Determinants of Normal Coronary Artery Dimensions in Humans

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Background. Studies of normal human coronary dimensions have been performed primarily in postmortem hearts. We evaluated the influence of age, body habitus, and regional myocardial mass on coronary dimensions in living patients with normal coronary vessels.

Methods and Results. Arteriographically normal coronary angiograms were analyzed from the following groups of subjects: group 1 (age, 15–34 years) consisted of 30 post–cardiac transplant patients with donor hearts from male subjects aged 15–34 years, group 2 (age, 35–54 years) consisted of 12 post–cardiac transplant patients with donor hearts from male subjects aged 35–54 years and 26 male subjects investigated for atypical chest pain, and group 3 (age, 55–74 years) consisted of 26 male subjects investigated for atypical chest pain. All angiograms were performed after sublingual nitroglycerin. Measurements of the dimensions of the left main, proximal left anterior descending, proximal left circumflex, and proximal right coronary arteries were made using a computer-assisted edge-detection algorithm. The regional myocardial mass supplied by each vessel was derived from echocardiographically derived total left ventricular mass and a semiquantitative angiographic territory scoring system based primarily on the number and length of its terminal nutrient branches.

Conclusions. Linear regression analysis showed that coronary vessel cross-sectional area and total coronary cross-sectional area increase with regional myocardial mass and decrease linearly with age. Multivariate regression analysis revealed that regional myocardial mass and age were independent predictors of cross-sectional area for each vessel and for the total coronary cross-sectional area. We speculate that age-related decline in physical activity, in part, may be responsible. (Circulation 1991;84:2294–2306)

Accurate description of the extent of coronary atherosclerosis is predicated on the understanding of the normal coronary anatomy. However, studies of the luminal dimensions of truly normal coronary arteries are limited. Although several studies have evaluated the dimensions of postmortem coronary arteries,1–4 few studies have been performed using quantitative coronary arteriographic techniques in living patients with presumably normal arteries.5,6

Previous studies have shown that pathological conditions such as hypertension that substantially increase left ventricular mass are associated with increased epicardial coronary vessel size.7–9 There are also postmortem observations and animal studies suggesting that the amount of myocardium supplied by a coronary vessel is correlated with the size of that proximal vessel.3,10 Other reports show larger coronary vessel size for the male sex relative to the female.5 Intrinsic vascular pathology such as atherosclerosis generally tends to narrow vessel lumens.

It is the purpose of this study to analyze determinants of epicardial coronary vessel size in subjects selected to avoid pathological conditions that could directly or indirectly affect coronary dimensions. In the present study, we use a territory scoring system for the semiquantitative angiographic estimate of regional coronary vessel distribution. Measurement of coronary vessel distribution and echocardiographic assessment of total left ventricular mass permits evaluation of the relation of proximal coronary artery dimensions to regional left ventricular mass. In addition, the influence of age and body habitus on coronary dimensions determined by quantitative coronary arteriography are evaluated in living patients with normal coronary vessels.

Methods

Selection of Subjects

Entirely normal coronary angiograms based on visual assessment of absence of any luminal irregu-

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larities were reviewed from 94 male subjects. The angiograms were divided into three age groups: group 1, age 15–34 years; group 2, age 35–54 years; and group 3, age 55–74 years. The sources of coronary angiograms for the different age groups were as follows.

**Group 1.** To obtain coronary angiograms of young male subjects without history of cardiac disease, the angiograms of 30 post-cardiac transplant patients with donor hearts from male subjects aged 15–34 years were analyzed. Angiograms from transplant subjects were performed with a mean interval post-allograft surgery of 38±9 days as part of a prospective study of posttransplant coronary artery disease. Information on body habitus (weight and height) was obtained from donor relatives.

**Group 2.** This included 12 post-cardiac transplant patients with donor hearts from men aged 35–54 years and 26 men (aged 35–54) investigated for atypical chest pain. The cardiac transplant subjects were similarly studied with a mean of 38±7 days after transplantation. The angiographic results from the transplant and atypical chest pain patients were combined because comparison of the coronary dimensions of the 12 post-cardiac transplant angiograms and 26 angiograms from patients with atypical chest pain showed no significant differences.

**Group 3.** This included 26 men (aged 55–74 years) investigated for atypical chest pain. All subjects with atypical chest pain (in groups 2 and 3) had either normal or equivocal exercise stress test results.

Subjects (or donor subjects) with systemic hypertension, left ventricular hypertrophy, valvular heart disease, cardiomyopathy, or history of other cardiac disease were excluded because such patients may have pathologically different coronary artery diameters. Only male subjects were included in this study because of the well recognized sex difference in coronary dimensions and the lack of sufficient number of normal-appearing coronary angiograms from female subjects for all age ranges.

