Anatomical Progression of Coronary Artery Disease in Humans as Seen by Prospective, Repeated, Quantitated Coronary Angiography
Relation to Clinical Events and Risk Factors

Paul R. Lichtlen, MD; Peter Nikutta, MD; Stefan Jost, MD; Jaap Deckers, MD; Birgitt Wiese, PhD; Wolfgang Rafflenbeul, MD; and the INTACT Study Group

Background. At present, there is extensive knowledge on the clinical course of coronary artery disease (CAD), whereas data on the underlying anatomical changes and their relation to clinical events are still limited.

Methods and Results. We investigated progression and regression of CAD prospectively over 3 years in 230 patients (average age, 53.2 years) with mild to moderate disease by applying quantitated, repeated coronary angiography. Minimal stenotic diameters, segment diameters, and percent stenosis were analyzed by the computer-assisted Coronary Angiography Analysis System (CAAS). Progression was defined either as an increase in percent stenosis of preexisting stenoses by ≥20% including occlusions or as formation of new stenoses ≥20% and new occlusions in previously angiographically “normal” segments. At first angiography, we found 838 stenoses ≥20% (average degree, 39.3%) and 135 occlusions in the four major coronary branches (4.23 lesions per patient). At second angiography, 82 (9.8%) of the preexisting stenoses had progressed, 15 of them up to occlusion (1.8%; precoclusion degree averaging 46.6%; 29.7–65.6%). In addition, there were 144 newly formed stenoses (average degree, 39.2%) and 10 new occlusions. Hence, 25 (2.6%) of all stenoses had become occluded. Altogether, 129 patients (56.1%) showed progression: 68 (29.6%) with new lesions only, 27 (11.7%) with preexisting lesions, and 34 (14.8%) with both types. Regression (decrease in degree of stenoses ≥20%) was present in 29 stenoses (3.6%) and 28 patients (12%). The incidence of new myocardial infarctions was low, with three originating from occluding preexisting stenoses and one from new stenoses; hence, only four (16%) of the 25 new occlusions led to myocardial infarctions. Risk factor analysis showed that cigarette smoking correlated significantly with the formation of new lesions (p=0.001), whereas total cholesterol correlated with the further progression of preexisting stenoses (p=0.017) but not with the incidence of new lesions.

Conclusions. In patients with mild to moderate CAD, the angiographic progression is slow (in this study 18.7% of patients and 7% of stenoses per year) but exceeds regression (4.1% of patients and 1.2% of stenoses per year). Progression is predominantly seen in the formation of new coronary stenoses and less in growth of preexisting ones. Most of the stenoses were of a low degree (<50%), clinically not manifest including those going into occlusion and leading to myocardial infarction. Progression was influenced by risk factors, especially cigarette smoking (formation of new lesions) and high cholesterol levels (progression of preexisting stenoses). (Circulation 1992;86:828–838)

Key Words • coronary artery disease • occlusion, coronary artery • angiography, coronary • myocardial infarction • risk factors, coronary

Today's knowledge on the progression of coronary artery disease (CAD) in humans is mainly derived from clinical studies analyzing the incidence of serious coronary events such as fatal and nonfatal myocardial infarction or sudden coronary death over a prolonged period of time.1–5 These studies, however, reflect the corresponding anatomical alterations in coronary arteries only indirectly, and the conclusions concerning progression of the underlying disease often remain equivocal.

Modern coronary angiography offers the possibility to evaluate the evolution of CAD in humans in a more direct way.6–13 For this purpose, angiographic studies must be performed prospectively, with a fixed time interval between the two interventions, the indication for the second study being independent of clinical events.6,14–22 In addition, coronary angiograms should be quantitated by applying computer-assisted evaluation systems for the analysis of the various coronary structures and their changes over time.23–27 This approach yields a higher accuracy when comparing the two angiograms years apart than subjective estimates based on score systems.14–16 The present study follows this design by applying CAAS (Coronary Angiography Analysis System)23,27 for quantitated coronary angiography.
Table 1. Clinical Baseline Data at Entrance Into Study and After 3 Years

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At entrance</th>
<th>After 3 years</th>
<th>p (entrance data vs. 3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.25±7.63</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Male (No.)</td>
<td>261.1±69.9</td>
<td>214</td>
<td>264.2±54.6</td>
</tr>
<tr>
<td>Female (No.)</td>
<td>58.9%</td>
<td>126</td>
<td>64.3%</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>178.1±41.0</td>
<td>37</td>
<td>172.6±56.0</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>50.3±16.1</td>
<td>37</td>
<td>45.0±16.6</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>3.93±1.52</td>
<td></td>
<td>4.94±3.87</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensives systolic</td>
<td>124.8±13.5</td>
<td>207</td>
<td>134.9±15.4</td>
</tr>
<tr>
<td>Hypertensives systolic</td>
<td>79.1±6.9</td>
<td>207</td>
<td>84.2±9.2</td>
</tr>
<tr>
<td>Hypertensives diastolic</td>
<td>165.0±17.9</td>
<td>23</td>
<td>144.0±18.6</td>
</tr>
<tr>
<td>Angina pectoris (Canadian Cardiovascular class)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>52.2%</td>
<td>226</td>
<td>64.6%</td>
</tr>
<tr>
<td>Class II</td>
<td>35.8%</td>
<td>26.9%</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>12.0%</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>0</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarctions by ECG criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior wall</td>
<td>14.3%</td>
<td>33 of 230</td>
<td></td>
</tr>
<tr>
<td>Posterior wall</td>
<td>16.1%</td>
<td>37 of 230</td>
<td></td>
</tr>
<tr>
<td>Lateral wall</td>
<td>3.9%</td>
<td>9 of 230</td>
<td></td>
</tr>
<tr>
<td>Positive exercise tests (ST &gt;0.1 mV)</td>
<td>37.3%</td>
<td>75 of 201</td>
<td>29.4%</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; HDL, high density lipoprotein.  
*McNemar test.  
†Wilcoxon matched pairs, signed ranked test for all two-sided tests.

