Basic Structure–Function Relations of the Epicardial Coronary Vascular Tree

Basis of Quantitative Coronary Arteriography for Diffuse Coronary Artery Disease

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**Background.** Quantitative coronary arteriography has been validated for stenotic segments of coronary arteries. However, it does not currently account for diffuse coronary artery disease, because the normal size of the coronary artery for its distal myocardial bed size is not known and cannot be measured directly with diffuse involvement of the artery.

**Methods and Results.** From clinical coronary arteriograms of 12 patients without coronary artery disease (group 1) and in 17 patients with coronary artery disease (group 2), we determined by quantitative coronary arteriography 1) the relations among measured coronary artery cross-sectional lumen area, summed distal branch lengths, and regional myocardial mass distal to each point in each coronary artery; 2) the ratio of coronary artery lumen area between parent and daughter vessels at 50 bifurcations; and 3) which of three different theoretical physical principles could underlie the tree structure of the human coronary artery system, by comparing the coronary artery size, branch lengths, regional mass, and relations between parent-to-daughter lumen area ratios with those for the different theoretical physical principles to test which principle best fit the observed data and therefore which principle most probably characterizes the human coronary artery tree structure. The results showed that 1) there is a close correlation between the lumen area of a coronary artery at each point along its length and the corresponding summed distal branch lengths and regional myocardial mass in patients without and with coronary artery disease; 2) measured coronary artery lumen area in patients with coronary artery disease is diffusely 30–50% too small for distal myocardial bed size compared with normal subjects; and 3) the observed relations among coronary artery size, distal summed lengths, myocardial bed size, and parent-to-daughter size ratios are not consistent with the theoretical principle of constant mean blood flow velocity in coronary circulation but are consistent with the principles of minimum viscous energy loss and of limited/adaptive vascular wall shear stress characterized by a ½ power law relating coronary artery lumen area to distal summed branch lengths and regional mass or parent-to-daughter branching ratios.

**Conclusions.** These observations provide a basis for quantifying diffuse coronary artery disease on clinical arteriograms. *(Circulation 1992;85:1987–2003)*

**Key Words** • coronary artery stenosis • quantitative coronary arteriography • diffuse coronary artery disease

The severity of coronary artery stenoses shown by arteriograms is most commonly measured as percent diameter stenosis or narrowing relative to the “normal” lumen size adjacent to the narrowed segment. Quantitative coronary arteriographic (QCA) analysis accounting for all geometric dimensions including absolute lumen area of the stenosis and length also requires the dimension of the normal arterial segment.1,2 However, the correctness of this normal size reference is open to question, because coronary atherosclerosis is often diffuse and the normal reference segment is also narrowed.3,4 Finally, serial segmental narrowing, representing a type of diffuse disease, is not accounted for by simple percent narrowing or by current methods of QCA analysis because of the absence of a true normal reference segment.

For assessing the severity of diffuse coronary artery disease (CAD), with or without segmental narrowing, it is necessary to know what the normal arterial lumen size would have been in the absence of coronary atherosclerosis at each point along a coronary artery for the vascular bed size distal to each of those points. The observed lumen diameter along the arterial length compared with the normal diameter expected for the vascular bed size distal to each point then indicates the effect of diffuse coronary artery narrowing. Several experimental reports have documented a direct relation between coronary artery lumen size and heart weight or size of distal myocardial bed5–8 and between myocardial mass distal to any point along a coronary artery and the...
sum of arterial branch lengths distal to that point in the coronary tree. Freiman et al demonstrated in post-mortem canine hearts that the ratio between the summed lengths distal from each point in the left coronary artery and the total distal cumulative lengths of the left coronary artery is linear and directly proportional to the size of the myocardial bed distal to that point.

Accordingly, we developed methodology applicable to clinical coronary arteriograms to ask three basic questions in humans: 1) Is there a systematic quantitative relation of coronary artery lumen diameter to distal vascular bed size in normal subjects? 2) Is this relation altered in subjects with segmental coronary artery stenosis, indicating that lumen diameter at any location within the artery is too small for distal bed size? 3) Does the observed relation between arterial lumen size and distal bed size indicate a fundamental physical principle(s) or design characteristic(s) underlying the anatomic structure of the human coronary vascular tree? This approach to the analysis of the entire coronary vascular tree on clinical arteriograms provides quantification of diffuse coronary artery narrowing with or without segmental stenoses and identifies the basic design principles underlying coronary vascular tree structure in humans.