Adequate echocardiographic examinations were obtained in 77 of the 94 (82%) subjects (87% of group 1, 79% of group 2, and 81% of group 3). Standard parasternal and apical views were used. According to the recommendations of the American Society of Echocardiography, the thickness of the posterior wall and interventricular septum, the left ventricular end-diastolic and end-systolic dimensions were measured. The left ventricular mass was derived from an anatomically validated formula:

\[
\text{Left ventricular mass (g)} = 1.04[(\text{LVEDD} + \text{PW} + \text{VS})^3 - (\text{LVEDD})^3] - 13.6; \\
\text{where LVEDD is left ventricular end-diastolic dimension, PW is posterior wall thickness, and VS is ventricular septal wall thickness. Subjects with echocardiographic evidence of left ventricular hypertrophy based on wall thickness measurements were excluded from the study.}
\]

**Cardiac Catheterization**

All angiograms were performed using 5–7-inch intensifier modes and were reviewed as suitable for analysis by quantitative coronary arteriography. All patients gave written informed consent for coronary angiography. Selective coronary arteriography was performed using the percutaneous femoral approach. Sublingual nitroglycerin (0.4 mg) was given 2–3 minutes before the contrast injections used for quantitation to minimize the effect of varying vasomotor tone on vessel lumen diameters. Patients received nitroglycerin before quantitative angiography, irrespective of whether the patient was studied early after transplantation or for evaluation of atypical chest pain. Patients with suspected coronary spasm based on prior clinical or electrocardiographic evidence were not included in this protocol because of potential need for ergonovine challenge. Catheters of known diameters were used for calibration. Multiple projections including cranial and caudal angulated views were obtained for all patients.

**Quantitative Coronary Arteriography**

Diameters of the left main coronary artery (LMCA), proximal left anterior descending artery (pLAD), proximal left circumflex artery (pLCX), and proximal right coronary artery (pRCA) were measured. Coronary segments that were proximal to major diagonal or marginal branches were selected for quantitation. Only coronary segments that best visualized the vessel in elongated profile of at least 0.5 cm in length were quantitated and used for analysis. In general, to avoid vessel overlap, the cranial left anterior oblique view was chosen for pLAD, caudal right anterior oblique view for LMCA and pLCX, and left anterior oblique view for pRCA.

Coronary cineangiographic films were analyzed by computer-assisted edge detection by using a 35-mm cine film transport mechanism mounted on a movable stage (Vanguard Instruments, Melville, N.Y.). Single end-diastolic cine frames, identified by an electrocardiogram-triggered mark on the frames and selected for optimal coronary vessel opacification, were focused and magnified (×3.5). Coronary segments were centered in the image field, and the image was digitized with a video processor (model 5524, De Anza Systems, Fremont, Calif.) controlled by a Hewlett-Packard 2100 computer (Andover, Mass.). The digitized image was displayed on a graphic computer terminal linked to a light pen. The margins of either the catheter or coronary segment were traced manually using the light pen. Using these lines as initial search locations, the automatic edge-finding algorithm drew and smoothed the edges, defining the edge as the peak of the first derivative of the gray-scale density gradient, perpendicular to the long axis of the catheter or vessel as estimated from the initial manual tracings. When the computer algorithm was unable to resolve vessel boundaries in areas of noise or vessel crossings, manual editing of short segments of boundary with the light pen was used to correct the computer-generated boundary. At no time did the length of a manually entered margin exceed 20% of the total length of the quan-
Coronary artery map used for territory scoring illustrates proximal coronary segments quantitated and potential terminating nutrient branches used to calculate territory scores. LMCA, left main coronary artery; pRCA, proximal right coronary artery; pLCX, proximal left circumflex artery; pLAD, proximal left anterior descending artery.

diagonal branches, the distal left anterior descending segment, and the left anterior descending septal branches. Terminal branches of the pRCA include the posterior descending and potential posterolateral branches. Terminal branches of the pLCX include the obtuse marginal branches, distal left circumflex artery segment (if it is the terminating segment), and potential posterolateral branches.