Methods

These patients, analyzed for their natural, anatomical course of CAD, are part of a multicenter, prospective, double-blind intervention trial in which the effect of the calcium antagonist nifedipine (80 mg/day) versus placebo on the angiographic progression over 3 years (INTACT)19 was studied. For the present purpose, all patients undergoing either percutaneous transluminal coronary angioplasty (PTCA) (n=112) or bypass surgery (n=6) before recruitment were excluded because these interventions might have changed their progression. Statistical analysis of the remaining 230 of the original 348 patients of INTACT revealed no significant differences between the placebo and nifedipine groups for angiographic baseline and follow-up data; this includes progression and regression of existing lesions assessed either by changes in percent degree (p=0.123) or in minimal diameters of stenoses (p=0.927) and the generation of new lesions; for the latter, there was still a marked but insignificant group difference (63 new lesions in the nifedipine group and 91 in the placebo group; p=0.193). As all differences between groups were insignificant, we felt justified to pool the data for the analysis of progression (probability values for all group differences varying between 0.08 and 0.96).

No group differences in clinical data were observed at entrance or after 3 years (Table 1). This includes total low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, blood pressure, smoking habits, class of angina pectoris, incidence of myocardial infarction at entrance, and positive exercise tests.

Statistically, these 230 patients (average age, 53.2±7.63 years; 108 receiving nifedipine, 122 receiving placebo), all undergoing two angiograms with an interval averaging 1,094±145 days, represent a homogenous group both clinically and angiographically.

Inclusion Criteria

The inclusion criteria for INTACT19 was aimed at patients with mild to moderate CAD; hence, these patients had mainly low-grade angina (Canadian Cardiovascular Society class I or II) and small or no infarcts (ejection fraction >40%). The majority of coronary segments were angiographically “normal,” with the number of occluded coronary arteries restricted to one large branch per patient and the number of stenoses ≥20% rarely exceeding four per patient (Table 2 and Figure 1).  

Clinical Baseline Data and Follow-up

At entrance, total, LDL, and HDL cholesterol (the latter measured in a randomized subgroup) were high
TABLE 2. Angiographic Changes, Number of Lesions* (Stenoses ≥20% or Occlusions) at First and Second Angiography in 230 Patients, Percent Stenosis, New Lesions, and Distribution of Lesions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>First angiogram (at entrance into study)</th>
<th>Second angiogram (after 3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenoses (No.)</td>
<td>838</td>
<td>936 (includes 144 new stenoses and six spontaneous recanalizations)</td>
</tr>
<tr>
<td>Stenoses per patient</td>
<td>3.64</td>
<td>4.07</td>
</tr>
<tr>
<td>Occlusions (No.)</td>
<td>135</td>
<td>150 (includes 15 developing from old stenoses and 10 from new stenoses)</td>
</tr>
<tr>
<td>Occlusions per patient (average No.)</td>
<td>0.59</td>
<td>0.65</td>
</tr>
<tr>
<td>Total number of lesions (stenoses and occlusions)</td>
<td>973</td>
<td>1,086 (includes 786 from first angiogram; 144 new stenoses, six recanalizations, and 150 occlusions)</td>
</tr>
<tr>
<td>Lesions per patient (average No.)</td>
<td>4.23 (n=0–21)</td>
<td>4.72 (n=0–19)</td>
</tr>
</tbody>
</table>

*Stenoses ≥20% or occlusions.
†From the 838 stenoses at first angiogram, 801 could be included in the second angiogram; the 37 losses are as follows: 15 stenoses going into occlusion including 12 stenoses distal to the occlusion, the latter being lost; 25 stenoses were lost because of poor film quality, not allowing an accurate measurement in the second angiogram. In addition, four occlusions of the first angiogram were lost and six occlusions were recanalized; therefore, only 125 occlusions from the first angiogram were recovered in the second angiogram.

