientation and one was excluded due to persistent interobserver disagreement on orientation. Of the remaining 65 cases 40 were predominantly myocardial lesions while 25 were predominantly pericardial. The clinical, angiographic and IVUS morphological features of these two groups are shown in Table 1.

3.2. Plaque orientation and remodeling

At the reference site mean VA, PA and LA were similar in the Pericardial (P) and myocardial (M) groups. Consistent with their presentation for revascularization, LA at the lesion site was similar in both groups. However, VA and PA were significantly larger in the pericardial than the myocardial group (Table 2). NVA was significantly greater in the pericardial group (Fig. 2). Positive, intermediate and negative remodeling was present in nine, nine and seven lesions in the pericardial group and in four, 10 and 26 lesions in the myocardial group respectively (\( P < 0.01 \) by \( \chi^2 \)). While normalized plaque area was also greater in the pericardial group, comparison of the remodeling index between groups showed there was significantly more outward remodeling for every mm2 of plaque growth in the pericardial group (Fig. 2). By multivariate analysis plaque orientation was a highly significant predictor of NVA (\( P < 0.001 \)) and RI (\( P = 0.007 \)).

4. Discussion

In this study it has been shown that eccentric coronary atherosclerotic lesions on the myocardial side of the vessel wall undergo less outward remodeling than
those on the free or pericardial side. It suggests that mechanical resistance or splinting from perivascular tissues may influence arterial remodeling.

The mechanisms underlying atherosclerotic remodeling have been uncertain. Remodeling in normal vessels is predominantly shear-responsive and endothelium dependent [9]. Such events may be markedly attenuated by endothelial dysfunction in the presence of atherosclerosis, and it has been proposed that flow-dependent arterial remodeling does not occur once significant plaque has accumulated [10]. This has prompted some authors to propose that localized outward remodeling may result from the effect of outward radial pressure gradient on a vessel wall weakened by the inflammation from the lipid laden plaque which overlies it. Certainly there has been circumstantial evidence to support such a proposal. Both histopathological and IVUS studies have shown that atherosclerotic remodeling with eccentric lesions occurs in a localized manner directly beneath the plaque and is associated with medial thinning [2,3]. These morphological changes likely result from enzymatic degradation of vessel wall components by matrix metalloproteinases (MMPs), which are central components of flow-induced vascular remodeling [11], and are induced by the inflammatory response to lipids [12]. Furthermore, inflammatory induction of MMPs is an important mechanism by which atherosclerotic aortic aneurysms, a putative form of overexhuberent outward remodeling, form [13], and recent studies have also shown a correlation between markers of inflammation in the vessel wall and outward remodeling [14]. In addition metalloproteinase activity may also be increased by vessel wall stretch [15,16].

If these mechanisms were important one would expect that extravascular splinting would attenuate outward remodeling. External splinting of coronary arteries by the myocardium is sufficient to significantly influence both atherosclerosis and response to angioplasty. It is well known that mechanical external splinting reduces atherogenesis: atherosclerotic stenoses are rare in arterial segments surrounded by bone [17], while intima formation in saphenous vein grafts is reduced by externally stenting [18]. External splitting of the coronary arteries which are wholly intramyocardial, such as the septal perforators, is sufficient to prevent atherosclerosis even when the epicardial arteries are severely diseased [19]. In the epicardial coronary arteries, where only half of the vessel abuts myocardium, extravascular resistance is sufficiently heterogeneous within the circumference of the vessel to influence the orientation of angioplasty-induced coronary dissections. Intimal tears are far more frequent on the free or pericardial side of the vessel than on the myocardial side [20]. It therefore seems quite likely that the differences observed in remodeling are due to heterogeneity in splinting.

4.1. Limitations

However, it is also quite possible that other factors that influence remodeling may be different in pericardial and myocardial lesions. Myocardial lesions were twice as common in this study and the unknown local factors responsible for the preponderance in lesion location may also influence remodeling. For example, shear stress would be slightly less on the inner curve or myocardial side of the vessel [21] and any flow-responsive remodeling might be attenuated. However, these differences in shear stress are small and of doubtful significance when flow dependent remodeling is already attenuated in the presence of advanced atherosclerosis. Secondly, this study was limited to lesions in the LAD, and the effect of myocardial splitting may be less in the right and circumflex coronary arteries, which abut the atria in their proximal segments as well as the pericardium and myocardium. The right coronary also predominantly abuts right ventricular myocardium which is thinner and lower pressure than the left ventricle and may not splint the artery so effectively. However, the importance of the observations do not relate to their direct clinical applicability, but in the implications for the mechanisms which influence atherosclerotic remodeling.

Fig. 2. Remodeling in eccentric coronary lesions which are predominantly pericardial and myocardial in orientation. Graphs represent mean (± S.E.M.) normalized vessel area (NVA, VAlesion/VAreference), mean normalized plaque area (NPA, PAlesion/VAreference) and remodeling index (RI, VAlesion − VAreference/PAlesion − PAreference). * P < 0.01 vs. myocardial.
In summary, it has been demonstrated that extravascular structures influence not only atherogenesis, but also the remodeling which accompanies lesion formation. It remains to be determined whether the data may also have relevance to the influence of iatrogenic splinting, such as stenting, on remodeling.

Acknowledgements

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References