**Methods**

**Patient Selection**

Twenty-nine patients were studied for clinical reasons with right and left coronary arteriograms in 9-in. mode and with left ventricular angiograms. Informed consent was obtained as approved by the Committee for the Protection of Human Subjects of the University of Texas Medical School at Houston. These patients had coronary arteriography for evaluation of dyspnea (n=5), typical (n=12) or atypical (n=6) chest pain in the presence (n=6) or absence (n=17) of known CAD, with history of myocardial infarction (n=4), or for evaluation before renal transplantation (n=3) or other operations (n=2). The study population was classified into two subgroups. Group 1 included 12 normal patients (seven men, five women; mean age, 57±15 years) without evidence of significant segmental coronary artery stenoses on coronary arteriograms (>50% narrowing in diameter), without evidence of CAD on thallium exercise testing or by cardiac positron emission tomography (PET). One of these 12 patients in group 1 showed an insignificant, 35% diameter stenosis of the proximal obtuse marginal branch of the left circumflex coronary artery, which did not meet criteria for CAD. This patient’s ECG and thallium exercise test were normal. Any bias from including this patient in group 1 would be against our hypothesis; therefore, including him in group 1 was scientifically conservative. There were 17 patients in group 2 (eight men and nine women; mean age, 56±11 years) with a diagnosis of CAD based on coronary arteriograms (one or more segmental coronary artery stenoses greater than 50% in diameter narrowing) or abnormal thallium exercise testing or abnormal cardiac PET images. Three of the 17 patients in group 2 had an abnormal ECG and thallium exercise test with exercise-induced chest pain (n=2) or atypical chest pain (n=1) indicating the presence of CAD (n=3) but had no significant segmental coronary artery stenoses on coronary arteriograms. These patients could be judged to have diffuse CAD and were therefore included in group 2. Any bias from including them in group 2 would be against our hypothesis; therefore, including them in group 2 was scientifically conservative. The frequency of one or more cardiac risk factors was not different between the two groups except for smoking, which was more prevalent in group 2 than in group 1 (nine of 17 versus two of 12, p<0.05). The clinical characteristics of the study subjects are shown in Table 1.

**Arteriographic Analysis**

QA analysis was carried out on biplane coronary arteriograms obtained simultaneously in standard magnification, 9-in. mode in order to include the entire coronary vascular tree in the cine plane. The automated system for quantitative analysis of biplane QCA consists of a 35-mm film projector (Tagarno 35 CX), a slow-scan charged coupled device (CCD) camera for film image digitizing, and a computer workstation (Apollo DN 3010) for image storage and processing. The high-resolution CCD line scanner camera (2,048×3,072 pixels) used for image digitizing was developed at the University of Zurich.11,12 The quantitative accuracy of diameter determination of this QCA system, including discussion of the reproducibility of these measurements, has been described recently.11,12 Digitized coronary arteriograms (Figure 1A) were processed by three-dimensional reconstruction of the entire epicardial coronary tree structure (Figure 1B) in order to obtain lumen diameters along each artery and corresponding coronary artery branch lengths distal to each point (Figures 1C and 1D). The processing technique of three-dimensional reconstruction of the coronary artery tree is based on work by Parker et al13 and Wollschlager et al14 as described in detail below. The quantitative accuracy of image reconstruction was validated by phantom measurements. Foreshortening of coronary artery branch lengths was accounted for and corrected in final length measurements.

**Method of Three-dimensional Reconstruction and Image Calibration**

**Measured characteristics of the x-ray system.** For three-dimensional reconstruction13 and calibrating14 simultaneous biplane arteriograms, the position of the image views with respect to the rotational center of the x-ray system, usually right anterior oblique 30°, left anterior oblique 45° was determined. The distances from x-ray tube focal spot to isocenter and from x-ray focal spot to the image intensifier planes were measured and indicated as distances F1I and F1I1 and F2I and F2I1, respectively, in Figure 1E. Thus, a three-dimensional Cartesian coordinate system (x,y,z) with the isocenter at its origin was defined by transformation of either of the two two-dimensional coordinate systems (u,v with origin at the projection of the isocenter) of the two image planes by a rotation matrix determined by the rotation angles of the image planes.

**Processing steps.** Step 1. First, one image frame of each view of the coronary arteriogram was selected on the basis of the following criteria: good filling of the entire
### Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Group (CAD +/−)</th>
<th>Reason for catheterization</th>
<th>History of hypertension</th>
<th>Other risk factors</th>
<th>R &gt; L</th>
<th>L_{tot} (cm)</th>
<th>M_{tot} (g)</th>
<th>BP (mm Hg) (at cardiac catheterization)</th>
<th>HR (bpm)</th>
<th>Predominant coronary lesion</th>
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<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>−</td>
<td>Preoperative</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>75.4</td>
<td>195</td>
<td>123/85</td>
<td>85</td>
<td>−</td>
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<tr>
<td>2</td>
<td>33</td>
<td>F</td>
<td>−</td>
<td>Renal transplant</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>81.3</td>
<td>207</td>
<td>117/93</td>
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<td>−</td>
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<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>−</td>
<td>Dyspnea</td>
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<td>−</td>
<td>+</td>
<td>60.3</td>
<td>201</td>
<td>112/75</td>
<td>78</td>
<td>−</td>
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<td>−</td>
<td>+</td>
<td>68.0</td>
<td>181</td>
<td>152/90</td>
<td>85</td>
<td>−</td>
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<td>+</td>
<td>71.4</td>
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<td>−</td>
<td>−</td>
<td>97.7</td>
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<td>+</td>
<td>−</td>
<td>58.8</td>
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<td>112/90</td>
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<td>−</td>
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<td>59</td>
<td>F</td>
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<td>Renal transplant</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>99.2</td>
<td>269</td>
<td>151/82</td>
<td>85</td>
<td>−</td>
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<tr>
<td><strong>Mean±SD</strong></td>
<td><strong>57±15</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td><strong>78±17</strong></td>
<td><strong>241±76</strong></td>
<td><strong>137±18/82±9</strong></td>
<td><strong>85±14</strong></td>
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</tbody>
</table>

