Impact of Compensatory Enlargement of Atherosclerotic Coronary Arteries on Angiographic Assessment of Coronary Artery Disease

Georg M. Stiel, MD, MSc, Ludmilla S.G. Stiel, MD, MA, Joachim Schofer, MD, Karl Donath, MD, DDS, and Detlef G. Mathey, MD

To determine whether compensatory enlargement of atherosclerotic coronary arteries occurs and to what degree it affects the angiographic assessment of coronary artery disease, we performed postmortem coronary angiography of 30 human hearts with suspected coronary artery disease and studied 70 histologic cross sections of the proximal left anterior descending artery and proximal right coronary artery. Angiographic and morphometric analyses of 50 stenoses in proximal and middle sections of the left anterior descending artery, right coronary artery, and left circumflex artery were performed. The control group of 10 human hearts without suspected coronary artery disease was evaluated in the same way. For this purpose, coronary arteries were filled with a methylmethacrylic radiopaque resin at a pressure of 100 mm Hg and closely embedded in a methylmethacrylic resin by use of which shrinkage and mechanical artifacts could be avoided. The area circumscribed by the internal elastic lamina was taken as a measure of the area of the arterial lumen if no plaque had been present. The angiographic and corresponding morphometric degree of stenosis was assessed. A significant correlation ($r=0.85, p \leq 0.0001$) was found between the internal elastic lamina area and the area of the plaque (lesion area), suggesting that coronary arteries may enlarge as lesion area increases. With the morphometric degree of stenosis, the expected anatomic diminution of the coronary artery was abolished ($r=0.79, p \leq 0.0001$), indicating compensatory enlargement in atherosclerotic segments. Accordingly, the degree of stenosis assessed from in vitro angiograms was underestimated. Compensatory coronary enlargement of the stenotic segment was the main reason for angiographic underestimation. The underestimation factor of up to 3.50 for very mild stenoses decreased to 1.37 at an angiographic degree of 50% area stenosis and 30% diameter stenosis. In contrast, at higher degrees of stenosis, angiographic underestimation resulted mainly from compensatory enlargement due to disease in the prestenotic reference segment. The underestimation factor was 1.37. These studies show that compensatory enlargement in stenotic coronary artery segments occurs resulting in significant angiographic underestimation of coronary atherosclerosis during the early stage of coronary artery disease. (Circulation 1989;80:1603–1609)

Coronary angiography is widely accepted as a useful clinical and investigative tool to assess coronary artery disease (CAD). There are, however, some limitations of the technique that are important to recognize. Usually, the extent of CAD is estimated as percent reduction of luminal diameter determined by comparing the diameter at the site of maximal reduction with the diameter in adjacent areas that appear either normal or only minimally diseased. However, there is significant intraobserver and interobserver variability in the conventional assessment of coronary artery lesions.1–4 Computer-based visual5 and automated6–8 methods of luminal border definition from cine film images seem to improve the reproducibility and accuracy of coronary diameter measurements.
On the other hand, several investigators have shown a poor agreement of angiographic findings with direct postmortem measurements.\textsuperscript{9}–\textsuperscript{13} Recently, Glagov et al\textsuperscript{14} studied the left main coronary artery histologically and found compensatory enlargement during the early stage of plaque formation. This new morphological finding offers a logical explanation why coronary angiography often underestimates the severity of vessel stenosis. A controversial discussion followed this report.\textsuperscript{15}–\textsuperscript{19}

In the present study, we were able to prove conclusions of Glagov et al\textsuperscript{14} for the proximal segments of the left anterior descending (LAD) coronary artery and right coronary artery (RCA). We could also show that the compensatory enlargement occurs in the proximal circumflex (Cx) coronary artery and in the middle segments of the LAD and RCA by determining the diminution ratio (DR) of normal and diseased coronary arteries. In a next step, we examined to what degree compensatory coronary artery enlargement affects the angiographic assessment of CAD.

