Determinants of Coronary Artery Compliance in Subjects With and Without Angiographic Coronary Artery Disease

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OBJECTIVES
The goal of this study was to determine factors contributing to the biomechanical properties of coronary arteries in people with and without angiographic coronary artery disease (CAD).

BACKGROUND
The stiffness of the aorta is known to increase with increasing age and in the presence of CAD. However, little is known about the mechanics of coronary arteries, which may have important clinical consequences.

METHODS
Intravascular ultrasound was used to determine the mechanical properties of coronary arteries and plaque behavior in subjects with CAD (n = 38), those with chest pain but angiographically normal coronary arteries (N) (n = 9) and those early (<2 weeks) after cardiac transplant (T) (n = 14).

RESULTS
Coronary arteries dilated during systole in all groups, but cross-sectional compliance and distensibility were lowest in the proximal left anterior descending artery (LAD) in the subjects with CAD compared with the N and T groups (compliance: 1.2 ± 0.2 vs. 1.7 ± 0.5 and 2.7 ± 0.6 × 10⁻² mm² mm Hg⁻¹ [mean ± SEM] respectively, p < 0.02 CAD vs. T; distensibility: 0.8 ± 0.2 vs. 1.7 ± 0.5 and 1.7 ± 0.3 × 10⁻³ mm Hg⁻¹, p < 0.05 CAD vs. T). There was extensive plaque in the CAD group, and plaque was also present in the N group, but minimal atheroma was present in the T group. Plaque cross-sectional area diminished significantly during systole in both the LAD and circumflex arteries. Absolute changes were: 0.50 ± 0.30, 0.33 ± 0.11 and 0.68 ± 0.13 mm² in the proximal LAD, distal LAD and proximal circumflex arteries, respectively. In subjects with atheroma, there was a significant correlation between cross-sectional compliance and plaque compression at all sites, and plaque compression was a significant determinant of cross-sectional compliance at both proximal sites in multiple regression analyses with age, mean arterial pressure and extent of plaque as the other independent variables.

CONCLUSIONS
A major determinant of the systolic increase in coronary luminal area in patients with atheroma is a reduction in plaque cross-sectional area during systole. (J Am Coll Cardiol 2002;39:1637–43) © 2002 by the American College of Cardiology Foundation

Increased stiffening of the large arteries is associated with the presence of coronary artery disease (CAD) (1–3) and is an independent predictor of mortality (4). Cardiac effects may be due to a consequential increase in pulse pressure (PP) (5,6) with an increased afterload (5) and reduced coronary perfusion due to lower diastolic perfusion pressure (7). In contrast with the large arteries, the biomechanical properties of coronary arteries themselves have been much less studied. Thus, although the effects of aging (8) and coronary disease (8,9) have been previously investigated, very little is known about their interaction or about the role of plaque behavior per se. We have, therefore, examined such properties in three groups of subjects, namely those with symptomatic angiographic disease (coronary artery disease [CAD]), similarly aged normal subjects investigated for chest pain but without angiographic disease (N) and in cardiac transplant (T) recipients. Heart age was significantly less in the T recipients, and they were examined very early after T, a time well before the development of the widespread coronary changes typically seen later in these patients (10,11).

METHODS
All patients gave their informed consent to this study, which was approved by the human ethics committee of the Alfred hospital.

Patient population. Studies were performed in patients undergoing coronary angioplasty of stenoses in the left anterior descending (LAD) or circumflex (Cx) coronary arteries, in patients who had previously presented with chest pain but had angiographically normal coronary arteries and in patients who had received a cardiac T within the previous two weeks.