(average total cholesterol, 261 mg/dl; LDL cholesterol, 178 mg/dl; HDL cholesterol, 50 mg/dl) and remained so during follow-up (p=0.330). LDL and HDL cholesterol showed an insignificant decrease of −4% and −10%, respectively, and were possibly influenced by nifedipine. At entrance, the majority of patients (82%) were cigarette smokers. Smoking habits changed during follow-up, with the majority of patients (60.7%) becoming nonsmokers either at entrance or during the study. According to INTACT's inclusion criteria, there were few patients with hypertension (n=23; diastolic pressure average, 100 mm Hg). Whereas blood pressure in patients with hypertension was normalized during the study due to treatment (either nifedipine or β-blockers), blood pressure in the normotensives increased mildly but significantly (p = 0.0001). Angina pectoris was mild: The majority of patients (52%) at entrance were in Canadian Cardiovascular Society class I. The number of improved cases increased significantly during the study (p=0.0196), probably as a consequence of anti-ischemic treatment (44.6% of patients on oral nitrates; 34.4% on β-blockers; 47.0% on nifedipine); in accordance, after 3 years, there were fewer patients with positive exercise tests than at entrance (29.4% versus 37.3%; p=0.0339; McNemar test). At entrance, there were no patients with insulin-dependent diabetes or gout. Seventy-nine patients (34.3%) had old myocardial infarctions by ECG criteria. (See Table 1.)

**Angiographic Analysis**

Coronary angiograms were evaluated by applying CAAS. Angiograms of the left and right coronary arteries were carried out in six to 10 projections, including half-axial projections. Two projections (in the majority of orthogonal projections) best representing the segments and stenoses to be analyzed were selected for further processing. All angles were recorded in a special protocol, allowing the repetition of the second angiogram in exactly the same projections, and by this, assuring optimal comparison between the two angiograms 3 years apart. Ten minutes before angiography, patients received 10 mg isosorbide dinitrate (ISDN) sublingually in order to achieve maximal vasodilation of coronary segments and eccentric stenoses. ISDN was administered as chewing capsules in approximately one third of patients and in the other two thirds as chewing tablets. The dilatory effect of the two galenic forms was found to be equal (maximum dilation capacity of normal segments averaged ~30% for both forms). Two experienced cardiologists (S.J., J.D.) selected coronary artery segments and stenoses to be analyzed by CAAS from high-quality cineframes, using a Tagarno projector. The inclusion of segments followed the recommendations of the American Heart Association; segments <1.0-mm diameter (the majority ≥1.5 mm) and all those located distally to occlusions, opacified only by collaterals, were excluded from further analysis.

The two algorithms of CAAS are designed for automatic edge detection of coronary arteries: one for the analysis of the entire length of coronary segments and the other for stenoses. The first algorithm with diameter measurements at intervals of 0.1 mm resulted in a "diameter function curve," indicating the course of the diameter over the entire segment length and providing...
an average segment diameter. At first angiography, a total of 3,125 segments was measured in two different projections (6,250 measurements); length averaged 2.3±1.3 cm (range, 0.3–7.2 cm). The second algorithm assessed the minimal stenotic diameter (expressed in millimeters) and calculated percent stenosis by comparing the minimal stenotic diameter with a “normal” (reference) segment diameter; the latter was defined automatically by a special algorithm extrapolating the original reference contours at the site of the stenosis based on the adjacent subsegments; this reconstructed line was then accepted as the original normal contour of the stenosis.

The system was calibrated by measuring the tip of the coronary catheter (Judkins or Sones) immediately after angiography, applying a caliper with an accuracy of 0.05 mm. Pincushion distortion was corrected by a special algorithm based on a filmed grid with lines 1 cm apart.

Data were stored in PDP 11/24 and PDP 11/44 computers; further processing was done with the data base management system SIR/DBMS and the statistical programs SPSSX, BMDP, and SAS.

For the definition of progression and regression of preexisting coronary stenoses, changes in the minimal stenotic diameter and percent stenosis were statistically evaluated based on criteria obtained previously from long-term measurements of these parameters with CAAS. For the lower limit of changes in percent stenosis to be accepted as progression or regression (cutoff point) we applied three single standard deviations of the degree of stenosis (6.25%) found in two cineframes of identical projections from two different movies performed at intervals of 90 days, i.e., ±20%. Similarly, a normal segment had to reveal a new localized narrowing of at least 20% to be accepted as a newly formed stenosis. This angiographic definition recognizes that some of these “new lesions” might have been present already at the time of first angiography and were not large enough to be visualized or, if <20%, were not accepted by the discrimination rules. For the lower limit of changes in minimal stenotic diameter (cut-point) to be accepted as true progression or regression of a preexisting lesion or as formation of a new lesion, we chose 0.5 mm. This value corresponds very closely to the 20% cut-point when the cumulative distribution curve of changes in minimal stenotic diameters is compared with the one of changes in percent stenoses (Table 4). These cumulative curves of positive and negative changes in stenoses, expressed as minimal stenotic diameters or percent stenosis, were established to decide on the best cut-points. They show that the cut-points chosen here are above the levels of noise and therefore support our aim to keep the number of false-positive findings as low as possible, even at the risk of increasing the number of false-negatives. We recognize, however, that all settings of cut-points to identify biologically true changes in percent stenosis or minimal stenotic diameter, so far, must be arbitrary. At this time, no data are available that are based on comparison between computerized angiographic and anatomical findings (postmortem histology) or intravascular ultrasound to serve as a standard. Our values obtained in this way, both for percent stenosis as well as minimal stenotic diameters, are in close agreement with those published elsewhere.