By conventional postmortem preparation of coronary arteries, shrinkage and mechanical artifacts cannot be avoided. The results of postmortem angiographic studies, therefore, may reflect neither the natural status of the coronary arteries nor the results of coronary angiograms performed in vivo. For our studies, we performed an angiographic and morphometric analysis of postmortem human coronary arteries using a new method of preparation that is free of these artifacts.\textsuperscript{22}

Methods

\textbf{Study Material}

Forty human hearts were obtained at autopsy within 24 hours of death. In the study group of 30 hearts, disease of left, right or left, and right coronary artery was demonstrated by postmortem angiography. The age of the subjects was 47–90 years (67±18 years, mean±SD). Seventeen were men and 13 were women. The weight of the hearts before fixation was 350–710 g (485±79 g, mean±SD).

The control group consisted of 10 hearts without suspected CAD. The age of the subjects was 42–72 years (55±11 years, mean±SD). Four were men and six were women. The weight of the hearts before fixation was 310–390 g (345±28 g, mean±SD).

\textbf{Study Methods}

All hearts were prepared in an identical manner. The hearts were weighed and examined for gross changes. After the usual preparation,\textsuperscript{20,21} the coronary arteries were injected at a pressure of 100 mm Hg with a casting mixture consisting of barium sulfate and methylmethacrylic resin.\textsuperscript{22} After coronary casting, the hearts were fixed in cold formalin (4° C) and placed in a dummy thorax for the normal x-ray recording simulation. Postmortem radiographs of the whole heart were made in several standard projections (Figure 1); for each, a complementary perpendicular projection was obtained.

The morphometric analysis of 10 proximal and nine middle segments of the LAD coronary artery, nine proximal and 10 middle segments of the RCA, and six proximal and six middle segments of the left Cx coronary artery was performed for the study group according to the method of Brown et al.\textsuperscript{5} By this method, the angiographic percent-diameter stenosis and percent-area stenosis for 50 coronary lesions were calculated.

After angiography of the whole hearts of the study group and control group, the aforementioned arterial segments were removed. The samples were embedded in methylmethacrylic resin\textsuperscript{23} and retrimmed by contact radiography to characterize the state and configuration of the atherosclerotic plaques (Figure 1). The acrylic samples were sawed exactly in the area of minimal lumen diameter and the corresponding “normal” lumen estimated by contact radiography. The distance between both cross sections was the same as for the morphometric analysis. In the control group, localization of and distance between both cross sections were chosen to be comparable with the study group. The cut surfaces were ground and stained with the Masson-Goldner trichrome procedure and with Weigert’s resorcin-fuchsin procedure for differentiation of connective tissue (Figure 1).

For histologic measurements, a contour-tracing system consisting of a microscope with a video camera, a digitizer for semiautomatic measurements, a video monitor, and an IBAS 2000 computer system was used.

The lumen, the internal elastic lamina (IEL), and the outer limit of the media in 38 proximal LAD and 32 proximal RCA diseased sections were traced as proposed by Glagov et al.\textsuperscript{14}

For the present study, the proximal LAD was used before origin of the first diagonal branch and the proximal RCA before origin of any major side branch. In most adult hearts, these segments are similar in diameter and lumen area.\textsuperscript{25} For 50 morphometric analyzed stenoses the cross sections with a minimal lumen and corresponding prestenotic “normal” lumen could be defined and were traced by the same method.

From these tracings, the actual cross-sectional area of the lumen (lumen area), the lesion area (the cross-sectional area occupied by plaque), and the IEL area were determined from the contours (Figure 1). Using the same definition as Glagov et al.,\textsuperscript{14} the IEL indicates the inner limit of the arterial wall and describes an area that is nearly identical to the lumen area when there is little or no intimal thickening. In the presence of plaque, the IEL area represents the “potential” lumen area, that is, what the actual lumen area would be if there was no plaque. The diameter of a circular area equivalent to each area traced was calculated. The IEL area
for distal and proximal cross sections of 30 control samples was determined by the same method. The degree of stenosis as calculated from the cross section of an artery was defined as the extent...
to which the lesion area occupies the "potential" lumen area, and the morphometric percentage of stenosis was expressed as: \( \% \text{ASm} = (1 - \text{lumen area/IEL area}) \times 100 \).

Analyses of the coronary angiograms and of the pertinent histologic slices were performed by two independent observers, each of whom was unaware of the other's results.

The corresponding angiographic and morphometric measurements were compared using least-squares regression analysis and Pearson's correlation coefficient. Statistical significance was assigned when \( p \) was less than or equal to 0.05.