**Group 2**

| 13      | 59          | F   | +               | Chest pain                 | +                       | −                  | +     | 66.2        | 227          | 135/59                              | 72        | Plaquing LCx                  |
| 14      | 55          | F   | +               | Chest pain (MI)            | −                       | +                  | −     | 63.7        | 260          | 104/61                              | 74        | Plaquing LAD; RCA prox.        |
| 15      | 39          | M   | +               | Chest pain (MI)            | −                       | +                  | −     | 84.0        | 279          | 146/84                              | 70        | LCx prox./distal               |
| 16      | 44          | F   | +               | Chest pain (pPTCA)         | −                       | +                  | −     | 93.5        | 338          | 120/68                              | 65        | LAD prox.                    |
| 17      | 48          | F   | +               | Chest pain                 | +                       | +                  | −     | 68.0        | 236          | 111/60                              | 93        | LAD/LCx (thallium)            |
| 18      | 42          | M   | +               | Chest pain (atyp)          | −                       | +                  | −     | 75.8        | 237          | 140/69                              | 78        | LCx (thallium)                |
| 19      | 69          | F   | +               | Chest pain (pPTCA)         | +                       | +                  | −     | 63.4        | 136          | 134/87                              | 102       | LAD prox.                    |
| 20      | 44          | M   | +               | Chest pain                 | +                       | +                  | +     | 75.8        | 338          | 178/67                              | 73        | LAD,LCx (both prox.)          |
| 21      | 58          | F   | +               | Chest pain                 | +                       | −                  | −     | 87.4        | 299          | 164/65                              | 67        | LAD diffuse plaquing           |
| 22      | 55          | M   | +               | Chest pain (atyp)          | +                       | +                  | −     | 82.0        | 327          | 117/66                              | 80        | LAD (LCx)                     |
| 23      | 55          | M   | +               | Chest pain                 | −                       | +                  | +     | 82.0        | 283          | 168/83                              | 94        | LAD prox.                    |
| 24      | 55          | M   | +               | Chest pain (MI)            | +                       | +                  | −     | 76.9        | 396          | 136/84                              | 85        | LCx prox.                    |
| 25      | 68          | F   | +               | Dyspnea                    | −                       | +                  | −     | 60.2        | 239          | 99/52                               | 92        | LAD prox., LCx distal          |
| 26      | 80          | F   | +               | Preoperative               | +                       | +                  | −     | 80.0        | 255          | 145/82                              | 68        | LAD mid, plaquing              |
| 27      | 46          | F   | +               | Chest pain (MI)            | +                       | +                  | +     | 82.2        | 249          | 180/96                              | 65        | RCA mid                      |
| 28      | 55          | M   | +               | Chest pain                 | −                       | +                  | +     | 60.1        | 195          | 130/90                              | 85        | LAD (+ETT)                    |
| 29      | 55          | M   | +               | Chest pain (atyp)          | +                       | −                  | +     | 60.0        | 186          | 132/82                              | 68        | LAD (thallium)                |
| **Mean±SD** | **55±11**   |     |                 |                            |                         |                    |       | **74±17**   | **263±64** | **138±24/74±13**                  | **78±12** |                           |

CAD, coronary artery disease (+/−, positive or negative); R > L, right dominant coronary artery; L_{tot}, total coronary artery tree length; M_{tot}, total left ventricular mass (after correcting for R > L); BP, blood pressure; HR (bpm), heart rate (beats per minute); M, male; F, female; atyp, atypical; CMP, dilated cardiomyopathy; LCx, left circumflex; MI, myocardial infarction; LAD, left anterior descending; RCA, right coronary artery; prox., proximal; pPTCA, post percutaneous transluminal coronary angioplasty; LAD (thallium), ischemic lesion in the LAD supply area detected by thallium exercise test or cardiac positron emission tomography; +ETT, positive exercise treadmill test.
coronary artery vasculature with contrast medium, minimum overlapping of neighboring vessels, and end-diastolic frames for least movement of the heart between consecutive frames. Second, information on imaging geometry as described above and selected frame numbers were entered into the computer.

Step 2. Image acquisition was started with digitization of a blank image of the film projector to correct for inhomogeneous background illumination. The film projector with a digital frame counter interfaced to the computer workstation then advanced the film to the previously chosen frames, which were digitized by the high-resolution CCD camera. Because standard arteriographic technique does not give resolution below 0.1 mm, the resolution of the CCD camera was restricted to 1,380×1,024 pixels.