Computerization of angiograms was performed in two centers (Hannover Medical School, Thoraxcenter Rotterdam) applying identical computer systems and programs (CAAS). The procedures were standardized and periodically cross-checked by the two supervising cardiologists (S.J., J.D.) comparing random samples. Altogether, 12,478 segment measurements were performed in the 460 angiograms analyzed in the 230 patients at first and second intervention (=6,250 segment measurements each for the first and second angiogram and ~27 segment measurements per patient in each angiogram). Less than 2% of cineframes and 3.5% of stenoses were lost for reanalysis due to poor film quality.
FIGURE 2. Graph shows distribution of percent stenosis found in the 838 stenoses of the first angiogram; the average degree amounted to 39.3% (the 150 occlusions are disregarded); there were 13 stenoses with a degree between 10 and 20%.

Statistics

Statistics distinguished between patient-related and segment- or stenosis-related analysis. For patient-related comparisons, different two-sided statistical tests were applied: between groups, Cochran’s test for linear trend for quantitative variables with only a small number of categories was used; for all other quantitative variables, the modified t test with separate variance estimation was used.

Differences between categorical variables were examined by χ² test or Fisher’s exact test, depending on the number of cells and cell contents. To compare changes between the first and second angiogram within groups, the McNemar test was applied for dichotomous variables; the Wilcoxon matched pairs, signed rank test was applied for other categorical variables; for quantitative parameters, a two-sided t test was applied. Correlations between not-normally distributed parameters were calculated applying Spearman’s rank correlation coefficient.

For stenoses or segment-related evaluations in which subjects are not statistically independent, the standardized procedure of the mixed-model ANOVA was applied to allow for dependence between observations.

Results

Anatomical Findings: Coronary Lesions at Entrance

In the first angiogram, there were 838 stenoses (13 with stenosis <20%) and 135 occlusions, hence, a total of 973 coronary lesions (4.23 per patient; see Table 2). Sixty percent of patients had one to four lesions, and 40% had five or more (Figure 1). In addition, 26.1% of patients had one-vessel disease, 32.6% had two-vessel disease, and 35.2% had three-vessel disease. For the distribution of lesions on the various coronary branches, see Table 3.

Percent stenosis averaged 39.3% (ranging from 10% to 78%), with the majority (94.0%) in the clinically asymptomatic range between 20% and 60% (Figure 2). The minimal stenotic diameter averaged 1.6 mm (ranging from 0.47 to 3.81 mm). These values correspond closely to those reported by similar studies.

Progression and Regression of Preexisting Stenoses

This analysis is primarily based on a change in stenosis ≥20% to be accepted as biologically meaningful; this is in accordance with a long-term study on the

variability of CAAS (see “Methods”). Therefore, the cut-point for changes in minimal stenotic diameter was adjusted to that of the percent stenosis (Figures 3 and 4). A table with the corresponding figures for changes in percent stenosis (steps in 10%) and three ranges of changes in minimal stenotic diameter (steps of 0.3, 0.4, and 0.5 mm) is added (Table 4). It shows that the

FIGURE 3. Graph of progression and regression of preexisting stenoses; on the abscissa the differences (Δ) in percent stenosis between the second and first angiogram (steps of 1%) for progressing and regressing stenoses (ranging from 0% to 78% and from 0% to 41%, respectively); differences for stenoses becoming occluded are included. The ordinate indicates the number of progressing and regressing stenoses for each difference in percent stenosis.

FIGURE 4. Cumulative distribution curves for progression and regression of preexisting stenoses, expressed as changes of percent stenosis (upper panel) and of minimal stenotic diameter (millimeters) (lower panel); decrease in percent stenosis equals regression; increase equals progression; decrease in minimal stenotic diameter equals progression; increase equals regression (see text).
Preexisting Stenosis and Minimal Percent Stenosis

Minimal stenotic diameter (in steps of 0.3, 0.4, and 0.5 mm)

<table>
<thead>
<tr>
<th>Percent stenosis</th>
<th>Unchanged</th>
<th>&gt;0.0–0.3 mm</th>
<th>&gt;0.0–0.4 mm</th>
<th>&gt;0.0–0.5 mm</th>
<th>&gt;0.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unchanged</td>
<td>1.1%</td>
<td>36.9%</td>
<td>43.6%</td>
<td>47.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td>&gt;0.0–0.3 mm</td>
<td>21.3%</td>
<td>28.9%</td>
<td>33.9%</td>
<td>36.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>&gt;0.0–0.4 mm</td>
<td>1.1%</td>
<td>21.3%</td>
<td>6.6%</td>
<td>36.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>&gt;0.0–0.5 mm</td>
<td>1.2%</td>
<td>11.8%</td>
<td>21.4%</td>
<td>84.1%</td>
<td>14.8%</td>
</tr>
<tr>
<td>&gt;0.5 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=801

cut-point for changes in percent stenosis (≥20%), taken as the standard (see “Methods”), corresponds best with ≥0.5 mm as cut-point for changes in minimal stenotic diameter (10.2% and 10.6% progressing versus 3.5% and 4.2% regressing stenoses, respectively, when assessed with both parameters). (See Table 4.)

