Arterial remodelling of native human coronary arteries in patients with unstable angina pectoris: a prospective intravascular ultrasound study

M Gyöngyösi, P Yang, A Hassan, F Weidinger, H Domanovits, A Lagrner, D Glogar

Abstract

Objective—To investigate the use of intravascular ultrasound (IVUS) in detecting the presence of arterial remodelling in patients with unstable angina.

Patients—60 of 95 consecutively admitted patients with unstable angina (41 male, 19 female), mean (SD) age 61.2 (8.1) years.

Interventions—Qualitative and quantitative coronary angiography and IVUS.

Main outcome measures—Adaptive or constrictive remodelling (AR, CR) was considered present when the cross sectional area of the external elastic membrane at the lesion site was larger than the proximal cross sectional area or smaller than the distal cross sectional area, respectively.

Results—22 of the 60 patients (37%) showed AR and 14 (23%) showed CR. No remodelling was seen in 24 patients (group NR). The plaque contained more thrombus and plaque rupture in group AR than in groups CR and NR (thrombus: 91% v 50% and 67%, respectively, p = 0.023; rupture: 73% v 29% and 42%, p = 0.020). AR was associated with a larger plaque cross sectional area (12.6 (SD 4.6) mm² v 10.8 (6.3) and 9.2 (3.7) mm², p = 0.001) and larger external elastic membrane cross sectional area (16.5 (5.8) mm² v 13.2 (5.2) and 14.4 (3.6) mm², p = 0.01 in group AR v groups CR and NR, respectively), while the plaque burden was larger in groups AR (74.9 (9.1)%) and CR (72.4 (16.6)%) than in group NR (66.2 (18.1)%, p = 0.005).

Conclusions—IVUS is capable of detecting adaptive and constrictive remodelling of target lesions and its relation to plaque morphology in unstable angina.

(Heart 1999;82:68-74)

Keywords: unstable angina; intravascular ultrasound; arterial remodelling; angiography

Methods

PATIENT POPULATION

Between September 1995 and March 1997, 95 consecutive patients with unstable angina (70 men and 25 women, mean (SD) age 62 (12) years) were admitted to the department of emergency medicine and enrolled in a prospective study with the following inclusion criteria: new onset of severe or accelerated angina (< 2 months of duration) (25 patients); angina at rest (52 patients); angina within two weeks of acute myocardial infarction (18 patients) (Braunwald class IA, IIA, IIA, IB, IIb, IIIC, or IIIIC). The Braunwald categories of unstable...
Arterial remodelling of coronary arteries in unstable angina

angiographic and IVUS findings, severe multi-
was detectable (normal or nearly normal
artery. If, for any reason, no clear culprit lesion
were used to identify the ischaemia related
severe stenosis or complex lesion morphology
graphic appearance of thrombus, and the most
tivessel disease, the localisation of the ECG
ischaemia related artery. In patients with mul-
the diseased artery was considered to be the
culprit lesion was identified according to
CULPRIT LESION IDENTIFICATION

CORONARY ANGIOGRAPHY AND IVUS PROCEDURES
After administration of 150 to 200 µg of intra-
coronary glyceryl trinitrate, all patients under-
went selective coronary angiography. Baseline
angiograms were recorded in at least two
projections. After completion of coronary
angiography, culprit lesions were localised and
IVUS imaging was performed. Intracoronary
glyceryl trinitrate (200 µg) was given before
intracoronary ultrasound imaging to prevent
vasospasm, and the imaging catheter was
introduced through an 8 F guiding catheter
over a guide wire.

Intracoronary ultrasound images were ob-
tained with 2.9 F or 3.2 F mechanical imaging
catheters (CVIS, Sunnyvale, California, USA)
or 3.0 F electronic imaging catheters (En-
dosonics, California, USA). The IVUS cath-
eter was advanced distally and subsequently
withdrawn manually. Correct assessment of the
IVUS catheter position and the site of the cul-
prit lesion was achieved by fluoroscopic control
or angiographic documentation of the tip of the
catheter, or both. All IVUS images were
obtained at 30 frames/second and recorded on
super VHS videotapes for subsequent offline
analysis. Selected images from the videotape
were digitised and stored in computer based
patient data files.