Step 3. For registration of the digitized images and three-dimensional reconstruction of the coronary artery tree, a technique was adapted from that of Parker et al13 consisting of three steps: 1) specification of coronary tree landmarks, here being branching node points on both image planes; 2) computer determination of the coronary tree structure in the plane of both image views, including computer-determined vessel centerlines and vessel borders by an edge detection technique12; and 3) three-dimensional reconstruction of the coronary arterial tree from the intersection data of coronary trees from views in the two planes of acquisition images. The three-dimensional reconstruction technique used in this study differs from the one described by Parker et al13 in that the present system used simultaneous instead of sequential views, the processing was based on only two end-diastolic frames instead of multiple frames throughout the cardiac cycle, and the sequence of processing steps was slightly different from the one described by Parker et al.13 In both techniques, the two-dimensional tree structure of each image plane was defined as a hierarchy of vessel branches, each of which was connected to a parent branch, where the position of the branch elements was defined by two-dimensional coordinates in each plane (u,v).

For image registration with our QCA system, the isocenter position of the first and second image planes was entered into the computer, and on the first view, several branching node points were marked as landmarks. The projection lines formed by these node points were then projected onto the second view (line F1,P1 in Figure 1E), and the operator visually confirmed matching branch points on the second view as points lying closest to the projected x-ray path lines on the second view. The reconstruction algorithm then formed the closest point of intersection in three-dimensional space for these matched points.

Step 4. The next processing step for dealing with coronary artery branches consisted of entering manually into the computer the first coronary artery branch on the first view. An algorithm then generated branch centerlines based on the greatest image brightness. X-ray projection lines through the starting and end points of this branch were projected onto the second view to provide the limits for the computer to identify this branch on the second view. The three-dimensional reconstruction of the matched points of this branch, starting and end points, was accomplished by the least-distance algorithm described above. This algorithm also found the matching points for all the branch elements between starting and end points. This task was accomplished by finding the set of paired points (one from each view) that have the minimum total separation consistent with the constraint that adjacent points along the branch are connected. Thus, a three-dimensional centerline for each epicardial branch of the coronary artery was created, defined by the x,y,z coordinates of its branch elements relative to the isocenter.

Step 5. Fixing the entire tree structure was accomplished by defining all the parent and daughter branches.

Step 6. Data extraction consisted of measuring coronary artery branch lengths by summation of pixels along the three-dimensional reconstructed tree structure. Pixels were converted to actual distances by multiplication by the calibration factor. In the present study, images were calibrated by the isocenter method14 as illustrated by Figure 1E. The calibration factor, defined as the ratio between the actual object size and the image size of the object, was calculated from similar triangles by dividing the distance from focal spot to isocenter by the distance from focal spot to projected isocenter.

Data Acquisition

Data acquisition consisted of the following steps.

1) Coronary artery diameter (D) was measured by edge detection technique at an average of 52±15 locations throughout the left and right coronary artery trees for each of 29 patients. The criteria for selecting the locations within the coronary artery tree where values of D were obtained were as follows: a) D had to be obtained rectangularly to the long axis of the vessel segment (see also Figures 1C and 1D). b) D had to be measured in vessel segments with good filling of radiographic contrast medium. c) Regions of overlay of coronary arteries were considered unsuitable for measurements of D. d) Areas of x-ray overexposure within the coronary arteriogram were avoided for measurements of D. e) Segmental coronary artery stenoses were avoided as sites of measurements of D.

On the basis of these general criteria for selection of locations for obtaining D, an estimated 15–20% of all coronary artery diameter measurements were biplane; the rest were single plane meeting the same criteria. Based on D, the cross-sectional area, A, was calculated as A=π[D²−D²]/4.

2) For all the values of D, the corresponding summed coronary artery branch lengths were measured (Figure 1). All the summed coronary artery branch lengths were obtained on the basis of biplane coronary arteriograms.
3) Total epicardial coronary artery tree length ($L_{tot}$, ranging between about 50–100 cm) was obtained on the basis of three-dimensionally reconstructed biplane coronary angiograms.

