Influence of differential vascular remodeling on the coronary vasomotor response

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Abstract

Objectives: Arterial remodeling may increase or decrease the luminal encroachment of atherosclerotic plaques in the coronary circulation. However, the factors determining the nature and consequences of the remodeling process remain poorly characterized. The study aims were to assess whether the pattern of vascular remodeling influences the physical and vasomotor responses of the coronary arteries in vivo in man.

Methods: Coronary vessel area, distensibility and stiffness were determined in positively, negatively and non-remodeled arterial segments using intravascular ultrasound and Doppler flow measurement. Epicardial vasomotor responses were determined following intracoronary boluses of acetylcholine (10\textsuperscript{\mu}M and 10\textsuperscript{-4} M), adenosine (24–30 \textmu g) and nitroglycerin (200 \textmu g).

Results: Fifty-six coronary arterial segments were studied in 25 patients. In comparison to non- and positively remodeled segments, negatively remodeled segments had a higher stiffness index (67\pm 16 vs. 33\pm 5 and 38\pm 8, respectively; \textit{P}<0.02) and appeared to have lower compliance and distensibility (0.66\pm 0.17 vs. 1.65\pm 0.54 and 0.94\pm 0.18 \textmu l/mmHg; \textit{P}=\textit{NS}). Non-remodeled segments had a greater change in vessel area with 10\textsuperscript{\mu}M acetylcholine (4.9\pm 0.8\%), compared to positively and negatively remodeled segments (0.6\pm 1.8\% and -4.9\pm 1.8\%, respectively, \textit{P}<0.05). A significant degree of preservation of vasodilatation to 10\textsuperscript{-4} M acetylcholine was evident in positively remodeled compared with negatively remodeled segments (\textit{P}<0.05). Nitroglycerin caused greater vasodilatation in non-remodeled segments (7.2\pm 3.8\%) than either positively or negatively remodeled segments (4.7\pm 0.9 and 3.7\pm 0.6\%, respectively, \textit{P}<0.05).

Conclusions: Vascular remodeling is an important and major determinant of local epicardial vasomotor responses. Both structural and functional abnormalities are associated with negative remodeling that may contribute to the adverse effects of such lesions.

Keywords: Coronary circulation; Endothelial function; Blood flow; Remodeling; Acetylcholine

1. Introduction

Coronary arterial remodeling is described by the response of the arterial wall to the presence of an atherosclerotic plaque. In many cases, the artery expands to accommodate the developing plaque burden such that there may be little or no luminal encroachment: so-called positive remodeling [1]. However, this vascular expansion may be absent (non-remodeled) or reversed (negatively remodeled) leading to more rapid luminal encroachment and the development of significant flow-limiting stenoses. The remodeling process can consequently have a profound influence on the outcome of atheroma deposition with the same plaque burden leading to either an absent (positive remodeling) or significant (negative remodeling) luminal stenosis and myocardial ischemia. To date, the factors determining the nature and consequences of the remodeling process remain poorly characterized.

Since the seminal work of Furchgott and Zawadski, it has been widely recognized that the endothelium can influence vascular tone through an array of mediators [2]. Endothelial stimulation results in the rapid release of...
vasodilator mediators, including prostacyclin, nitric oxide and endothelium-derived hyperpolarising factor, as well as vasoconstrictor mediators, such as angiotensin II and endothelin-1. Indeed, both nitric oxide and endothelin-1 are released continuously by the endothelium to regulate basal vascular tone and blood pressure [3–6]. Thus, there is an inextricable interplay between these endothelium-derived vasodilator and vasoconstrictor mediators that have a local counter-regulatory paracrine action on the adjacent vascular smooth muscle [7].

The endothelium responds to physical changes within the vascular lumen, such as leucocyte adhesion and alterations in shear stress, and the vessel wall, such as barotrauma and lipid deposition. Given these interactions, the integrity of endothelial function may profoundly influence the local vessel wall response to lipid deposition and atheroma formation [8], and thereby determine the resultant pattern of vascular remodeling [9,10]. However, the exact relationship between endothelial function and the direction of vascular remodeling in atherosclerotic coronary arteries is unclear.

The purpose of the present study was to assess whether the pattern of vascular remodeling influenced the physical and vasomotor responses of the coronary arteries in vivo in man. Using intravascular ultrasound (IVUS) and Doppler flow velocity measurement, the resting physical characteristics of vascular remodeling were determined, and the endothelium-dependent and -independent vasomotor function was characterized in remodeled coronary artery segments.