Study protocol. CAD GROUP (N = 38, 34 MEN). Average age was 58.9 ± 1.8 years (mean ± SEM) and average total cholesterol was 5.0 ± 0.2 mmol/l. Medications are given in Table 1. Sixteen patients were being treated for hyperten-
Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>C</td>
<td>compliance</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>Cx</td>
<td>circumflex artery</td>
</tr>
<tr>
<td>D</td>
<td>distensibility</td>
</tr>
<tr>
<td>GTN</td>
<td>glyceryl trinitrate</td>
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<tr>
<td>IM</td>
<td>intima-media</td>
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<tr>
<td>IVUS</td>
<td>intravascular ultrasound</td>
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<td>LAD</td>
<td>left anterior descending artery</td>
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<tr>
<td>N</td>
<td>normal subjects investigated for chest pain but without angiographic disease</td>
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<td>PP</td>
<td>pulse pressure</td>
</tr>
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<td>T</td>
<td>transplant</td>
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Intracoronary pressure recordings were performed in the LAD, 15 in the Cx and 3 in both arteries. All but two of the patients had coronary stents deployed after balloon angioplasty. After revascularization, a 0.014-in angioplasty guidewire (Guidant Advanced Cardiovascular Systems, Temecula, California) was left in situ within the coronary artery. A 2F Millar (Houston, Texas) manometer tip catheter was introduced into the orifice of the left main coronary artery for continuous pressure recording; 100 μg of intracoronary glyceryl trinitrate (GTN) was then administered. An Ultracross 2.9F 30 MHz (Boston Scientific, Maple Grove, Minnesota) coronary imaging catheter was placed over the guidewire. An automatic pullback device was used to withdraw the catheter at a rate of 0.5 mm/s, with images recorded continuously onto Super VHS tape. Electrocardiogram and pressures within the left main coronary artery were also continuously recorded.

Recent studies with intracoronary pressure recording have demonstrated that, in normal coronary arteries, proximal and distal pressures differ by no more than 1 mm Hg. However, in the presence of atheroma, the difference averages 5 mm Hg (in nonstenotic vessels) (12). In view of this, comparisons involving the T group have been limited to the proximal LAD.

NORMAL CORONARY ARTERY GROUP (N GROUP) (N = 9, 5 MEN). Average age was 53.0 ± 3.2 years, and average total cholesterol was 5.6 mmol/L. Medications are given in Table 1. Two were current smokers, and two were diabetic. All had previously presented with chest pain and had undergone diagnostic coronary angiography, which had shown seven to have angiographically normal arteries while two had stenoses <40%. Intravascular ultrasound (IVUS) and assessment of coronary compliance (C) was performed at least one week after their initial angiogram, as described above.

CARDIAC T RECIPIENTS (T GROUP) (N = 14, 13 MEN). Patients were aged 46.9 ± 3.2 years with a heart age of 28.7 ± 3.2 years. A total of 43% (6/14) had been transplanted because of ischemic and 57% (8/14) because of nonischemic cardiomyopathy. At the time of investigation, all patients were treated with cyclosporin and prednisolone and either azathioprine (n = 5) or sirolimus (n = 9). All cardiac medications are shown in Table 1. Two patients had required intravenous methylprednisolone for acute rejection demonstrated on cardiac biopsy. In both cases, subsequent biopsy, before their involvement in this study, showed no evidence of persistent rejection. All patients in the T group underwent initial diagnostic angiography of the left and right coronary arteries. Subsequently, IVUS was performed in the LAD after intracoronary GTN as previously described for the CAD group.

Data analysis and statistics. Videotape images were subsequently digitized at television frame rates (25 frames/s). They were then analyzed off-line using Optimas program 6.2 (Media Cybernetics Inc., Silver Spring, Maryland). Images for analysis were selected from sites in the proximal and distal LAD and proximal Cx, which did not contain angiographically apparent flow limiting stenoses and which had not been the site for previous angioplasty and stent deployment. The two LAD sites were separated by an average of 56 mm, and proximal LAD and Cx sites were all within 5 mm of the origin of the respective vessels.

Images from a complete cardiac cycle were stored for each site (15 to 20 images). In preliminary studies in ten patients, we traced the lumen of each image for one complete cardiac cycle. These were then analyzed, and lumen size was related to the corresponding point in the electrocardiogram trace. It was found that minimum and maximum lumen areas were all within two images of the beginning of the QRS complex and the peak of the T-wave, respectively. Thus, in subsequent analyses, images corresponding to these points in the cardiac cycle were selected. Previous studies have also used similar criteria to measure maximum and minimum lumen areas (13). At each site, and in random order (systole vs. diastole), manual tracings on the digitized image were made of the lumen–intima wall border and of the outer limit of the intima-media (IM) layer (Fig. 1).