4) The ratio between parent ($A_0$) and daughter ($A$) mean cross-sectional lumen areas was obtained at 50 bifurcations in 12 normal left coronary artery trees by measuring $D$ of the parent and the two daughter vessels.
FIGURE 1. Analysis of coronary arteriograms in a normal patient. Panel A shows two digitized x-ray views that serve as the basis for the three-dimensional reconstruction of the entire coronary artery tree structure. Panel B shows centerlines tracking the length of each coronary artery and its branches down to 0.5 mm in diameter. The small squares indicate the sites where coronary artery diameter (D) and the sum of arterial branch lengths distal to that point (L) were obtained (n=47, biplane measurements of D=5). Panel C demonstrates the determination of the diameter (D) of a left main coronary artery and the sum of distal lengths (L), which is equal to almost the entire epicardial coronary artery tree length, L_{ep}=68.6 cm. Panel D illustrates determination of D and L for a proximal left circumflex (LCx) point; in this case D is equal to 0.38 cm and the corresponding sum of all epicardial LCx branches distal to that point, L, is equal to 33.1 cm. Based on Equation 13, the regional myocardial mass (M) at this point is equal to 33.1 cm/68.6 cm x 165 g= 79.6 g, where M_{ep}=165 g. Panel E: Schematic of three-dimensional reconstruction of a matched coronary artery branch point. With knowledge of the three-dimensional position of the x-ray system for both image planes (e.g., right anterior oblique 30° for image plane 1 and left anterior oblique 60° for image plane 2), the distances of focal spot (F) to isocenter (I) and focal spot to image plane (I, or Ij), a three-dimensional coordinate system (x,y,z) with its origin at the isocenter can be defined on the basis of the two-dimensional coordinate systems (u1,v1 and u2,v2). Because of existing geometric distortion in the x-ray system, the projection lines of P, P_F, and P_{Fj}, do not intersect at P. An iterative computer algorithm determines P by slightly changing the three-dimensional position of the image planes such that the distance between FjP1 and FjP2 is minimal. The image calibration factor, CF, is calculated as: CF=Fj/Ij/Fj/Ij or Fj/Ij/Fj/Ij.

Immediately proximal and distal to the bifurcation. This subset of measurements was used in the criteria for selecting sites for D measurement as described above. 5) From left ventricular angiograms, the total left ventricular mass (M_{lv}) was calculated for each patient by the method of Rackley et al.13 to compute values of regional myocardial masses (M) by Equation 13. In cases of dominant right coronary artery supplying the inferior left ventricular wall, a correction factor for M_{lv} of 0.7 was used.16 For normal right ventricular masses, a value of 50 g was assumed.17

Validation of QCA System

The QCA system for measuring diameters has been validated to be accurate within ±0.1 mm for coronary artery phantoms down to 0.5 mm in diameter in scattering media.11,12 As is conventionally reported for x-ray systems. The reproducibility of cross-sectional lumen area measurements in coronary arteriograms has been reported to be good, with an interobserver variability of 4.1% (SEE in percent of the mean vessel cross-sectional area) and an intraobserver variability of 2.1%. The SEE for repeated measurements by one observer was 0.072 mm² in cross-sectional lumen area, and the SEE for interobserver variability was 0.137 mm².12 The validation of the system for coronary artery length measurements consisted of determining by QCA of cine x-ray film three different phantom lengths (L_{QCA}). The phantoms were steel wires 0.6 mm in diameter, positioned corresponding to the left anterior descending, left circumflex, and right coronary arteries of a heart model. Length by QCA of cine films of this model was correlated to the actual known phantom lengths (L_{QCA}=6.0, 10.5, and 8.6 cm). QCA measurements were accurate with a correlation equation: L_{QCA}=1.008L_{QCA}+0.079 cm, r=0.998, SEE=0.22 cm; SEE expressed as percent of the mean of real and QCA-measured phantom lengths (SEE,) was 2.63%. The main source of variability in measurement of coronary artery branch length by QCA resulted from including different numbers of small branches into the coronary tree analysis by different observers. Interobserver variability between observer 1 and observer 2 for total coronary tree length measurements (L_{ep}) among 13 study patients (seven normal subjects and six patients with CAD): L_{ep}QCA=0.76L_{ep}+10.93 cm, r=0.88, SEE=6.39 cm, SEE=8.8%; the mean difference between measurements of observer 1 and observer 2 was -7.16±6.96 cm out of a total length of 76 cm. Intraobserver variability was L_{ep}QCA=0.88L_{ep}+9.58 cm, r=0.987, SEE=2.15 cm, SEE=2.8%; mean difference between measurements was 0.20±3.16 cm.

Physical Principles Underlying the Anatomic Structure of the Coronary Arterial Tree

The anatomic structure of the epicardial coronary arterial tree can be described in terms of lumen cross-sectional areas, arterial branch lengths, and branching patterns. The relation among these variables can be empirically observed as described above from clinical arteriograms and can be theoretically derived from one or more basic physical principles or design characteristics. By comparing theoretically derived lumen area—branch length relations and theoretical parent—daughter branching relations to the empirically observed relations, the best-fitting physical principle underlying the anatomic structure of the coronary artery tree can be identified. There is precedence in expecting some physical design principle underlying biological tree structure. In botany, the weight of a tree and its branch size are closely curvilinear.18 In canine lungs, the diameters of pulmonary bronchi, their position in the bronchial tree, and bronchial air flow follow a tight curvilinear relation.19,20 Beginning in 1926, a small number of reports have proposed several principles underlying the epicardial coronary arterial tree21-26 as well as microvascular structure.27,28 However, the basic physical principles underlying the anatomic structure of the coronary epicardial arterial tree have not been tested experimentally or studied in humans. Accordingly, in this section of the methods, three basic physical principles are outlined with theoretical derivations of lumen area—length—mass relations and parent—daughter branching characteristics for comparison with those observed empirically in order to test which principle(s) best characterize the human coronary vascular tree. Because the physical principles outlined below describe coronary artery lumen area as a function of the vessel's blood flow rate (see Equations 4, 6, and 8), observed lumen area—length relations have to be converted to lumen area—flow rate or lumen
area–regional myocardial mass relations to meet one goal of this study, namely, comparing theoretically derived and observed data. Based on a study in dogs by Freiman et al. relating regional myocardial mass to summed coronary artery branch lengths distal to any point in the coronary tree, distal length is closely and linearly related to regional myocardial mass. Regional mass itself cannot be determined directly from coronary arteriograms. Finally, for theoretical comparisons, regional myocardial mass was assumed to be related to coronary artery blood flow rate by myocardial perfusion under resting flow conditions of 0.8 cm³/min/g.20