The extent of myocardial territory supplied by a nutrient vessel is based on the relative size of the vessel and is judged by the length of the terminal vessel in an angiographic projection that best elongates the segment, although some consideration is given to the lateral spread of the terminating small branches. Terminating vessel length and corresponding territory is assigned a numerical value of 3, 2, 1, or 0 corresponding to large, medium, small, or absent for all segments on the coronary map that supply left ventricular myocardium (i.e., right ventricular marginal and atrial branches are excluded). A large territory is subtended by a terminal segment extending more than two-thirds of the distance from base to apex of the left ventricle (see Figure 2). A medium territory is subtended by a terminal segment extending from one third to two thirds of the base-to-apex length. A small territory is subtended by a terminal segment extending less than one third of the base-to-apex length. Very small twigs that extend less than one fifth of the base-to-apex length are typically thin and inconspicuous and are considered absent. Sizing of the distal left anterior descending coronary artery is based on the left anterior descending termination: A large vessel wraps around the apex, a medium stops at the apex, and a small terminates well before reaching the apex of the left ventricle. The ramus intermedius vessel territory, if present, is not included in either pLAD or pLCx territory score. The total septal territory is assigned three points and allocated to the pLAD.
The territory score of a proximal vessel is the sum of the scores of its terminal branches, which is an estimate of the summed length of the branches. Territory scores of the LMCA, pLAD, pLCx, and pRCA were assessed. The LMCA territory score is the sum of scores of pLAD, pLCx, and the ramus intermedius. The total left ventricular territory score is the sum of scores of LMCA and pRCA. The territory fraction for each vessel is defined as (territory score of the vessel divided by total left ventricular territory score \( \times 100\%\)). Figure 3 shows an illustration of the territory scoring method in a coronary angiogram. The left ventricular mass supplied by a vessel is defined as total left ventricular mass multiplied by territory fraction of the vessel. Reproducibility of the territory scoring system was assessed from paired blinded observations of 36 coronary angiograms read by two experienced individuals.

**Statistical Analysis**

Data are expressed as the mean with the standard deviation as the index of dispersion. Student’s unpaired t-test was used for comparing two groups of unpaired data. Analysis of variance was used if more than two groups of unpaired data were compared. Correlations between variables were assessed using univariate linear regression analysis and Pearson’s correlation coefficient. Multivariate regression analysis was performed to test dependence of coronary dimensions on age, body surface area, and vascular territory. Differences were considered significant when confidence limits exceeded 95% (\( p<0.05 \)).

**Results**

**Regional Left Ventricular Mass**

The mean left ventricular mass (left ventricular mass divided by body surface area) of the study population was 201±37 g (98±21 g/m²). There were no significant differences in left ventricular mass between the three age groups (group 1, 201±40 g; group 2, 199±35 g; group 3, 204±39 g) or between the hearts of transplant recipients and subjects with atypical chest pain in group 2 (200±37 versus 198±34 g). No significant differences were found in body weight, height, and body surface area between the three age groups or between the transplant donors and normal subjects in group 2.

The mean territory score for all subjects was 17.9±3.9 (range, 10–25) for the LMCA; 9.8±2.1 (range, 5–14) for the pLAD; 7.0±2.8 (range, 1–14) for the pLCx, and 4.6±1.7 (range, 1–9) for the pRCA. The LMCA territory score is more than the sum of the pLAD and pLCx territory scores, reflecting inclusion of ramus intermedius territory. The territory fraction for the LMCA was 75±8% (range, 55–95%); for the pLAD was 42±8% (range, 19–67%); for the pLCx was 29±10% (range, 6–52%); and for the pRCA was 20±7% (range, 4–41%). Comparison of territory scores and territory fractions by different observers in

**Table 1. Comparison of Two Blinded Readings of Myocardial Territory Scores and Territory Fractions in 36 Coronary Angiograms**

<table>
<thead>
<tr>
<th></th>
<th>Mean of territory scores (territory fractions) for all subjects</th>
<th>SD of subject by subject differences between observer 1 and observer 2</th>
<th>Coefficient of variation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observer 1</td>
<td>Observer 2</td>
<td></td>
</tr>
<tr>
<td>pLAD (n=36)</td>
<td>10.6 (43.1)</td>
<td>10.5 (43.7)</td>
<td>1.42 (4.72)</td>
</tr>
<tr>
<td>pLCx (n=36)</td>
<td>7.6 (30.4)</td>
<td>7.4 (30.7)</td>
<td>1.08 (4.14)</td>
</tr>
<tr>
<td>pRCA (n=36)</td>
<td>6.6 (26.5)</td>
<td>6.5 (26.8)</td>
<td>1.28 (2.96)</td>
</tr>
<tr>
<td>All vessels (n=108)</td>
<td>8.3 (33.3)</td>
<td>8.1 (33.7)</td>
<td>1.26 (3.95)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent values for territory fractions.

pLAD, proximal left anterior descending artery; pLCx, proximal left circumflex artery; pRCA, proximal right coronary artery; SD, standard deviation.