Table 1. Cardiovascular Medication Taken at the Time of the Study

<table>
<thead>
<tr>
<th>Medication</th>
<th>CAD (n = 38)</th>
<th>N (n = 9)</th>
<th>T (n = 14)</th>
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<tr>
<td>ACE inhibitors</td>
<td>12 (32%)</td>
<td>3 (33%)</td>
<td>4 (29%)</td>
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<tr>
<td>Aspirin</td>
<td>38 (100%)*</td>
<td>8 (89%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Statins</td>
<td>24 (63%)</td>
<td>6 (67%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>20 (53%)*</td>
<td>3 (33%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Ca antagonists</td>
<td>20 (53%)</td>
<td>6 (67%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>OHG</td>
<td>8 (21%)</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
</tr>
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Absolute numbers, percentages given in brackets. *p < 0.05 CAD versus T.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; N = normal subjects investigated for chest pain but without angiographic disease; OHG = oral hypoglycemic agents; T = transplant.
The following measurements were then made:

1. Vessel lumen cross-sectional area (mm$^2$) during diastole and systole.
2. Total vessel cross-sectional area (mm$^2$), determined as the area (including lumen) within the outer margin of the IM layer, during systole and diastole.

From these measurements cross-sectional C (mm$^2$ mm Hg$^{-1}$) was determined as (systolic lumen area-diastolic lumen area)/PP where PP is the pulse pressure measured within the left main coronary artery by the pressure tip catheter. Coronary artery cross-sectional distensibility (D) (mm Hg$^{-1}$) determined as C/diastolic lumen area. Absolute IM thickness was determined as the difference between total and luminal cross-sectional areas and was determined during both systole and diastole. The IM thickness (plaque) was also expressed as percent of total vessel area, again during both systole and diastole.

In order to determine the effect of pull-back, lumen and total vessel areas were measured at corresponding points (onset QRS or peak of “T” wave) in successive cardiac cycles in 10 subjects. In each subject measurements were made at two locations. There were no significant differences ($p > 0.3$ for all) between successive measurements for any of the variables or for the derived plaque areas. Thus, systolic luminal and total areas (mm$^2$) were $7.17 \pm 0.91$ and $6.97 \pm 1.02$ and $12.31 \pm 1.23$ and $12.12 \pm 1.41$, respectively, in successive measurements. Group data are presented as mean $\pm$ SEM. Statistical analyses were performed using SPSS 9.0. Comparisons between groups were made by analysis of variance (with appropriate covariates as listed), $t$ test or Wilcoxon signed rank test in the case of a nonnormal distribution. Categorical variables were compared using the chi-square test. Multiple regression analyses used stepped entry and removal with $F$ to enter set at $p = 0.1$ and $F$ to remove at $p = 0.05$.

RESULTS

Anthropometric and baseline hemodynamic data at the time of the IVUS study is shown in Table 2. There were no significant differences in LAD lumen area during diastole between CAD and N groups in the proximal LAD (Table 3). Prominent IM (plaque) was evident in the proximal LAD.

![Figure 1](image-url) Intravascular ultrasound images in diastole (right) and systole (left). The inner tracing marks the lumen-intima boundary, and the outer tracing the outer margin of the intima-media layer. Plaque area was calculated as the difference between these areas. Plaque cross-sectional area decreased from $7.8 \text{ mm}^2$ during diastole to $6.9 \text{ mm}^2$ during systole.

| Table 2. Hemodynamic Parameters for the Three Groups at the Time of IVUS Study of the LAD |
|---------------------------------|-------|-------|-------|
| Heart rate$^a$ (beats/min)     | CAD   | 67.6 ± 2.0‡ | 64.7 ± 3.5 | 82.5 ± 2.4 |
| Systolic blood pressure (mm Hg) | CAD   | 125.1 ± 5.0 | 126.7 ± 5.8 | 111.9 ± 6.3 |
| Diastolic blood pressure (mm Hg) | CAD   | 69.7 ± 2.7  | 81.3 ± 3.8  | 69.3 ± 6.5  |
| Pulse pressure$^b$ (mm Hg)     | CAD   | 55.4 ± 3.4$^\ddagger$ | 45.4 ± 4.3 | 42.6 ± 1.7 |
| Mean arterial pressure (mm Hg)  | CAD   | 93.2 ± 3.3  | 101.3 ± 4.2 | 88.9 ± 6.4  |
| Heart age$^c$ (years)          | CAD   | 58.9 ± 1.8$^\ddagger$ | 53.0 ± 3.3 | 28.7 ± 3.2  |

ANOVA $p < 0.001$; $\dagger p < 0.05$ for difference between groups; $\ddagger p < 0.001$; $\ddagger p < 0.05$ for post-hoc difference (Bonferroni) between CAD and T.