**Results**

Because a methylmethacrylic resin was used to fill and embed the coronary arteries, no shrinkage artifacts could occur. By the sawing and grinding technique, mechanical artifacts were avoided. With this new method of preparation, the anatomy of distended coronary artery was well preserved, thereby offering comparable conditions for angiographic and histologic evaluations.

The IEL area in 38 proximal LAD and 32 proximal RCA, diseased cross sections was 3.0–20.0 mm\(^2\) (9.8±3.3 mm\(^2\), mean±SD). The smallest measured lesion area was 1.1 mm\(^2\), and the largest was 15.2 mm\(^2\) (6.0±3.8 mm\(^2\), mean±SD). The actual lumen area was 0.0–9.0 mm\(^2\) (4.4±2.0 mm\(^2\), mean±SD).

Ten proximal and nine middle stenotic segments of the LAD, nine proximal and 10 middle stenotic segments of the RCA, and six proximal and six middle stenotic segments of the Cx coronary artery were analyzed angiographically and histologically.

The percent-area stenosis by angiographic measurements was 10.0–95% (41.6±24.7%, mean±SD) and by morphometric measurements, 18.3–96% (61.1±24.5%, mean±SD). The morphometric percent-area stenosis in the prestenotic region (normally the reference for angiographic measurements) was 10.9–59.9% (28.7±9.1%, mean±SD).

The examined arterial sections of the control group were chosen to be identical in number and location with those of the study group.

**Figure 2.** Scatterplot of comparison of internal elastic lamina area (IEL Area) ("potential" lumen area) with lesion area (Lesion Area). Linear regression.

**Figure 3.** Definition of diminution ratio for anatomical diminution of coronary artery and diagrammatic representation of changes in internal elastic lamina (IEL) area for minimal and more severe lesion (Le).

In the control group, the proximal IEL area was 5.5–10.6 mm\(^2\) (8.9±1.2 mm\(^2\), mean±SD) and the distal IEL area was 5.4–10.5 mm\(^2\) (8.3±1.2 mm\(^2\), mean±SD). The mean distance and its variation was almost identical for the study and the control group (range, 5–25 mm; mean 12±5 mm).

IEL area increased with the lesion area \((r=0.85, p \leq 0.0001)\) (Figure 2). The standard error of the IEL area in relation to the lesion area along the regression line was 2.0 mm\(^2\).

The anatomical diminution of the coronary artery was expressed as the ratio of the distal to the proximal IEL area (Figure 3). A DR 0.93±0.05 was found in the arterial segments of the control group. If the IEL area does not change with growth of the lesion, no increase of the DR would have been expected. Figure 3 shows the diagrammatic representation of the changes in the IEL area if the lesion is only minimal and later more severe, resulting in different DRs.

The relation between the DR of the coronary artery and the degree of stenosis (percent-area stenosis and percent-diameter stenosis obtained by

**Figure 4.** Scatterplot of diminution ratio of coronary artery (DR) plotted against morphometric degree of stenosis (percent-area stenosis [%ASm] and percent-diameter stenosis [%DSm]). Polynomial regression. Expected diminution ratio is indicated by broken line.
morphometric measurements) is shown in Figure 4
\( r=0.73, p<0.0001, \text{SEE}=0.12 \). The regression line approximates the DR of 2.0 at higher degrees of stenosis.

Figure 5 shows the relation between the cineangiographic and morphometric degree of stenosis. The line of best fit expressed as polynomial regression gives a high coefficient of correlation \( r=0.93, p<0.0001, \text{SEE}=9.2\% \) between the angiographic percent-area stenosis and the morphometric percent-area stenosis. Cineangiography significantly underestimates coronary atherosclerosis at all degrees of stenosis.