*Coefficient of variation is SD of subject by subject differences divided by mean territory score or mean territory fraction.
108 paired observations showed that the overall coefficients of variation (standard deviation of subject by subject differences/mean value) were 15% and 11%, respectively (Table 1).

Regional left ventricular mass was calculated by multiplying the territory fraction by the echocardiographically measured total left ventricular mass in those subjects with available data. Regional left ventricular mass for the LMCA was 152±33 g (range, 68–215 g); for the pLAD was 85±21 g (range, 38–123 g); for the pLCx was 57±24 g (range, 9–110 g), and for the pRCA was 40±14 g (range, 8–74 g).

Quantitative Coronary Arteriography

Table 2 shows the total coronary cross-sectional area and mean cross-sectional area of each vessel for the three age groups. There is a progressive decrease with age in the total coronary cross-sectional area and cross-sectional areas of the LMCA, pLAD, pLCx, and pRCA. Compared with group 1 (age, 15–34 years) patients, the group 2 (age, 35–54 years) and group 3 (age, 55–74 years) patients had smaller total coronary cross-sectional areas (p<0.05 for both groups). The difference between group 2 and group 3 was also significant (p<0.05). There was no significant difference in total coronary cross-sectional area between the transplant and nontransplant subjects in group 2 (26.97±7.04 versus 28.12±7.83 mm²).

Table 3 and Figures 4, 5, and 6 show the relation between the mean vessel cross-sectional area and total coronary cross-sectional area and age, regional or total left ventricular mass, body weight, body height, and body surface area. Total left ventricular mass had a strong positive correlation with TCSA (r=0.642, p<0.001; Figure 4, right panel). Regional left ventricular mass correlated significantly with mean cross-sectional areas of LMCA (r=0.591, p<0.001), pLAD (r=0.756, p<0.001), pLCx (r=0.733, p<0.001), and pRCA (r=0.744, p<0.001) (Figure 5). Age was found to have a significant negative correlation with TCSA (r=−0.531, p<0.001; Figure 4, left panel) and with mean cross-sectional area of LMCA (r=−0.453, p<0.001), pLAD (r=−0.407, p<0.001), pLCx (r=−0.440, p<0.001), and pRCA (r=−0.322, p<0.005) (Figure 6). No significant correlation was found between cross-sectional area of each vessel and total coronary cross-sectional area with body weight, height, and body surface area.

Equations predicting the cross-sectional area of each vessel and the total coronary cross-sectional area from the regional or total left ventricular mass, age, and body surface area were sought using multivariate regression analysis. Age and regional or total left ventricular mass were found to be significant independent predictors of the cross-sectional area for each vessel and of the total coronary cross-sectional area (Table 4). Body surface area was not a significant predictor of either vessel cross-sectional area or total coronary cross-sectional area.

Substantial information regarding normal coronary artery dimensions in proximal coronary artery segments can be derived based on territory fraction and age alone. Table 5 provides the normal mean diameters of each vessel by age and territory fraction groupings. The ranges in parentheses are based on

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**Table 2. Mean Coronary Cross-sectional Areas and Total Coronary Cross-sectional Area for Different Age Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>LMCA (mm²)</th>
<th>pLAD (mm²)</th>
<th>pLCx (mm²)</th>
<th>pRCA (mm²)</th>
<th>TCSA (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (15–34 years)</td>
<td>18.66±4.10</td>
<td>11.80±4.49</td>
<td>9.66±3.74</td>
<td>10.82±3.29</td>
<td>32.88±7.34</td>
</tr>
<tr>
<td>Group 2 (35–54 years)</td>
<td>15.83±4.30*</td>
<td>10.02±3.49</td>
<td>8.12±3.24</td>
<td>9.70±3.98</td>
<td>27.75±7.32*</td>
</tr>
<tr>
<td>Group 3 (55–74 years)</td>
<td>14.51±3.65*</td>
<td>8.53±2.58*</td>
<td>6.44±2.70*</td>
<td>8.11±3.12*</td>
<td>23.47±5.83*</td>
</tr>
</tbody>
</table>

CSA, cross-sectional area; TCSA, total coronary cross-sectional area; LMCA, left main coronary artery; pLAD, proximal left anterior descending artery; pLCx, proximal left circumflex artery; pRCA, proximal right coronary artery.

* p<0.05 vs. group 1.
† p<0.05 vs. group 2.