CULPRIT LESION IDENTIFICATION

The culprit lesion was identified according to
the ECG pattern and angiographic vessel mor-
phology. In patients with single vessel disease,
the diseased artery was considered to be the
ischaemia related artery. In patients with mul-
tivessel disease, the localisation of the ECG
changes during anginal episodes, the angi-
ographic appearance of thrombus, and the most
severe stenosis or complex lesion morphology
were used to identify the ischaemia related
artery. If, for any reason, no clear culprit lesion
was detectable (normal or nearly normal
angiographic and IVUS findings, severe multi-
vessel disease, and so on), the case was treated
as a drop out.

ANGIOGRAPHIC ANALYSIS
Cineangiograms were analysed by two experi-
enced observers blind to the ultrasound results
in two different sessions, using a computer
assisted quantitative coronary arteriographic
edge detection algorithm (Cardiovascular
Measurement System, Medis, the Nether-
lands). Minimum lumen and reference diam-
eters, lengths of stenoses, per cent diameter
stenoses, and per cent area stenoses were
measured at end diastolic frames to minimise
the variation caused by the cardiac motion and
to maximise the contrast filling of the coronary
vessel. The TIMI (thrombolysis in myocardial
infarction study) flow, culprit lesion morphol-
ogy, and the presence of thrombi or filling
defects, native vessel dissections, calcification,
and collateral vessels were analysed visually.28
Concentric angiographic lesions with a smooth
border were considered to be simple angi-
ographic lesions, while eccentric lesions with a
narrow neck, overhanging edges, or irregular
borders were regarded as complex lesions.18
Lesion length was measured as the distance
(mm) from the proximal shoulder to the distal
shoulder in the projection with the least
foreshortening.29

IVUS ANALYSES
IVUS images were analysed in offline mode by
two experienced observers with a computer
assisted IVUS analysis system (TapeMeasure,
Indec Systems Inc, California, USA).

Qualitative IVUS analysis
Consensus between the two independent
observers was reached in all cases with regard
to the qualitative features of the culprit lesion.
The atherosclerotic plaque encompassing the
culprit lesion was characterised as follows.

Plaque composition—Soft (fibromuscular, lipids,
or both) or fibrocalcific (fibrotic but also calci-
cified) lesions. Tissue less dense than the
reference adventitia was classified as soft.
Plaque tissue producing echoes that were as
bright as or brighter than the reference adven-
titia, with or without acoustic shadowing was
classified as fibrocalcific. Bright echoes with
acoustic shadowing were considered to repre-
sent calcification.

Plaque eccentricity—Plaque was considered ec-
centric if the ratio of plaque thickness on
opposite sides of the lumen was < 0.5 or if
there was an arc of disease-free vessel wall.

Plaque disruptions or thrombi—These were iden-
tified visually. Plaque disruption was defined as
an abrupt, focal, superficial break in the linear
continuity of the plaque that extended in a
radial direction only. Vascular thrombi were
considered to exist when speckled echoes softer
than the dense atheroma echo signal within soft
plaque were seen.

Quantitative IVUS analysis
The site of the minimum lumen cross sectional
area was identified by carefully scrolling the
tape forwards and backwards. For each lesion
site, the lumen area and external elastic membrane area (defined as the area encompassed by the adventitia) were measured at the point of maximum lumen narrowing and in adjacent proximally and distally located segments (that is, reference sites). The reference segments were selected on the basis of the segment morphology determined by angiography (minimal or no lumen narrowing, no major side branch originating between the lesion site and the reference site) or IVUS (normal or less diseased vessel segment with < 50% area stenoses and without active plaques), or both. The location of the culprit lesion and the proximal and distal reference sites was determined after consensus by two observers. Quantitative analyses were performed by two independent observers. For further comparison, the measurements of the three observers were averaged. For each lesion the lumen cross sectional area (area within the lumen–intima border (mm²)) and external elastic membrane cross sectional area were manually traced. Plaque cross sectional area was measured as intima + media area, calculated as external elastic membrane cross sectional area – lumen cross sectional area (mm²). Per cent plaque burden was calculated as (plaque cross sectional area/external elastic membrane cross sectional area) \times 100 \,[\%].

Assessment of reproducibility
Cross sectional measurements on 19 different coronary artery lesions were analysed by two observers in separate sessions, and the interobserver variability was calculated on the basis of IVUS images measured by these observers. For determination of the intraobserver variability, 24 lesions were measured five times by one observer. The different analyses included the error involved in repeatedly selecting the same image slice and the error involved in repeatedly performing the cross sectional measurements.