The factor of angiographic underestimation is defined as the ratio of morphometric percent-area stenosis to angiographic percent-area stenosis. The angiographic underestimation factor (UF) for each of the stenoses studied with respect to the angiographic degree of stenosis is shown in Figure 6. The line of best fit shows the following course: a hyperbolic slope with an angiographic UF between 3.50 and 1.37 for angiographic percent-area stenoses smaller than 50% and angiographic percent-diameter stenosis smaller than 30%, followed by a linear course with an approximately constant UF of 1.37 for angiographic area stenoses ranging 50–75% and diameter stenoses ranging 30–50%, then followed by a downward slope to an UF of 1.00 for stenoses of more than 75% area stenosis and 50% diameter stenosis. The horizontal broken line at an UF of 1.37 mainly indicates the degree of angiographic underestimation due to disease in the prestenotic area averaging 28.7±9.1% area stenosis, which corresponds to an underestimation of 0.29. The remaining underestimation of 0.08 has methodologic reasons related to the formula used to calculate the angiographic degree of stenosis.

**Discussion**

This study provides evidence that the compensatory enlargement of human atherosclerotic coronary arteries occurs during the early stage of plaque formation and demonstrates its impact on the in vitro angiographic underestimation of coronary atherosclerosis.

Arterial size measured as the cross-sectional area enclosed by the IEL correlated significantly with the cross-sectional area of the plaque (Figure 2). This result is in agreement with previous studies. Glatov et al. interpreted this observation as evidence for the compensatory enlargement in the stenotic coronary artery segments of equal size.

Using a different approach, we could prove compensatory enlargement in the present study. Normally, the coronary artery becomes smaller along its course, both in lumen diameter and in size. This results in the DR of 1.0 or less if IEL area remains constant when the lesion increases (Figure 3). As shown in Figure 4, the DR increases with the degree of stenosis indicating that the normal anatomical diminution in arterial size is abolished by compensatory enlargement in the stenotic coronary arterial segment. For mild CAD (stenoses less than 35–40%) no change in lumen area was found, because IEL area significantly increased. The projected relation between the DR and the degree of stenosis for this range of mild stenosis is shown by the broken line in Figure 4. These observations relate to measurements in the proximal and middle segments of the coronary artery tree. As suggested by Zarins et al., different segments of the same coronary artery can respond differently.

The compensatory enlargement has a significant influence on the in vitro angiographic underestimation of stenosis up to an angiographically determined degree of approximately 50% area stenosis and 30% diameter stenosis (Figure 6). This important observation shows that compensatory enlargement is a major source of error in the assessment of coronary lesions by angiography up to the aforementioned degree of stenosis. At a higher degree of
stenosis, compensatory enlargement is a less important factor for angiographic underestimation. The UF for lesions ranging from 50% to 75% area stenosis and from 30% to 50% diameter stenosis is relatively constant (UF=1.37). In this range of stenoses, in vitro angiographic underestimation is mainly the result of two opposing factors, compensatory enlargement in the stenotic and the prestenotic reference segment. In stenoses of more than 75% area and 50% diameter reduction, no compensatory enlargement could be observed in both segments.

Beyond that, a well-known methodical underestimation resulting from the formula used to calculate percent stenosis influences the in vitro angiographic assessment steadily but insignificantly independent of the degree of stenosis.

In previous studies, it was shown that the assessment of CAD by angiography does not predict the severity of atherosclerosis. In this study, we provide evidence that coronary angiography underestimates the degree of coronary atherosclerosis over the entire range of stenoses (Figure 5). The mechanism of compensatory enlargement in a stenotic coronary arterial segment is recognized as a new factor of underestimation in addition to the well-known methodical factors. Compensatory enlargement has its greatest impact on the angiographic measurement of CAD during the early stage of plaque formation, leading to a significant underestimation of the disease in this low range of stenoses.

The explanation of the mechanism of the compensatory enlargement in stenotic coronary arteries is unknown. Glagov et al. explained this mechanism as a two-step process. In the early stage of CAD, the atherosclerotic plaque is usually eccentric. The stenosis might enlarge in the area of the plaque or in the uninvolved wall segment. In the first instance, atrophy of the wall or degradation of mullar connective tissue fibers could result in an outward bulging of the plaque and the underlying wall. In the second instance, narrowing of the lumen would result in an increased flow velocity, thereby leading to expansion of the uninvolved segment of the wall.

As a clinical consequence of these findings, the accuracy of coronary angiography to determine the early stage of CAD has to be questioned. In view of the ongoing and future angiographic studies to determine progression and regression of CAD in clinical trials, our findings are very important for the interpretation of these data.

References


**KEY WORDS** • arteriosclerosis • angiography • coronary vessels • stenoses
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