CAD = coronary artery disease; IVUS = intravascular ultrasound; LAD = left anterior descending artery; N = normal subjects investigated for chest pain but without angiographic disease; T = transplant.
LAD site in the CAD group but was less in the N group and virtually absent in the T group (Table 3). One T recipient received an extensively diseased heart and was not included in the analysis. The CAD, N and T groups all showed a significant increase in lumen area during systole. Both C and D were significantly less proximally in the CAD group compared with the T group (Table 3). Compliance and D were higher for the N group compared with the CAD group, but differences were no longer significant when adjusted for multiple comparisons. There were significant differences between the groups not only in the amount of plaque but also in heart age, which may have contributed to the observed differences in C. With adjustment for heart age, differences in C and D between CAD and T groups were no longer significant.

We anticipated that the presence of plaque would be important in explaining variability in local mechanical properties. In view of this, we undertook a more detailed examination of plaque behavior during the cardiac cycle by making measurements during systole and diastole. Absolute plaque area was significantly less during systole than diastole. Absolute plaque compression during systole was $0.50 \pm 0.30, 0.33 \pm 0.11$ and $0.68 \pm 0.13 \text{mm}^2$ at proximal and distal LAD and Cx sites, respectively (Fig. 2). In view of differences in absolute plaque area, comparison between sites was undertaken for relative changes (i.e., change in plaque area as a percentage of absolute plaque area measured during diastole). Correlations ($r$) between Cx and proximal LAD were significant at $0.64$ ($p < 0.005$), while those between proximal and distal LAD sites were $0.44$ ($p < 0.05$). In contrast with the significant luminal expansion during systole, the increase in total vessel area during systole was not significant at any of the sites. Thus, the expansion in the lumen was dependent on the reduction in IM area.

We, therefore, further examined the extent to which plaque compression contributed to the measured C. Bivariate correlation coefficients between plaque compression and cross-sectional C were $0.57$ ($p < 0.001$) for the proximal LAD, $0.48$ ($p < 0.05$) for the Cx and $0.47$ ($p < 0.05$) for the distal LAD. These relations are shown in Figure 3. Multiple regression was then undertaken with absolute plaque compression, age, mean arterial pressure and percent plaque area (in diastole) included as independent variables and cross-sectional C as the dependent variable. Regression was significant at the proximal LAD

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**Table 3. Morphologic and Mechanical Properties of the Proximal LAD in the Three Groups**

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>N</th>
<th>T</th>
</tr>
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<tbody>
<tr>
<td>Lumen area in diastole (mm$^2$)</td>
<td>$13.5 \pm 1.0$</td>
<td>$11.5 \pm 1.4$</td>
<td>$16.1 \pm 0.7$</td>
</tr>
<tr>
<td>IM (%) in diastole*</td>
<td>$32.7 \pm 3.4$§</td>
<td>$18.9 \pm 7.3$</td>
<td>$4.0 \pm 1.7$</td>
</tr>
<tr>
<td>$C \times 10^2$</td>
<td>$1.2 \pm 0.2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D \times 10^3$ (mm Hg$^{-1}$)†</td>
<td>$0.8 \pm 0.2$¶</td>
<td>$1.7 \pm 0.5$</td>
<td>$1.7 \pm 0.3$</td>
</tr>
</tbody>
</table>

ANOVA *$p < 0.001$; †$p < 0.02$; §$p < 0.05$; ¶$p < 0.001$; ‡$p < 0.02$; ¶¶$p < 0.05$ for post-hoc comparison (Bonferroni) between CAD and T groups.

C = compliance; CAD = coronary artery disease; D = distensibility; IM = intima-media; LAD = left anterior descending artery; N = normal subjects investigated for chest pain but without angiographic disease; T = transplant.