The coefficient of correlation of the interobserver variability was \( r = 0.956 \) (\( p < 0.001 \)).

The intraobserver variability and the reproducibility of IVUS measurements were determined by using one way analysis of variance with repeated measurements. The methodological error was calculated from the standard error of the estimate of the analysis of variance.

The coefficient of variation of the repeated measurements of the lumen and external elastic membrane diameter was 3%, while that of the lumen and external elastic membrane cross sectional area was 1.7%. The methodological error of the measurement of the lumen and external elastic membrane diameter was 0.19 mm, and that for the lumen and external elastic membrane cross sectional area, 0.38 mm².

Arterial remodelling
Adaptive remodelling (compensatory vessel enlargement) was assumed to be present when the external elastic membrane cross sectional area at the lesion site was larger than that at the distal reference site. Constrictive remodelling (coronary shrinkage) was considered to be present when the external elastic membrane cross sectional area at the lesion site was smaller than that at the distal reference site.

STATISTICS
All data are expressed as means (SD) for continuous variables. Qualitative data are presented as frequencies. Comparisons between groups were made with the Student’s \( t \) test, or with analysis of variance for differences in means, or with the \( \chi^2 \) test for categorical variables. Regression analysis was used to assess the interobserver variability, and one way analysis of variance with repeated measurement was applied to assess the reproducibility of repeated measurements for determination of the intraobserver variability. Differences were considered significant when \( p < 0.05 \).

Results
Qualitative and quantitative data on the culprit lesion and the proximal and distal reference segments could be determined in 60 patients (41 men and 19 women, mean age 61 (8) years). Culprit lesions could not be identified in 17 of the 95 patients because of multivessel disease (nine patients) or a normal coronary angiogram (eight patients). In these eight patients, even IVUS did not detect any possible pathological substrate in any of the three coronary arteries. These eight patients were in class IA, IIA, or IIIA of the Braunwald classification of unstable angina. In another 12 patients, IVUS could not be performed owing to a severe main stem stenosis (four patients) or total vessel occlusion (eight patients). Furthermore, in six patients quantitative IVUS measurements were not possible because of extensive calcification (calcification occupying more than 90° of the vessel wall) (two patients), or the presence of a side branch at the

Figure 1 Flow chart of patients with unstable angina pectoris.
site of the culprit lesion (four patients), which did not allow delineation of the vessel wall contour (fig 1). Thus the present results are the data on the remaining 60 patients.

In three patients, transient coronary spasm occurred after the introduction of the IVUS catheter, but after withdrawal of the catheter and administration of a further dose of intracoronary glyceryl trinitrate, the IVUS procedure could be performed. Before the IVUS procedure, an intracoronary bolus injection followed by intravenous infusion of abciximab (ReoPro; Eli Lilly) was given to two patients because of extensive intracoronary thrombus on angiography.

### Table 1
Clinical data for patients with adaptive remodelling of the culprit lesion (group AR), patients with constrictive remodelling (group CR), and patients without remodelling (group NR)

<table>
<thead>
<tr>
<th></th>
<th>Group AR (n = 22)</th>
<th>Group CR (n = 14)</th>
<th>Group NR (n = 24)</th>
<th>Total (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) (mean (SD))</strong></td>
<td>56.5 (14.0)</td>
<td>65.4 (8.1)*</td>
<td>60.9 (9.8)</td>
<td>61.2 (8.1)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>16 (73)</td>
<td>8 (57)</td>
<td>17 (71)</td>
<td>41 (68)</td>
</tr>
<tr>
<td><strong>Angina score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5 (23)</td>
<td>0 (0)</td>
<td>8 (33)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Medium</td>
<td>13 (59)</td>
<td>6 (43)</td>
<td>10 (42)</td>
<td>29 (48)</td>
</tr>
<tr>
<td>High</td>
<td>4 (18)</td>
<td>8 (57)†</td>
<td>6 (25)</td>
<td>18 (30)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (18)</td>
<td>5 (36)</td>
<td>4 (17)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (36)</td>
<td>10 (71)‡</td>
<td>12 (50)</td>
<td>30 (50)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>13 (59)</td>
<td>8 (57)</td>
<td>16 (67)</td>
<td>37 (62)</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (59)</td>
<td>7 (50)</td>
<td>13 (54)</td>
<td>33 (55)</td>
</tr>
</tbody>
</table>

*Values are n (%) except where stated.