Changes of Percent Stenosis

Of the 801 stenoses analyzable in the second angiogram (96% of those present at entrance), 58.6% showed changes in stenosis between 1% and 10%, with an almost equal incidence of progression (30.8%) and regression (27.8%); for changes between 10% and 20%, there were twice as many stenoses progressing than regressing and above 20% even three times as many (Table 4). In accordance with our rather rigid criteria for progression and regression, 10.2% of stenoses were classified as truly progressing; this includes 15 stenoses going into occlusion (1.8% of all stenoses present at first angiography), their percent stenosis before occlusion averaging 46.6±8.9%. Three of these stenoses amounted to <40%, six were between 41% and 47%, five were between 50% and 55%, and one was at 65%. Furthermore, stenoses of low percentage (<40%) had a higher incidence of progression than those of a high percentage (>61%) (p=0.001). The average increase in percent stenosis for those classified as progressing averaged 27.2±7.1%.

By similar criteria, 29 preexisting stenoses were classified as spontaneous regression (3.6%) (Table 4). As expected, the incidence of regressing stenoses was significantly higher in the high-grade (≥60%) than in the low-grade group (≤40%) (24.1% versus 6.9% of the 29 regressing stenoses; p=0.001); the decrease averaged −24.8±6.0%.

Changes in Minimal Stenotic Diameter

By applying 0.5 mm as cut-point, 10.6% of stenoses were progressing and 4.2% regressing, a distribution close to the one observed for percent stenosis (Table 4). In summary, wherever one chooses to draw the cut-point for changes classifying biologically valid alterations of preexisting plaques, there are two to three times more stenoses progressing than regressing (Table 4). Altogether, by the accepted cut-off criteria, the incidence of stenoses changing their size spontaneously, either progressing or regressing over 3 years, amounted to ~14%.

Progression of ‘Normal’ Segments

Progression was also observed in the 2,412 segments classified as normal at first angiography; they showed a small but significant decrease in mean segment diameter by −0.041±0.319 mm (p=0.01).

Progression Manifested as Formation of New Lesions

In the second angiogram, 154 new coronary lesions (144 stenoses ≥20% and 10 new occlusions; 0.6% lesions per patient) were identified in previously angiographically “normal” coronary sections; their stenosis averaged 39.25±10.3% (range, 48.0–81.4%); the majority was clinically asymptomatic with stenosis <50% (Figure 5). The minimal stenotic diameter of these new stenoses averaged 1.67±0.5 mm.

Total Progression and Regression Per Patient

Based on changes in stenosis ≥20%, progression (including old and new lesions) involved a total of 129 patients (56.1%). Sixty-eight patients (29.6%) progressed only with newly formed lesions, 27 patients (11.7%) only in preexisting ones, and 34 (14.7%) both with preexisting and new lesions. Of the 61 patients with progressing preexisting stenoses, 45 progressed in one and 16 in two or more stenoses. Of the 102 patients (44.3%) with new lesions, 68 had one, 22 had two, seven had three, four had four, and one patient had five new lesions. Twenty-eight patients (12.2%) showed regressing stenoses, all with one lesion except one; five of these patients also showed progressing stenoses (2.3%). Considering absolute values (changes ≥0.5 mm), 26 patients (11.3%) showed regression only, six both regression and progression, and 55 patients had progression only. (See Table 5.)
TABLE 5. Angiographic Progression of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patients progressing (18.7%/year)</th>
<th>Distribution among all patients progressing (n=129)</th>
<th>Distribution among all patients (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients progressing with new lesions</td>
<td>129</td>
<td>100</td>
</tr>
<tr>
<td>Patients progressing only in new lesions</td>
<td>102</td>
<td>79.1</td>
</tr>
<tr>
<td>Patients progressing with preexisting lesions</td>
<td>68</td>
<td>52.7</td>
</tr>
<tr>
<td>Patients progressing only with preexisting lesions</td>
<td>61</td>
<td>47.3</td>
</tr>
<tr>
<td>Patients progressing both with preexisting and new lesions</td>
<td>27</td>
<td>20.9</td>
</tr>
</tbody>
</table>

Clinical Findings: Relation Between New Coronary Occlusions and New Myocardial Infarctions

In the second angiogram, 25 new coronary occlusions were observed, 15 developing from preexisting stenoses and 10 from new stenoses. Although newly formed stenoses had a three-times-higher tendency to occlude than old ones (6.5% of new versus 1.87% of old stenoses, \( p=0.111 \)), altogether, the incidence of new occlusions was low and concerned 2.6% of all stenoses.

During the 3 years, five new myocardial infarctions developed, one as a reinfarction at the same location, with the infarct-related artery being diffusely diseased already at first angiography. From the four remaining new infarcts, three resulted from the 15 occlusions developing in preexisting stenoses (preinfarction stenosis averaging 45.6%) and one originated from the 10 occlusions of the newly formed stenoses. Hence, the 25 new occlusions led to four myocardial infarctions, a ratio of approximately one myocardial infarct per six new occlusions. (See Table 6.)