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**Table 3. Coefficients and Values for Comparison of Cross-sectional Areas of Coronary Vessels With Potential Determinants of Artery Size**

<table>
<thead>
<tr>
<th>Age</th>
<th>Regional left ventricular mass∥</th>
<th>Body weight</th>
<th>Body height</th>
<th>Body surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCSA</td>
<td>−0.531†</td>
<td>0.642†</td>
<td>0.168</td>
<td>0.052</td>
</tr>
<tr>
<td>LMCA</td>
<td>−0.453†</td>
<td>0.591†</td>
<td>0.204</td>
<td>0.080</td>
</tr>
<tr>
<td>pLAD</td>
<td>−0.407†</td>
<td>0.756†</td>
<td>0.146</td>
<td>0.003</td>
</tr>
<tr>
<td>pLCx</td>
<td>−0.440†</td>
<td>0.733†</td>
<td>0.124</td>
<td>0.118</td>
</tr>
<tr>
<td>pRCA</td>
<td>−0.322*</td>
<td>0.744†</td>
<td>0.049</td>
<td>0.045</td>
</tr>
</tbody>
</table>

TCSA, total coronary cross-sectional area; LMCA, left main coronary artery; pLAD, proximal left anterior descending artery; pLCx, proximal left circumflex artery; pRCA, proximal right coronary artery.

* p<0.005.
† p<0.001.
∥ Total left ventricular mass was used for TCSA because percent territory score corresponding to TCSA is 100%.
mean ± 2 SD. Regression equations that allow determination of anticipated normal diameter measurements in proximal coronary arteries based on territory fraction and age are included in Table 5. This table and the regression equations are applicable to male subjects with angiographic measurements made after nitroglycerin.

**Discussion**

Previous studies of normal human coronary dimensions have been performed primarily in postmortem hearts. Although most of these studies obtained coronary measurements under physiologically distending pressures, postmortem alterations in smooth muscle distensibility might affect actual coronary caliber. In addition, postmortem studies do not account for dynamic changes in coronary blood flow. Therefore, necropsy examination may not accurately reflect angiographic coronary dimensions measured during diastole. Moreover, the hearts examined in postmortem studies often have preexisting cardiac diseases such as left ventricular hypertrophy, cardiomyopathy, valvular heart disease, and congenital heart disease that could affect coronary dimensions. For these reasons, the applicability of pathological data to vessels studied in vivo under normal distending pressure is dubious.

Studies of normal coronary artery size in vivo are few. Although these angiographic studies measured dimensions on coronary arteries that appeared to be normal, most subjects had significant cardiac lesions such as valvular heart disease, cardiomyopathy, and left ventricular hypertrophy that may directly or indirectly affect coronary dimensions. Furthermore, the age range of patients in these studies was primarily centered in the middle-age group, limiting the assessment of age-related changes in coronary dimensions. Variation in coronary vasomotor tone among different individuals was not accounted for in these studies that were carried out in the 1960s and early 1970s. Because factors including sex, coronary segment location, valvular lesions, ventricular hypertrophy, and coronary vasomotor tone have been shown to affect vessel dimension, we tried to minimize these variations in this study. We included only male subjects, excluded patients with any cardiac disease, and used a vasodilator (nitroglycerin) to eliminate the effect of variations in coronary vasomotor tone. Because variation in anatomic distribution of coronary vessels might reasonably be expected to influence coronary dimensions, the regional myocardial territory and left ventricular mass supplied by the measured arteries were quantitated.

To encompass a wide age range in the present study (especially subjects below age 35 years), we analyzed coronary angiograms of hearts from young male donors early after transplantation. This approach raises the possibilities of confounding effects of cardiac denervation and transplant coronary artery disease on coronary dimensions. However, the use of nitroglycerin in both transplant and nontransplant subjects before angiography causes maximal vasodilatation. This response is not likely to be affected by denervation or by abnormalities of endothelium derived relaxing factor (EDRF) release, reflecting the fact that nitrates have a direct effect on vascular smooth muscle. The fact that angiography was obtained early (mean, 38 days) after transplant surgery minimizes the possibility that transplant coronary artery disease could affect coronary lumen dimensions. Histopathological findings of subintimal fibrocellular proliferation in transplant coronary vessels is not usually present until 3 months after transplantation, and even then, the changes are minimal. The lack of difference in coronary dimensions between transplant hearts and native nontransplanted subjects in the 35–54-year age group further suggests the validity of inclusion of donor-heart angiograms in this group.

Coronary diameter measurements in this study were obtained from measurements of a single angio-
graphic projection of the segment being analyzed. It is not often possible to obtain truly orthogonal projections of the proximal coronary artery segments analyzed in this study. In previous studies, 14–50% of coronary segments could not be adequately imaged in orthogonal projections.19–21 Furthermore, coronary intravascular ultrasound studies of normal or nearly normal coronary arteries have demonstrated a circular cross-sectional profile so that a single diameter measurement accurately reflects the diameter of the lumen from all perspectives.22 Thus, diameter measurements from multiple projections should not alter the conclusions of this study.