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**Figure 2.** The figure shows plaque area measured during diastole (gray bar) and systole (black bar) in the proximal and distal left anterior descending artery (LAD) and in the proximal circumflex (Cx). *$p < 0.05$; **$p < 0.01$ for the difference between systole and diastole.
Figure 3. The figure shows the relation between cross-sectional compliance and plaque compression (+ve values indicate smaller systolic than diastolic plaque area). Cx = circumflex artery; LAD = left anterior descending artery.
DISCUSSION

The principle new finding from this study is that compression of the IM layer (plaque) occurs during systole in the coronary circulation of patients with coronary atheroma, and this significantly contributes to the expansion of the lumen, which occurs during systole. Indeed, there was no significant increase during systole in the cross-sectional area contained within the outer IM boundary. Such plaque compression was similar at different, nonstenotic, sites within the coronary tree of an individual. In addition, we observed coronary C to be greater in subjects early after T.

Coronary C. Previous studies using IVUS have established a systolic expansion in the cross-sectional area of major coronary arteries (8,9,14,15). There are a number of possible determinants of coronary expansion. These include topography, age and the presence of atherosclerosis or other disease. In this study we found a difference in coronary expansible properties between the CAD and T groups. These groups differed in two major respects. Thus, even though ultrasound images were obtained at sites angiographically free of disease, there was, nonetheless, substantial plaque evident in the CAD group, whereas the transplanted hearts were virtually free of disease. In addition, heart age was markedly less in the T group.

Large artery stiffness is known to be increased in subjects with CAD (1,16) and, in addition, related to the severity of coronary disease (17). Although coronary artery C and D were reduced in the CAD group compared with subjects investigated for chest pain but not found to have angiographically significant disease, such differences were no longer significant when adjusted for multiple comparisons, probably, in part, as a result of the difficulty in recruiting a larger number of subjects in this group. Another factor probably limiting the magnitude of difference between CAD and normal groups was that these normal patients were also found to have a substantial degree of plaque (intimal thickening) despite their angiographic status. Previous studies in CAD patients have shown that circumferential, but not eccentric, lesions were negatively correlated with coronary C (9,18). Furthermore, a recent study in long-term transplanted hearts found coronary C to be greater in areas of eccentric compared with concentric lesions, implying a restrictive effect of the latter (19). Compliance of conduit arteries is pressure-dependent (20); however, there were no significant differences in mean blood pressure between the three groups at the time of study. Sixteen of the CAD group had a history of hypertension, which may have contributed to the changes in arterial behavior (21).

It is known that vasoconstrictor drugs alter mechanical properties of conduit arteries independently of their affect on blood pressure (21). To minimize such an effect, all vasoactive medications were withheld on the morning of the study. Furthermore, all patients received intracoronary GTN immediately before the IVUS study. Any study medication induced differences in vasoactive responses would, therefore, have largely been nullified after the administration of the endothelium-independent vasoconstrictor, GTN.

Plaque compressibility. Reduction of plaque area in systole has been noted previously but was not related to C (13). The mechanism of this reduction in plaque cross-sectional area during systole is undetermined. A reduction in cross-sectional area due to stretching is unlikely because epicardial vessels would not be expected to lengthen during systole. Even in other conduit vessels, lengthening during systole in vivo is very small. Patel et al. (22) found that the thoracic aorta lengthens 0.011% per mm Hg. A second possibility is that not only plaque cross-sectional area but also volume diminishes during systole. In view of the essential incompressibility of normal vessel wall (23,24), the likeliest explanation for such a phenomenon is reduction in tissue blood volume. It is known that the vessel wall is traversed by blood vessels (25,26) and that this vascularity is considerably increased in areas of plaque in comparison with normal coronary artery vessel wall (27). Compression of these vascular spaces during systole is plausible although it is not clear whether they are of sufficient magnitude to account for the changes seen. Alternative explanations, such as folding of the extracellular macromolecules during systole or the operation, during systole of cell membrane water channels seem less likely (28).

The finding of systolic compression of the IM region in subjects with CAD is of interest for several reasons. It is a significant determinant of the mechanical properties of the arterial wall that may be expected to influence stresses on “at-risk” plaque regions. There is evidence for some, although not complete, uniformity in these properties within the same individual (29), suggesting an innate difference in plaque characteristics. Differences in these properties between individuals may, therefore, contribute to the likelihood of presentation with an acute coronary syndrome because repetitive wall deformation during the cardiac cycle will likely increase plaque vulnerability.

In summary, coronary artery mechanical properties are dependent on both age and the presence of disease, even at angiographically normal sites. The presence of encircling atheroma appears to limit the potential for luminal expansion, which is then dependent on the degree to which such plaque is compressed during systole.

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REFERENCES