Influence of Risk Factors on Progression

Cigarette smoking. No differences were found between smokers and nonsmokers regarding progression or regression of preexisting stenoses \( (p=0.862) \); however, significant differences were observed regarding the formation of new lesions. In patients smoking throughout the study (group 4), a significantly higher number of new lesions per patient \( (1.17) \) was found than in the other groups: 83% more than in group 3 (patients smoking up to the second year of the study), 98% more than in group 2 (ex-smokers, stopping before entering the study), and 192% more than in group 1 (nonsmokers \( (p=0.001) \). It should be pointed out that in all smoking groups, there was a substantial number of patients (between 48% and 56%) without new lesions; however, even when considering only patients developing new lesions, current smokers still showed 95% more new lesions than nonsmokers. (See Table 7.)

Total cholesterol. Cholesterol levels correlated significantly with the number of progressing preexisting stenoses per patient (increase in stenosis by \( \geq 20% \)). Patients with two or more progressing preexisting stenoses had significantly higher cholesterol levels (average, 278 mg/dl) than those with only one (average, 270.8 mg/dl) or those without progressing preexisting stenoses (average, 261 mg/dl) \( (p=0.017) \). However, there was no influence of cholesterol on the formation of new lesions \( (p=0.854) \), as cholesterol levels averaged \( \approx 265 \text{ mg/dl} \) for patients without or with new lesions. (See Table 8.)

Discussion

This study of the angiographic progression of CAD differs from most previous studies insofar as it is a prospective one with a fixed time interval between the two angiograms. Most previous angiographic progression studies are retrospective, with varying duration for individual patients, as the second angiogram was usually

TABLE 6. Relation Between New Occlusions and New Myocardial Infarctions

<table>
<thead>
<tr>
<th>Patients without new acute myocardial infarctions (No.)</th>
<th>Patients with new acute myocardial infarctions (No.)</th>
<th>Occlusions without new acute myocardial infarctions (No.)</th>
<th>Occlusions with myocardial infarctions (No.)</th>
<th>Total number of new coronary occlusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without new occlusions</td>
<td>208</td>
<td>207</td>
<td>1*</td>
<td>...</td>
</tr>
<tr>
<td>With new occlusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From preexisting stenoses</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>One from preexisting and one from new stenoses</td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>From newly formed stenoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One occlusion/patient</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Two occlusions/patient</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>230</td>
<td>225</td>
<td>4</td>
<td>21</td>
</tr>
</tbody>
</table>

*Reinfarction with a diffusely diseased coronary artery.

Fifteen new occlusions \( (1.87\%) \) from 801 existing stenoses=one occlusion per 53.4 stenoses vs. 10 new occlusions from 154 new stenoses \( (6.5\%)=one\; occlusion\; per\; 15.4\; stenoses \( (p=0.111) \); three myocardial infarctions from 15 occlusions in existing stenoses \( (\geq 20\%)=one\; myocardial\; infarction\; per\; five\; occlusions\; vs.\; one\; myocardial\; infarction\; from\; 10\; occlusions\; in\; new\; stenoses\; \( (\geq 20\%)=one\; myocardial\; infarction\; per\; 10\; occlusions \( (p=NS) \).
TABLE 7. Influence of Smoking Habits* on Progression of Coronary Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>Total number of patients</th>
<th>Patients without new lesions (No.)</th>
<th>Patients with new lesions (No.)</th>
<th>New lesions per total number of patients (No.)</th>
<th>Number of new lesions per patient with new lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers (group 1)</td>
<td>40</td>
<td>26</td>
<td>14</td>
<td>16</td>
<td>0.4</td>
</tr>
<tr>
<td>Ex-smokers (stopping before study begin) (group 2)</td>
<td>123</td>
<td>69</td>
<td>54</td>
<td>73</td>
<td>0.59</td>
</tr>
<tr>
<td>Smoking before and during the first 2 years (group 3)</td>
<td>25</td>
<td>13</td>
<td>12</td>
<td>16</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoking before and throughout the study (group 4)</td>
<td>42</td>
<td>20</td>
<td>22</td>
<td>49</td>
<td>1.17†</td>
</tr>
<tr>
<td>Total</td>
<td>230</td>
<td>128</td>
<td>102</td>
<td>154</td>
<td>0.668 (average)</td>
</tr>
</tbody>
</table>

*Cigarette consumption.