**Principle of Minimum Viscous Energy Dissipation Per Unit Time**

For pulsatile flow in the cardiovascular system, the pressure drop (ΔP) along the streamline can be assumed to result solely from viscous friction.30,31 Thus, ΔP can be expressed by the Poiseuille equation:

\[ ΔP = F \cdot 8μl/πr^4 \]  

where F is blood flow rate in the coronary artery system, μ is viscosity of the blood (=0.03 dyne · sec/cm²), l is length of the vessel section, and r is radius of the vessel.

First described by Murray in 192631 and subsequently applied by others22-26 to a theoretical analysis of blood flow through arterial branch points, the principle of minimum energy loss per unit time states that the arterial lumen size of a vascular system carrying Poiseuille blood flow is determined by an energy balance (E) between viscous energy loss per unit time and the energy content of the blood volume per unit time (potential energy) expressed as follows:

\[ E = F \cdot ΔP + bπr^4l \]  

where E is energy balance per unit time, F is blood flow rate through the coronary artery tree, ΔP is pressure gradient between the aorta and the distal epicardial coronary artery tree described by Poiseuille’s law (Equation 1), b is the potential energy coefficient of the blood volume in dynes/cm¹ · sec calculated as the product of mean proximal coronary artery pressure times coronary blood flow rate divided by the coronary artery vascular volume, r is radius of the vessel, and l is length of the vessel section. Differentiating Equation 2 with respect to r, E becomes a minimum when dE/dr is zero:

\[ dE/dr = 0 = -4F^2 \cdot 8μl/πr^5 + 2blπr \]  

It follows that the luminal area (A = πr²) of a coronary artery at each point in the coronary artery tree can be expressed in a general form as a power equation:

\[ A = K \cdot F^n \]  

where K=0.004 (under resting flow conditions, determined by the energy coefficient b and μ, the viscosity of blood) and a=0.67 in the case of the principle of minimum energy loss per unit time. The principle of minimum energy loss of blood distribution throughout the coronary epicardial arterial tree is illustrated in Figure 2.

**Principle of Limited and Adaptive Wall Shear Stress**

The principle of limited and adaptive wall shear stress states that arterial lumen would be of such a size as to prevent coronary blood flow rate from causing endothelial damage during a short-term, acute maximum flow state (limited shear stress) as well as chronically under maximum flow conditions (adaptive shear stress). Limited shear stress determines coronary artery size such that during acute increases to maximum coronary flow rate, the endothelial wall shear stress does not exceed a level destructive to the endothelium, which occurs at about 200 dynes/cm².32 Adaptive shear stress determines coronary artery size such that shear stress is maintained at a normal value of about 25–35 dynes/cm² chronically33 at maximum coronary flow levels. It can be demonstrated that the relation between cross-sectional vessel area and maximum coronary flow at limited and adaptive wall shear stress obeys a ½ power law as follows:

\[ \tau = \mu \cdot \frac{dv}{dr} \]  

where \( \tau \) is shear stress (dyne/cm²), \( \mu \) is viscosity of the blood (0.03 dyne · sec/cm²), and \( dv/dr \) is shear rate (sec⁻¹) = rate of change of velocity between different fluid layers in Poiseuille fluid flow. Based on the principle of conservation of mass,30,31 which must be obeyed by the blood flow in the human circulatory system,

\[ F = \bar{v} \cdot A \]  

where \( \bar{v} \) is mean cross-sectional blood flow velocity in the coronary artery system, A is cross-sectional lumen area of the coronary artery, and F is coronary artery flow rate.
blood flow rate. Because blood flow in the coronary circulation can be regarded as being parabolic in profile, the shear rate at the vessel wall (dv/dr) was assumed to be constant and maximal, meaning that the vessel wall is exposed to a shear rate determined by the flow velocity at the centerline of the vessel (vmax=29) and the radius, R, of the vessel. In the case of laminar flow, which was assumed to be present, the shear rate at the vessel wall is multiplied by a factor of 2.30,33 Accordingly, the shear rate at the vessel wall, dv/dr=4vR.