*p = 0.045, †p = 0.036, ‡p = 0.04 for comparisons between group CR and groups AR/NR.

### Adaptative and Constrictive Remodelling

**Clinical results**

Twenty two of the 60 patients (37%) showed adaptive remodelling on IVUS, while constrictive remodelling of the culprit lesion was observed in 14 patients (23%) (fig 2). Table 1 summarises the clinical data on the patients with adaptive (group AR) and constrictive remodelling (group CR) and the patients with no remodelling (group NR). Patients with constrictive remodelling were significantly older (65.4 (8.1) years, 95% confidence interval 60.7 to 70.0) than the patients in group AR (56.5 (14) years, 50.1 to 60.9) and group NR (60.9 (9.8) years, 56.8 to 65.1), p = 0.045, and had a significantly more severe angina score (table 1).
Constrictive remodelling tended to be more common in patients with hypertension (33% vs 13%, p = 0.067 in patients with or without hypertension). No other correlation was found between coronary risk factors and remodelling.

### Table 3 Qualitative intravascular ultrasound data on patients with adaptive remodelling (group CR), patients with constrictive remodelling (group AR), and patients without remodelling (group NR)

<table>
<thead>
<tr>
<th>Plaque eccentricity</th>
<th>Group CR (n = 24)</th>
<th>Group NR (n = 24)</th>
<th>Total (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric lesion</td>
<td>6 (25)</td>
<td>22 (37)</td>
<td></td>
</tr>
<tr>
<td>Eccentric lesion</td>
<td>16 (75)</td>
<td>38 (63)</td>
<td></td>
</tr>
</tbody>
</table>

There was no statistical difference in qualitative angiographic morphology of the culprit lesion in the different vessels and in relation with remodelling.

Table 2 summarises the qualitative and quantitative angiographic data. There was no significant difference between the three groups in minimum luminal diameter, reference diameter, or diameter or area stenosis of the culprit lesion. The average stenosis length was greater in group CR (10.2 ± 3.16 mm, 95% confidence interval 8.38 to 12.02) than in group AR (7.25 ± 4.31, 5.29 to 9.2) and group NR (8.19 ± 4.62, 6.25 to 10.14); p = 0.037.

### Qualitative IVUS data

Intracoronary thrombi and plaque disruption were more common in patients with adaptive remodelling than in those without (thrombus: 91% vs 50% and 67%, p = 0.023; rupture: 73% vs 29% and 25%, p = 0.020, in group AR v groups CR and NR). There were no other differences between the patient groups with regard to the plaque eccentricity and composition (table 3).

### Quantitative IVUS results

Adaptive remodelling was associated with a larger plaque cross sectional area (12.6 ± 4.6 mm², 95% confidence interval 10.46 to 14.66, p < 0.001) and a larger external elastic membrane cross sectional area (16.5 ± 5.8 mm², 13.9 to 19.13, p < 0.001) than in group NR (12.8 ± 10.95, group AR v groups CR and NR, respectively; p = 0.001 and a larger external elastic membrane cross sectional area (16.5 ± 5.8 mm², 13.9 to 19.13, p < 0.001) and a larger external elastic membrane cross sectional area (16.5 ± 5.8 mm², 13.9 to 19.13, p < 0.001) than in group NR (12.8 ± 10.95, group AR v groups CR and NR, respectively; p = 0.001), while the plaque burden was higher in groups AR (74.9 (9.1)%, 70.8 to 79.0) and CR (72.4 (16.6)%, 62.8 to 81.9) than in group NR (66.2 (18.1)%, 58.5 to 73.8; p = 0.005) (table 4).

The average minimum lumen, plaque, and vessel cross sectional areas of the proximal and distal reference sites were not different in the different remodelling processes.

### Discussion

In this prospective IVUS study we have demonstrated different arterial remodelling processes in native coronary arteries in patients with unstable angina.