\( p < 0.001.\)

performed due to diagnostic reasons indicated by new clinical events.7-13 In addition, in most previous studies, the abnormal coronary anatomy was evaluated through subjective estimates of coronary angiograms, fraught with large interobserver variabilities,36-39 whereas in the present study, quantitated coronary angiography was applied.23,27,39

Study Limitations

Despite prospective design, fixed time intervals between angiograms, and computer approach in defining coronary stenoses, this study has a number of limitations. First, as these patients were selected from INTACT,19 a prospective angiographic intervention study with nifedipine, they preferentially have mild to moderate CAD according to INTACT's inclusion criteria19 (26% with one-vessel disease, stenosis between 40% and 70%, and 70% of patients free of myocardial infarction). In addition, as all cases with invasive interventions (PTCA or bypass surgery) before entering INTACT were excluded from this analysis of the natural progression of CAD, the number of patients became relatively small (66% of patients included in INTACT). On the other hand, all statistical tests comparing subgroups at baseline and at study end became insignificant, especially those for the group differences between placebo and nifedipine. Nevertheless, a minor, insignificant influence of nifedipine on the formation of new lesions remained (28 fewer new lesions in the nifedipine group; \( p = 0.193 \)). Second, there are important angiographic limitations.36 Foremost, angiography is not able to visualize very early atherosclerotic lesions, or fatty streaks,40,41 because of their minimal size. In addition, atherosclerotic plaques initially often grow intramurally40,42 without impinging on the vessel lumen. Accordingly, the definition adopted here for a new lesion as a stenosis or occlusion observed after 3 years in a previously angiographically normal segment is relative, as it concerns not only lesions created anew during the 3 years but also preexisting ones not yet visible at first angiography. Third, the definition of localized narrowings is equivocal, as besides atherosclerotic plaques, it also includes spasm (not resolved by nitroglycerin) and platelet depositions. Therefore, to exclude false-positive findings, even at the risk of increasing the false-negative findings, our definition of an angiographically progressing or regressing stenosis to be accepted as biologically valid19,24-26,43 was based on the rather rigorous criterion of a change in stenosis by at least 20% or of the minimal stenotic diameter by \( \geq 0.5 \) mm. Finally, it cannot be excluded that progressing and regressing stenoses could have been defined more accurately by increasing the number of projections analyzed. Considering only one projection, especially the one of the smallest stenotic diameter, leads to a substantial overestimation of percent of stenosis. Both for practical as well as quality reasons, we restricted the number of projections to two orthogonal ones; this was based on evidence gathered from one of our preliminary studies.44

Percent Stenosis

In these patients with moderate CAD, percent stenosis, on the average, was \( \approx 40\% \) and remained almost unchanged during the 3 years (85% of stenoses showed changes in degree of \( \leq 20\% \)). This low percentage was not due to the exclusion of the 118 patients undergoing

**TABLE 8. Influence of Total Cholesterol on Progression of Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Preexisting stenoses progressing ( \geq 20% ) per patient (No.)</th>
<th>Patients (No.)</th>
<th>Mean total cholesterol (mg/dl)</th>
<th>New lesions ( \geq 20% ) per patient (No.)</th>
<th>Patients (No.)</th>
<th>Mean total cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>156</td>
<td>261.3</td>
<td>0</td>
<td>119</td>
<td>263.0</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>270.8</td>
<td>1</td>
<td>59</td>
<td>265.4</td>
</tr>
<tr>
<td>2 or more</td>
<td>13</td>
<td>278.3*</td>
<td>( \geq 2 )</td>
<td>32</td>
<td>266.5†</td>
</tr>
</tbody>
</table>

\(*p = 0.0174, r = 0.16404\) (cholesterol at end of the study, Spearman correlation coefficient).

\( f p = 0.854, r = 0.0127\) (cholesterol at end of the study).
revascularization, because in this group, percent stenosis averaged 38.8±8.4%. However, it cannot be ruled out that the relatively high prevalence of mild stenoses found in this study is due to the entry criteria giving preference to patients with mild to moderate disease. Nevertheless, similar low average values for percent stenosis were also found in studies including patients with more severe disease, as in the lifestyle study18 and especially in the nicardipine study.21 From these studies and our study, it can be concluded that in many patients, most coronary stenoses are in a range clinically not manifest and can only be detected by angiography.

The almost identical low percent stenosis of new and old preexisting stenoses suggests the possibility that this is due to a limited growth of new stenoses beyond the stage of fatty streaks41 after exhaustion of the production of growth hormones.45,46 After an initial phase of growth, the size of the majority of newly formed plaques seemed to remain stable over the 3 years, with percent stenosis in the subclinical range (Figure 5). The almost similar average values of percent stenosis of old and new plaques and the low incidence of a further progression of old plaques (=10% over 3 years) observed in this study are in agreement with other reports describing CAD as clinically silent for years, even in the presence of angiographically visible stenoses.17

Coronary Artery Occlusions and Myocardial Infarction

Most of the major coronary events, especially unstable angina, nonfatal and fatal myocardial infarction, but also sudden coronary death are based on secondary progression of coronary artery disease, plaque rupture, adhesion of platelet thrombi, and thrombotic occlusion.48,49 In our study, coronary artery occlusion was a rare event involving only 2.6% of all stenoses (<1% per year). As described in postmortem studies by Davies et al.,48 we also observed that the tendency to occlude was slightly higher for newly formed stenoses than for old preexisting stenoses (6.7% versus 1.8%, respectively); however, because of the small number, the difference was not significant (p=0.111).