Based on these assumptions, Equations 5 and 6 can be written as:

$$A \cdot R = \frac{\mu}{\tau} \cdot 4F$$

(7)

where R is vessel radius. From this principle, \(\tau\) has to have a constant adaptive value at maximum flow of about 30 dynes/cm² and a constant limited value at maximum flow of 200 dynes/cm². For both limits, the cross-sectional lumen area, A, is related to flow as follows:

$$A = \pi^{\frac{1}{3}} \cdot (4\mu/\tau)^{2/3} \cdot F^{2/3}$$

(8)

$$A = K \cdot F^{2/3}$$

where \(K = \pi^{\frac{1}{3}} \cdot (4\mu/\tau)^{2/3}\). The principle of limited and adaptive wall shear stress (\(\tau\)) defines the coronary artery lumen area, A, to be greater than (limited \(\tau = 200\) dynes/cm², \(K = 0.002\)) and equal to \(K \cdot F^{2/3}\) (adaptive \(\tau = 30\) dynes/cm², \(K = 0.005\)).

**Principle of Constant Mean Blood Flow Velocity in the Coronary Artery System**

For the principle of constant mean blood flow velocity in the coronary artery system,30 Equation 4, \(A = K \cdot F^a\), becomes linear (a=1), because the principle of conservation of mass (Equation 6) must be obeyed in the circulation. The constant, K, under resting flow conditions is then theoretically equal to \(1/\varphi = 1/20\) cm/sec = \(1/20\) cm/min = 0.00088 with units of min/cm.

**Relation of Coronary Artery Size at Bifurcations or Branching Structure to Physical Principles Underlying Coronary Tree Structure**

An essential analysis that is complementary rather than alternative to the above principles focuses on branching points from which the design characteristics of the entire coronary vascular tree structure can also be derived. At an arterial bifurcation, blood flow (F) divides from the parent (subscript 0) into two daughter (subscript 1 and 2) vessels expressed as follows:

$$F_0 = F_1 + F_2$$

(9)

Substituting F in Equation 9 by F = \((1/K)^{1/a} \cdot A^{1/a}\), which follows from Equation 4:

$$\frac{1}{K}^{1/a} \cdot A_0^{1/a} = \left(1/(K)^{1/a} \cdot A_1^{1/a} + (1/K)^{1/a} \cdot A_2^{1/a}\right)$$

where K and a are defined and determined by one of the three principles described above and in "Alternative Branching Analysis" below, and K can be assumed to have the same value for the parent and daughter vessels close to a bifurcation. Therefore:

$$A_0^{1/a} = A_1^{1/a} + A_2^{1/a}$$

(10)

In order to be able to determine theoretically and also experimentally the parent-to-daughter vessel lumen area ratio, one may write Equation 10 on the basis of an average daughter vessel size \(\bar{A} = \frac{1}{2}(A_1 + A_2)\). In this case:

$$A_0^{1/a} = \bar{A}^{1/a} + \bar{A}^{1/a} = 2\bar{A}^{1/a}$$

and

$$A_0 = 2^{a} \cdot \bar{A}$$

(11)

where \(2^{a}\) is the parent-to-daughter cross-sectional lumen area ratio. Equation 11 follows from Equation 10 only if one assumes that the two daughter vessels have the same cross-sectional lumen area, which would be correct in the case of two daughter vessels each having the mean size of two unequally sized daughter vessels.

For the principles of minimum energy loss, of limited/adaptive shear stress, and of minimum vascular volume at arterial junctions (see below), \(2^{a} = 2^{2/3}\). i.e., the ratio of parent-to-daughter mean lumen area would theoretically be 1.588. In the case of constant mean velocity of coronary blood flow, the theoretical value of the constant a would be 1 and the term \(2^{a} = 2^{1} = 2\), and the parent-to-daughter ratio would be 2.

**Alternative Branching Analysis Based on Minimum Vascular Volume at Arterial Bifurcations**

For a given coronary perfusion pressure and flow rate, this principle indicates that a coronary artery bifurcation is constructed such that its total vascular volume is a minimum.24 Under such conditions, the energy expenditure for blood flow through bifurcations is lower, and the transmission time of blood through the circulation is minimized.

The intravascular volume (V) at a coronary artery bifurcation can be expressed as a function of the parent and daughter vessels' segment lengths (I₀, I₁, I₂) and the parent and daughter vessels' radii (r₀, r₁, r₂):

$$V = \pi r_0^2 I_0 + \pi r_1^2 I_1 + \pi r_2^2 I_2$$

(12)

Each of these six variables is in turn a function of three underlying variables r₀, x, and y, where x and y express I₀, I₁, and I₂ in terms of rectangular coordinates. Given the blood flow rate and the pressure drop in the parent and daughter vessels, r₁ and r₂ can be expressed as a function of the vessel segments' length by means of the Poiseuille equation (Equation 1). Partial differentiation of V with respect to r₀ and setting dV/dr₀=0 leads to

$$\frac{r_0^6}{F_0} = \frac{r_1^6}{F_1} + \frac{r_2^6}{F_2}$$

(13)

For a given flow and parent coronary artery size, r₀/F₀² is constant, and this equation becomes

$$A = K \cdot F_0^{2/3}$$

where K=0.004 as determined by blood viscosity times intracoronary vascular volume divided by resting coronary blood flow rate times coronary perfusion pressure.