2. Methods

2.1. Patients

Twenty-five patients (20 male, mean age 59±2 years) with angiographic evidence of mild to moderate coronary artery disease were recruited at the time of coronary angiography in two centres (Royal Infirmary and Western General Hospital, Edinburgh, UK). Patients were excluded if they had severe left main stem disease, left ventricular hypertrophy or significant concurrent illness. All patients had their coronary risk factors determined by standard clinical criteria. Hypercholesterolaemia was defined as a fasting total cholesterol >200 mg/dl prior to initiation of lipid lowering therapy. The study was undertaken with the approval of the local research ethics committee, in accordance with the principles outlined in the Declaration of Helsinki, and the written informed consent of each subject.

2.2. Study protocol

All patients discontinued their medication on the study day, attended fasted and underwent diagnostic coronary angiography. Standard diagnostic images were taken using the Judkin’s technique with a non-ionic contrast agent (Niopam™, MERCK Pharmaceuticals, Middlesex, UK). A non-tortuous, non-branching segment of artery with a reference luminal diameter of ≥3.0 mm and luminal irregularity (diameter stenosis of 20–70%) was then identified for IVUS assessment. Where percutaneous coronary intervention was planned, the study was performed in an adjacent artery prior to the interventional procedure.

A 7 French guiding catheter was used to cannulate the left or right coronary artery and, following a 5000 IU intravenous bolus of heparin (Leo Laboratories Ltd., Princes Risborough, UK), a 0.014 in. 12.5 MHz Doppler wire (Flowire™, Endosonics, Rancho Cordova, CA) was passed across the arterial segment under study. A 3.2 F Ultracross™ 30 MHz IVUS imaging catheter (Atlantis SCIMED®, Boston Scientific Corporation, Maple Grove, MN) was advanced over the Doppler wire (Nitrocine™, SCWARZ Pharma Ltd, Chesham, UK).

The IVUS examination of the proximal artery was performed at 0.5 mm/s using a motorized pullback device (Boston Scientific Corporation). All IVUS images were recorded on high fidelity s-VHS videotape for later off-line quantitative analysis. Subsequent three-dimensional computerized reconstruction of the two-dimensional IVUS images was performed using the TomTec™ system (TomTec GmbH, Munich, Germany).

2.3. Assessment of remodeled segments

During the automated pullback, potential regions of interest (remodeled segments) were identified. Segments were selected for inclusion in the study if there was optimal image quality without rotational, angular or image artifacts; clear demarcation of the endoluminal and the external elastic laminal borders; and less than 180 degrees of calcification. Segment remodeling was defined according to existing criteria based on the vessel area at the index site relative to normal or near-normal proximal and distal reference segments. IVUS pullbacks were acquired to define these regions. This enabled classification of the remodeled segment by calculating the relative vessel area as the ratio of the vessel area at the index segment to the mean of the vessel area at proximal and distal reference segments. Categorization of segments was defined as follows: non-remodeled segments = vessel area ratio of >0.95 and <1.05; positively remodeled segments = ratio of >1.05; and negatively remodeled segments = ratio of <0.95.

2.4. Drug administration

Following the pullback examination, the IVUS imaging catheter was repositioned at the index segment. The Doppler guide wire was retracted to the tip of the imaging catheter and maintained in a stable position by the short monorail segment of the IVUS catheter [11,12]. Acetyl-
choline at a dose of $10^{-6}$ and $10^{-4}$ M (Miochol™, OMJ Pharmaceuticals Inc.), adenosine at a dose of 24–30 μg (Sanofi Winthrop Ltd., Guildford, UK) and nitroglycerin at a dose of 200 μg (Schwarz Pharma Ltd.) were given as 2 ml boluses, followed by 2 ml 0.9% saline flush via the guide catheter [12]. The IVUS images and Doppler ultrasound were recorded simultaneously to allow the measurement of luminal area and blood flow velocity for 2 min following each drug bolus.