**Effect of Regional Myocardial Territory and Left Ventricular Mass**

Previous studies showed that total left ventricular mass is an important determinant of coronary dimensions in either normal or hypertrophied hearts.7–10 However, there is no study to date that evaluates the relation of regional myocardial territory or regional left ventricular mass with proximal coronary dimensions in vivo. Data from previous studies suggested that the proximal cross-sectional area of a coronary vessel correlates with the myocardial volume within its territory.3,10 Rodriguez et al.3 by measuring the volume of barium sulfate–gelatin injected into post-mortem coronary arteries, found that there was a significant linear relation between the sums of the cross-sectional areas of the major coronary arteries (pLAD, pLCX, and pRCA) and the capacities of the coronary arterial tree. Koiwa et al.10 by measuring the regional myocardial volume in dogs with the use of the dynamic spatial reconstructor technique, also found that the cross-sectional area of a coronary artery supplying a volume of myocardium was related to that volume. Vieweg et al.6 showed that proximal coronary size is related to “right, left, or mixed emphasis (dominance).” In the present study, we used a reproducible, semiquantitative territory scoring system to estimate the regional myocardial territory supplied by a proximal artery. The scoring system is based on the distinction between conduit and terminal (i.e., nutrient) coronary vessels. Con-

**FIGURE 5.** Graphs showing relation between cross-sectional area of the left main (LMCA), proximal left anterior descending (pLAD), proximal left circumflex (pLCX), and proximal right (pRCA) coronary arteries and regional left ventricular (LV) mass. There is a linear increase in vessel dimension for each vessel with regional left ventricular mass.
duit coronary vessels serve as a pathway for blood flow to the terminal vessels, from which arterioles branch into the myocardium. The myocardial territory score is based on the presence of terminal coronary vessels and their relative length, although to some extent spread of vessel branches is considered. Evaluation of coronary territory score and fraction of total left ventricular myocardium supplied by a particular vessel, although based on specific rules, is subject to observer variability. The coefficient of variation was 13–19% for territory score but only 11–13% for territory fraction. One could develop a computer-assisted technique that integrates planimetry or manual tracing of coronary vessels on radiographic images acquired in several orthogonal planes to more precisely make these measurements. We chose an approach that although subjective and thus prone to greater observer variability is accessible to the practicing angiographer. It is probable that the relation between coronary cross-sectional area and regional left ventricular mass would have been even stronger if territory fraction were more precisely assessed. However, the strength of the observed correlations suggests adequacy of the current territory scoring system and validity of the territory fraction as a determinant of coronary vessel size.

Seiler et al. in a canine study, also showed that the regional myocardial territory is proportional to the summed arterial branch lengths distal to each point in the coronary artery where lumen area was measured. This is consistent with our findings because the territory score used in this study is based on the sum of the relative lengths of the distal branches. We then derived the regional left ventricular mass from territory fractions and echocardiographically measured total left ventricular mass. Our results show that regional left ventricular mass is the strongest independent predictor of coronary cross-sectional area. This level of correlation is comparable with previous postmortem and canine studies.

These results suggest that the effects of a stenosis in a conduit vessel on the total left ventricular myocardium may be expressed as the product of a measure of stenosis severity multiplied by the relative
### Table 4. Multivariate Regression Analysis of Total or Regional Left Ventricular Mass, Age, and Body Surface Area as Determinants of Coronary Vessel Dimensions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regional left ventricular mass*</th>
<th>Age</th>
<th>Body surface area</th>
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<tr>
<td>TCSA</td>
<td></td>
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<tr>
<td>$r$</td>
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<tr>
<td>$R^2$</td>
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<tr>
<td>$p$</td>
<td>&lt;0.001</td>
<td>&lt;0.001§</td>
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<td>LMCA</td>
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<tr>
<td>$r$</td>
<td>0.735</td>
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<td>$R^2$</td>
<td>0.540</td>
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<td></td>
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<tr>
<td>$p$</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>pLAD</td>
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<td>$r$</td>
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<td>$R^2$</td>
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<td>$p$</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>pLCx</td>
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<td>$r$</td>
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<td>$p$</td>
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Multiple regression equations for significant variables:
1) $TCSA = 16.571 + (0.115 \text{ total LVM}) + (-0.188 \text{ age})$
2) $\text{LMCA mean CSA} = 14.625 + (0.072 \text{ RLVM}) + (-0.107 \text{ age})$
3) $\text{pLAD mean CSA} = 2.651 + (0.138 \text{ RLVM}) + (-0.062 \text{ age})$
4) $\text{pLCx mean CSA} = 7.992 + (0.110 \text{ RLVM}) + (-0.077 \text{ age})$
5) $\text{pRCA mean CSA} = 8.899 + (0.187 \text{ RLVM}) + (-0.038 \text{ age})$