In addition, our study confirms previous retrospective findings of a significant number of low-grade stenoses in infarct-related coronary arteries (preinfarction percent stenosis in our study averaging 45.6).50-55 These reports, assessing percent stenosis either immediately after thrombolyis53,54 or from recent preinfarction angiograms,55 showed no correlation between percent stenosis values and the tendency to occlude. As many low-grade, asymptomatic stenoses (degree, 54-60%) led to myocardial infarctions as did high-grade, symptomatic ones. These important retrospective observations50-55 of low-grade, clinically asymptomatic stenoses as a major source for coronary occlusions and myocardial infarction are considerably strengthened by our prospective findings.

Our study further demonstrates that in patients with mild to moderate CAD, not only complete occlusion but even more so acute myocardial infarction is an infrequent phenomenon, at least regarding the individual patient. Only four new infarcts were generated in 25 new occlusions over 3 years. This observation might also explain why in patients with mild to moderate CAD, studies analyzing the effect of primary prevention merely based on the clinical progression of CAD need long follow-up periods, usually of 10 and more years, and must include a large number of patients, often several thousands to be significant.56-60

Progression and Risk Factors

As could be expected, angiographic progression was found to be influenced by risk factors, although to a moderate degree, at least in the short time interval of 3 years. Cigarette smoking was shown to be the strongest risk factor in our study (Table 7); however, its influence concerned exclusively the formation of new lesions, because current smokers developed a significantly higher number of new lesions than those who quit smoking during the study or who were nonsmokers before entry (p=0.001). This observation is supported both by animal experiments demonstrating a very early influence of nicotine on plaque evolution and by numerous epidemiological studies in humans.56,61-63 In accordance with other observations, smoking in our study had no effect on the progression of preexisting, established plaques.

In contrast to cigarette smoking, elevated total cholesterol levels were found to influence only the progression of preexisting stenoses and had no influence on the formation of new lesions. High cholesterol levels (average, 280 mg/dl) correlated significantly with an increased number of progressing preexisting plaques per patient.59,60 This further decrease in lumen size can be explained not only by an increase in plaque volume but also by a functional impairment of vasodilator responsiveness. Recent experiments in animals fed a high cholesterol diet demonstrated vasocostruction caused by cholesterol-induced endothelial dysfunction,64,65 a process reversible after lowering cholesterol.66,67 A similar loss of vasoresponsiveness was also observed in patients with high cholesterol levels, i.e., atherosclerosis, both in vitro in explanted coronary arteries as well as in vivo by testing responsiveness to endothelium-dependent dilators.69,70 Further studies analyzing responsiveness before and after cholesterol-lowering in humans will be necessary to elucidate this important problem.

Summary

In this study of patients with mild to moderate CAD, the incidence of angiographically progressing patients was rather low (<20% per year). In addition, progression concerned mainly the appearance of new lesions and, to a lesser degree, the progression of old ones. Also, the risk of developing a new clinical coronary event was quite low because of a rare incidence of new coronary occlusions generated from preexisting or from new stenoses. Nevertheless, even mild progression was influenced by risk factors, i.e., progression of preexisting stenoses by high cholesterol levels and formation of new lesions by cigarette smoking.

Appendix

Participating Centers and Physicians

The Division of Cardiology, Hannover Medical School, FRG (central office of the study): Paul R. Lichtlen, MD, study director; Wolfgang Rafflenbeul, MD, codirector; Ulrich Nellessen, MD; Stefan Jost, MD; Peter Nikutta, MD; and Ivo Amende, MD.
The Division of Cardiology, University Hospital Hamburg, FRG: Walter Bleifeld, MD, and Christian Hamm, MD.

The Division of Cardiology, University Hospital Frankfurt, FRG: Martin Kaltenbach, MD; Harald Klepzig, MD; and Gisbert Kober, MD.

The Division of Cardiology, University Hospital Erlangen, FRG: Kurt Bachmann, MD, and Siegfried Haeting, MD.

City Hospital Lukas der Weser, Wolfsen, FRG: Hans-Jürgen Engel, MD, and Holger Werner, MD.

The Division of Cardiology, University Hospital Berlin, FRG: Horst Schmutzler, MD, and Harald Bias, MD.

Erasmus Universiteit Rotterdam, The Netherlands: Paul Hugenholtz, MD, codirector of the study; Jaap Deckers, MD, study assistant; Patrick Serruys, MD; and Hans Reiber, PhD.

The Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands: Hans Bonnier, MD; Rolf Michels, MD; and Rael Troquay, MD.

Academic Ziekenhuis Groningen, The Netherlands: K. Lie, MD, and E.D. de Muinck, MD.

The Division of Biomedics, Hannover Medical School, FRG: B. Schneider, PhD; Hartmut Hecker, PhD; and Birgitt Wiese, PhD.

References


Anatomical progression of coronary artery disease in humans as seen by prospective, repeated, quantitated coronary angiography. Relation to clinical events and risk factors.
The INTACT Study Group.
P R Lichtlen, P Nikutta, S Jost, J Deckers, B Wiese and W Rafflenbeul

Circulation. 1992;86:828-838
doi: 10.1161/01.CIR.86.3.828

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/3/828