### 2.5. Ultrasound measurements

Coronary artery cross-sectional area (vessel and luminal area) was measured using computerized planimetry (Clearview™, Boston Scientific Corporation.) of the vessel lumen at the onset of the QRS complex (diastole) and the offset of the T wave (systole) [13]. Blood flow velocity was determined using average peak velocity of the Doppler wire signal. Coronary artery blood flow was previously defined as half the product of the average peak velocity and the diastolic luminal cross-sectional area [12,14]. The atheromatous plaque volume was calculated using a well-validated edge detection algorithm as previously described and was expressed as mm$^3$ per mm of vessel [12,15,16]. The distensibility index of the coronary artery was defined as $[(\Delta A/A) / \Delta P] \times 10^3$/mm Hg; where $\Delta A$ represents the luminal area change between systole and diastole, $A$ the smallest luminal area in diastole, and $\Delta P$ the difference in systolic and diastolic blood pressure [13,17,18]. The stiffness index, $\beta$, was calculated using the following equation: $\beta = [\ln(P_{sys}/P_{dia})]/(\Delta D/D)$, where $P_{sys}$ represents the systolic pressure, $P_{dia}$ the diastolic pressure, $\Delta D$ the difference between systolic and diastolic mean luminal diameters, and $D$ the diastolic mean luminal diameter [13,19].

### 2.6. Data analysis and statistics

Data were examined by analysis of variance (ANOVA) with repeated measures and Student’s $t$-test using StatView v5.0.1 (SAS Institute Inc., Cary, NC). Where ANOVA demonstrated significant differences in responses, post-hoc comparisons were made using the Fisher protected least significant difference test (StatView v5.0.1). All results are expressed as mean±standard error of the mean. Statistical significance was taken at the 5% level.

### 3. Results

Baseline patient characteristics are shown in Table 1. The majority of patients had at least one risk factor for coronary artery disease; in particular, a history of hypercholesterolemia (19/25). A maximum of three segments were selected in each artery to give a total of 56 segments: 28 non-remodeled, 15 positively remodeled and 13 negatively remodeled. The left anterior descending artery was studied in 12 patients, right coronary artery in six patients, and left circumflex coronary artery in seven patients. Heart rate and mean arterial pressure were stable throughout the study in all subjects. There were no procedural or post-procedural in-hospital complications.

### 3.1. Characteristics of vessel segments

Non-remodeled segments (4.4±0.8 mm$^2$) had significantly less plaque cross-sectional area than either positively remodeled (8.0±1.1 mm$^2$, $P<0.05$) or negatively remodeled (7.1±0.6 mm$^2$, $P<0.01$) segments. Total vessel cross-sectional area was similar for the three types of vessel remodeling (Fig. 1). Negatively remodeled segments had a higher stiffness index in comparison to non- and positively remodeled segments (67±16 vs. 33±5 and 38±8, respectively; $P<0.02$). Negatively remodeled segments also appeared to have a lower compliance and distensibility (0.66±0.17 vs. 1.65±0.54 and 0.94±0.18/mmHg; $P=NS$) but this was not statistically significant.
3.2. Vasomotor responses

3.2.1. Resistance vessels

Acetylcholine, adenosine and nitroglycerin all caused coronary resistance vessel vasodilatation and an increase in coronary artery blood flow (P<0.002; Fig. 2) with adenosine causing the largest increase (P<0.004 vs. other agents). There were no differences in the resistance vessel responses between the three remodeling groups.

3.2.2. Conduit vessels

All vessel segments vasodilated to adenosine and nitroglycerin, and vasoconstricted to 10^{-4} M acetylcholine (P<0.05 for all; Fig. 3). The vasomotor response to acetylcholine 10^{-6} M varied according to the category of vascular remodeling (P<0.001; Fig. 3). Non-remodeled segments had a greater change in vessel cross-sectional area with 10^{-6} M acetylcholine (4.9±0.8%), compared to positively and negatively remodeled segments (0.6±1.8 and -4.9±1.8%, respectively, P<0.05). A significant degree of preservation of vasodilatation to 10^{-6} M acetylcholine was evident in positively remodeled compared with negatively remodeled segments (P<0.05). There was a trend towards greater adenosine-induced vasodilatation in
non-remodeled segments (increase in vessel cross-sectional area of 6.2±1.0%) compared with positively (3.7±0.8%) and negatively (3.9±0.9%) remodeled segments (P=0.14, Fig. 3). Similarly, nitroglycerin caused greater vasodilatation in non-remodeled segments (increase in vessel cross-sectional area of 7.2±3.8%) than either positively (4.7±0.9%) or negatively (3.7±0.6%) remodeled segments (P<0.01, Fig. 3).

4. Discussion

We have demonstrated that, in keeping with a more fibrotic and vasospastic response to atheroma deposition, negatively remodeled coronary arterial segments are stiffer and less distensible. Moreover, we have shown that the type of vascular remodeling determines the local epicardial vasomotor response to both endothelium-dependent and -independent vasodilators. In particular, negatively remodeled segments have an exaggerated vasoconstrictor response to acetylcholine and impaired endothelium-independent vasodilatation. We conclude that negative remodeling is associated with more pronounced local vascular and endothelial dysfunction.