**IVUS VARIATIONS IN DIFFERENT REMODELLING PROCESSES**

We found that 37% of the patients with unstable angina had adaptive remodelling and 23% had constrictive remodelling. Tauth et al found that 35% of the target lesions showed adaptive remodelling while 34% of the lesions showed constrictive remodelling in a mixed patient group with stable and unstable angina. Mintz et al reported inadequate remodelling in at least 15% of chronic focal new coronary arterial stenoses in patients with stable angina. Nishio et al found that vessel enlargement failure occurred in 46% of target lesions. The differences between the our results and those of other investigators can be explained in terms of the different patient populations—in our study
we included only patients with unstable angina, because of growing evidence that remodelling of the coronary arteries related to unstable coronary syndromes is different from that in stable angina, just as the mechanisms of lesion progression are considered to be different as well.20 31

Qualitative IVUS revealed a high incidence of thrombi and plaque disruption in the patients as a whole. This finding is in agreement with the angiographic and pathological evidence that lesion progression in acute coronary syndromes follows recurrent minor fissuring of the most fatty atheromatous plaques, with subsequent thrombus formation.2 29 31 32 33 Moreover, presence of thrombi and plaque disruption was significantly more common in patients with adaptive remodelling than in patients with constrictive remodelling or without any remodelling. It may be hypothesised that vasoactive substances released by the intracoronary thrombi and the disrupted atherosclerotic plaques contribute to more pronounced vessel dilatation in patients with adaptive remodelling. However, if this pathophysiological concept were the only explanation, it would remain completely unclear why adaptive remodelling did not develop in the other patients with unstable angina associated with intracoronary thrombi and plaque disruption.

Another theory suggests that atrophy and thinning of the media induced by atherosclerosis could be responsible for vessel dilatation during remodelling, by weakening the arterial wall. This theory could be confirmed by calculation of the media thickness using additional measurements of the internal elastic membrane area (the difference between the external elastic membrane area and the internal elastic membrane area). Unfortunately, IVUS is not suitable for precise delineation of the internal elastic membrane area in most cases; therefore these measurements were not included in our study.34

METHODS OF ASSESSING THE DIFFERENT TYPES OF REMODELLING
The remodelling process may be assessed in different ways. In a serial study with quantitative coronary angiography or IVUS, the development of remodelling (adaptive or constrictive) may be determined in a given patient by serial arterial analyses. As the time course of the arterial wall changes was unknown in our study, we defined adaptive remodelling as an enlargement of the vessel cross sectional area in comparison with a proximal reference site, and constrictive remodelling as a culprit lesion vessel shrinkage in comparison with a distal reference site, in accordance with published reports.16 20 24 34 40

LIMITATIONS OF OUR STUDY
Our findings are based on the observation of 60 primary coronary lesions that excluded ostial lesions and also coronary lesions with severe calcification. Therefore, they might not be applicable to heavily calcified, restenotic and ostial lesions.

The number of the patients in the different groups was relatively small; however, this number was derived from a reasonable sample size of 95 consecutively recruited patients.

For determining the IVUS features in patients with unstable coronary syndromes, we used only a “snapshot view” of the culprit lesion.

Different degrees of vascular tone (spasm from the catheter at the lesion site, or vasodilatation because of glyceryl trinitrate) could produce an artificial narrowing or enlargement of the lumen and vessel area. However, all patients received the same basic antianginal treatment before and during the interventional procedure. If coronary spasm did occur, the IVUS was repeated after withdrawal of the...
cather and a repeated dose of glyceryl trinitrate, and the last record was used for quantitative analysis. Long term results are needed to determine the predictive value of the presence or absence of adaptive or constrictive remodelling in patients with unstable angina. We have started to follow up our patients both clinically and angiographically with IVUS, but this follow up study remains to be completed.

CONCLUSIONS

The clinical conclusions of our findings are as follows. Different arterial responses to luminal narrowing, both adaptive remodelling and constrictive remodelling, were found in patients with unstable angina. Patients with adaptive remodelling showed more thrombi and plaque disruption, and larger plaque and vessel cross sectional areas. Patients with constrictive remodelling were significantly older and had a higher angina score. Overall, intravascular ultrasonography is more suitable than angiography for determining target lesion characteristics in patients with unstable angina.

Arterial remodelling of native human coronary arteries in patients with unstable angina pectoris: a prospective intravascular ultrasound study

M Gyöngyösi, P Yang, A Hassan, F Weidinger, H Domanovits, A Laggner and D Glogar

*Heart* 1999 82: 68-74
doi: 10.1136/hrt.82.1.68

Updated information and services can be found at:
http://heart.bmj.com/content/82/1/68

These include:

**References**
This article cites 37 articles, 15 of which you can access for free at:
http://heart.bmj.com/content/82/1/68#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Acute coronary syndromes (2742)
- Drugs: cardiovascular system (8842)
- Clinical diagnostic tests (4779)
- Stable coronary heart disease (199)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/