*Total left ventricular mass was used for TCSA because percent territory score corresponding to TCSA is 100%.

amount of total left ventricular myocardium subtended by the stenosis. An algorithm of this type may be applied in the setting of multivessel disease. Furthermore, by comparing the measured diameter with the theoretical diameter derived from the territory fraction of a coronary segment, diffuse coronary atherosclerosis that is not angiographically apparent may be detected.

**Effects of Age and Body Habitus**

Published data on the effects of age on normal coronary dimensions yield inconsistent results.\(^1\text{-}^5,\text{26,27}\)

A slight tendency for adult coronary size to increase with age has been noted in three postmortem studies,\(^1\text{-}^2,\text{26,27}\) whereas no change in coronary size with age has been noted in three other postmortem studies\(^3\text{-}^4\) and in one angiographic study.\(^5\) However, as previously noted, the relevance of postmortem studies to coronary angiographic measurements in vivo is doubtful. An angiographic study by MacAlpin et al\(^3\) demonstrated that those cardiac lesions expected to substantially increase myocardial work and thus coronary blood flow were associated with larger coronary dimensions than those of normal subjects. The authors also noted smaller coronary diameters in female subjects, however, this difference was entirely accounted for by differences in body surface area. In the current study, all subjects were males without cardiac disease or hypertension; thus, the observed absence of significant relation between body height, weight, and surface area to coronary diameter was anticipated.

The results of this study show a progressive decline in coronary dimensions with increasing age that is not explained by factors such as myocardial atrophy. From the multivariate regression equations, age is a significant determinant of all proximal vessel cross-sectional areas and for total coronary cross-sectional area, although regional myocardial territory was a stronger predictor of vessel area. Rodriguez et al,\(^3\) in a postmortem study measuring the volume of injectate mass entering the coronary vessels under standard conditions, found that there was a trend toward larger capacity in younger compared with older sub-
Possible Mechanisms for Age-Related Change

The exact mechanisms by which coronary dimensions decrease with age is not certain. Possible explanations include 1) higher prevalence of concentric, angiographically inapparent atherosclerosis with increasing age, 2) nonatherosclerotic age-related subendothelial and medial vessel wall thickening, 3) attenuated coronary smooth muscle vasodilatory response to nitroglycerin in older subjects, 4) vessel size alterations resulting from age-related decline in coronary flow demands reflecting diminished physical activity, and 5) age-related change in myocardial composition and thus requirements for coronary blood flow.

Age is a well recognized factor in coronary atherosclerosis. Autopsy studies show that coronary atherosclerosis can start in childhood and progress with advancing age. The earliest lesion of atherosclerosis, the fatty streak, is commonly present by 10–14 years of age. After age 20 years, fatty streaks can increase threefold with appearance of advanced lesions, fibrous plaque, or atheroma that may cause localized and eccentric impingement on the coronary lumen and thus become angiographically apparent. It is evident from previous pathological studies and more recent angiographic studies that concentric, relatively homogeneous atherosclerosis may be present in vessels...
that appear angiographically normal.\textsuperscript{32–34} Although the use of a different imaging technology such as intravascular ultrasound may have detected concentric, age-related coronary atherosclerosis, we believe that by virtue of the stringent selection criteria, most of these patients were truly disease free. Moreover, it is unlikely that the 16% reduction in total coronary cross-sectional area in subjects from mean age 25–45 years and the further 15% reduction from mean age 45–65 years could occur without development of some luminal irregularity.

Age-related decline in nitroglycerin responsiveness is a potential factor. However, nitroglycerin in angiographically normal segments provokes 15–25% vasodilatation,\textsuperscript{35} the complete loss of which would be inadequate to explain the magnitude of age-related decline in vessel dimensions. Nonatherosclerotic age-related vessel wall changes have been documented in microscopic examination of coronary vessels of infants and children up to age 20 years.\textsuperscript{36} However, it is unlikely that this “normal” developmental change in the very young continues as an important factor beyond this age.