4.1. Endothelial function

At the lowest concentration of acetylcholine, there was preservation of endothelium-dependent vasodilatation in non-remodeled segments and, to a lesser extent, positively remodeled segments. However, in negatively remodeled segments, low dose acetylcholine caused vasoconstriction that was equivalent to that observed with high dose acetylcholine in all segments. The phenomenon of paradoxical epicardial vasoconstriction during acetylcholine administration in atherosclerotic coronary arteries was first described 15 years ago [20]. It has been attributed to the direct muscarinic vasoconstrictor action of acetylcholine on the vascular smooth muscle cells in the absence of functional endothelium-dependent vasodilatation. Consistent with previous work [21], our observation of low dose acetylcholine-induced vasoconstriction cannot be directly attributed to the atherosclerotic plaque burden since both positively and negatively remodeled segments had a similar plaque load but distinct vasomotor responses. It may, in part, be explained by the reduced vasodilatation response to the endothelium-independent vasodilator, nitroglycerin, suggesting impaired vascular smooth muscle sensitivity to nitric oxide in remodeled segments. However, this cannot be the only explanation since the reduced response to nitroglycerin was observed in both positively and negatively remodeled segments but only negatively remodeled segments demonstrated vasoconstriction to low dose acetylcholine. This suggests that negative remodeling is associated with endothelial dysfunction or alterations in muscarinic receptor responsiveness.

4.2. Vascular remodeling

The current finding of an association between negative remodeling and vascular dysfunction does not address the question of cause and effect. It is tempting to speculate that localized vascular and endothelial dysfunction may lead to a more vasospastic artery that would cause increased vessel stiffness and negative remodeling. Alternatively, these features may have a common etiology with the potentially more fibrotic and inflammatory reaction to atheroma formation not only leading to negative remodel-
ing but also vascular and endothelial dysfunction. In this regard, longitudinal studies would be of value to monitor the changes in vascular function and vessel remodeling over time in order to determine which is the dominant factor in determining these vascular effects. This would also determine if vessels negatively remodel from the beginning or go through an initial phase of positive remodeling which becomes exhausted through progressive endothelial dysfunction and fibrosis [22]. In a hypercholesterolemic rabbit model, endothelial dysfunction was associated with negative remodeling and restenosis after balloon injury implicating endothelial dysfunction in the causation of negative remodeling [23].

Irrespective of the causative relationship, the present study suggests that there are functional abnormalities associated with coronary artery remodeling in addition to anatomical and structural changes. There has been only one previous study to address this issue. Lerman and colleagues used quantitative coronary angiography to determine epicardial responses to \(10^{-4}\) M acetycholine and nitroglycerin in the left anterior descending coronary artery [9]. This study used a single dose of acetycholine and employed a different classification of vascular remodeling. However, consistent with our current findings, Lerman and co-workers suggested that positive remodeling is associated with endothelial dysfunction. We have now extended these observations by providing more detailed assessments of remodeled segments, and demonstrating that negative remodeling is associated with more pronounced endothelium-dependent and -independent vaso-motor abnormalities.

4.2.1. Study limitations

This study was conducted in the necessary clinical setting of patients with a combination of risk factors and concomitant therapies undergoing diagnostic coronary angiography. The modest sample size means that this study lacks sufficient power to address the influence of all the individual variables associated with coronary artery disease. The study was also performed at a single time point and temporal changes in the remodeling process are unknown.

We defined the remodeling segment with reference to proximal and distal segments. Because of the clinical setting of this study, some of these segments will have incorporated some mild degree of atherosclerotic plaque: the so-called 'near-normal' segments. Because this could theoretically affect the classification of the remodeling segments, we avoided arterial segments where the remodeling classification was unclear. It should also be recognised that our findings may not be representative of all coronary artery atherosclerotic plaques. Heavily calcified lesions were excluded because the resultant acoustic shadow makes it very difficult to measure vessel areas. In addition, whilst we excluded segments with rotational, angular or image artifacts, we cannot completely eliminate these effects and recognise this as a potential limitation.

5. Conclusions

Vascular remodeling is an important and major determinant of epicardial vasomotor responses. Both structural and functional abnormalities are associated with negative remodeling that may contribute to the adverse effects of such lesions.

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References