Recently, the use of intracoronary acetylcholine in subjects with angiographically normal coronary arteries shows diminished EDRF-mediated coronary vasodilation with age.\textsuperscript{37} These findings suggest the presence of angiographically inapparent endothelial abnormalities in most subjects studied beyond the age of 30 years.\textsuperscript{37} Although EDRF-mediated coronary vasodilatation decreases with age, nitroglycerin responsiveness is maintained in these studies. In addition, abnormality in EDRF-mediated coronary dilatation also occurs in transplant patients. Therefore, we used nitroglycerin before angiography in this study to induce maximal smooth-muscle vasodilatation and to eliminate the possible effects of altered EDRF release.

Physical activity has been associated with increases in coronary dimensions,\textsuperscript{38,39} particularly when assessed after nitroglycerin.\textsuperscript{40} Data from the Framingham Heart Study showed that physical activity declines with age.\textsuperscript{41} In that study, 24% of male subjects aged 18–29 years participated in at least 1 hour of conditioning activities (\(\geq 31.5\) kJ/min) per week compared with only 3% of those aged 50 years or older. This age-related decline in coronary flow demands resulting from diminished physical activity might account for the decrease in coronary vessel size. MacAlpin et al\textsuperscript{5} speculated that conditions that augment myocardial oxygen requirements and cause myocardial hypertrophy are associated with increased size of epicardial coronary arteries, raising the possibility that the converse might also occur. Recognizing the importance of pathological conditions that could augment myocardial work, patients in this study were screened by both clinical history and examination and by echocardiography (82% of subjects) to exclude myocardial hypertrophy. In addition, we found no difference in left ventricular mass between the three age groups. Previous studies have also shown that left ventricular mass usually remains unchanged or increases with age.\textsuperscript{42–44} Therefore, the decrease in coronary dimension with aging is probably not mediated through the effect of changing left ventricular mass. It is also possible that the composition of the myocardium may change with age. Elderly hearts may have more interstitial tissue in relation to myocytes and, hence, less coronary flow demand.

Within this cohort of male subjects with angiographic measurements obtained after nitroglycerin administration, there remains considerable subject-to-subject variability in measurements. Although, to some extent, this could reflect variability in our assessment of myocardial territory fractions, it is probable that genetic and developmental factors contribute. Table 5 provides a range of measurements that can be used as a basis for comparison. In patients with visually apparent coronary disease, it is common to find portions of the coronary anatomy, particularly the left main and other proximal arteries, that appear concentrically and smoothly narrowed but without discrete lesions.\textsuperscript{34} The results in Table 5, albeit limited to proximal segments and male subjects receiving nitroglycerin, provide an objective basis for assessing whether a particular diameter is within a 95% probability range. Adjustments for normal women, based on data reported by MacAlpin et al,\textsuperscript{5} suggest a downward reduction in cross-sectional area for women of 19% for the LMCA, 17% for the pLAD, 16% for the pLCx, and 12% for the pRCA.

It is well established that coronary dimensions are affected by short-term physiological and pharmacological interventions as well as by atherosclerosis and other vascular diseases. The close relation of epicardial coronary vessel size to myocardial oxygen demands is supported not only by past observations in diseases that increase myocardial oxygen demands (e.g., aortic stenosis and systemic hypertension) but also by our observation in normal subjects of the close correlation between proximal coronary vessel size and regional left ventricular mass. Presumably, resting myocardial oxygen demands and corresponding coronary blood flow are important determinants of basal coronary dimensions in humans.

The age-related decline in epicardial coronary dimensions raises the possibility that reduction in either basal coronary blood flow requirements or decline in the intermittent flow-mediated stimulus provided by exercise provocation accounts for altered coronary epicardial dimensions and compliance. Perhaps short-duration mediators of vasodilatation (e.g., EDRF) have longer-term effects that last beyond their immediate pharmacologically apparent vascular response.

The decline in coronary dimensions with age has multiple implications. Clinical trials using angiographic end points may need to consider the age of their subjects and the confounding effects of pharmacological and physiological interventions on vessel compliance and size of epicardial coronary vessels.
independent of antiatherosclerotic effects. It is also possible that reduction in epicardial coronary cross-sectional area relative to subtended myocardium might contribute to diminished exercise capacity of older individuals by increasing conduit vascular resistance and thus decreasing the transmyocardial pressure gradient that supports subendocardial perfusion during exercise.

Although multiple alternative explanations for the decline in coronary dimensions with age have been discussed, most possibilities are not as persuasive as the role of age-related decline in physical activity. If periodic stimulation by exercise provokes increases in coronary blood flow that, in turn, enhances basal coronary size and/or compliance, the converse is then likely; that is, that decline in physical activity with age diminishes coronary dimensions. This decline in coronary size may have potential adverse clinical consequences in the setting of acute ischemia resulting from partial vessel occlusion by either atheroma or thrombus.

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