**Consideration of Asymmetry of the Coronary Artery Tree and Design Principles Underlying Coronary Vascular Structure**

The theoretical design principles presented above imply that the coronary artery tree is built symmetrically.
ever, the coronary tree is in fact asymmetrical to a considerable degree, meaning that the shortest pathway to terminal arterioles has fewer generations or fewer branching points or branching orders than the longest one. Numbers of generations in a tree structure are commonly counted from proximal to distal. However, there are advantages in counting branching orders from distal to proximal. Counting branching orders is done by simultaneously tracking the path of all branches of a dichotomously branching system from distal to proximal; the first-order branch is at the first node point between two vessels; the branching order at the next, more proximal bifurcation is obtained by adding 1 to the previous branching order. In a symmetrical, dichotomously branching tree, counting the number of branch points from distally up to a given proximal branch node is the same for all segments of the coronary vasculature. In an asymmetrical tree, the number of branch points or the branching order counted from different supply areas to a proximal, common branch node is always different. The degree of this difference is directly proportional to the degree of asymmetry of the tree. Hence, to define the degree of asymmetry at any vessel bifurcation, one can calculate a delta that is the difference in branching order, counting from the periphery to proximal sites between two daughter vessels meeting at a given bifurcation.

For example, delta is zero at the level of the first bifurcation (which equals the highest branching order or first generation) for symmetrical tree structures. Also, as an example, Horsfield20 has recently shown that, on the basis of these concepts, the diameter ratio between generations of branches in bronchial trees increases as the degree of asymmetry increases, with an observed delta of 3, indicating moderate asymmetry. For a delta of 3 characterizing the asymmetry of the human bronchial tree, the cross-sectional parent-to-daughter mean lumen area ratio is 1.670 = 20.54, indicating that a = 0.74 in the term 2a above in Equation 11. By comparison, in the coronary vascular tree, the ratio of arterial cross-sectional area between parent and daughter vessel would theoretically equal 22/3 (=1.588), where a = 2/3 or 0.67 in the term 2a for a symmetrical coronary artery tree on the basis of a 3/5 power law relating coronary lumen size to flow. The observed value for the constant a, measured for arterial branches in human coronary arteriograms, is 0.72, and the observed parent-to-daughter lumen area ratio is 1.647 (Table 2), possibly indicating a modest asymmetry of branching structure.

### Relation Between Myocardial Mass and Coronary Artery Length

Regional left ventricular mass (M) distal from a certain point in the coronary artery tree where the coronary cross-sectional area (A) was measured was calculated as:

\[ M = M_{\text{tot}} \cdot \frac{L}{L_{\text{tot}}} \]  

where \( M_{\text{tot}} \) is the total left ventricular mass corrected for dominant right coronary artery supply of the inferior left ventricular wall.

Statistical analysis. For each individual patient as well as for all data from all study patients in each group lumped together, the cross-sectional coronary artery lumen areas were correlated with either the distal summed coronary artery branch lengths or distal myocardial masses. For these correlations, a general power-law equation of the form \( y = a + bx^c \) was determined that best fitted the observed data by a least-squares method to determine the specific values of a, b, and c. The regression coefficient (r), the SEE, and the 95% confidence interval for values of A were computed. Differences among normal subjects and patients with CAD in mean cross-sectional coronary artery lumen area of left and right coronary arteries at specified areas of vascular bed size were tested by a one-tailed, unpaired Student’s t test (Table 3). For comparative purposes, the observed and the theoretically derived correlations were superimposed for 12 normal left coronary arteries. Statistical differences between theoretically and experimentally determined parent-to-daughter mean lumen area ratios at bifurcations were tested by a one-tailed Student’s t test. The total left ventricular mass was correlated with total left coronary artery length. Statistical differences in clinical data between the two groups were tested by Student’s t test, Wilcoxon rank-sum test (Mtot), and \( \chi^2 \) test.

### Results

**Observed Arteriographic Data**

**Cross-sectional lumen area versus length and regional myocardial mass of the left coronary artery.** Figures 3 and 4 show the relation between left coronary artery cross-sectional area, the corresponding distal summed branch lengths, and the regional myocardial mass determined by Equation 13 in the normal group. The coronary artery lumen area at each point along the left coronary artery tree correlated closely to the corresponding summed distal branch lengths and to the regional myocardial mass. Figures 5 and 6 show corresponding relations of cross-sectional lumen area to distal summed lengths and distal regional mass for group 2 with abnormal coronary arteriograms. A comparison of the correlations of area versus length or mass between the 12 patients with normal coronary arteriograms (group 1) and the 17 patients with CAD (group 2) showed a marked deficit of 30–50% in left coronary artery lumen area for the size of its distal lengths and mass in group 2 with CAD. This difference between the two groups was statistically significant for distal summed branch lengths greater than 2 cm (Table 3); this value of length is equal to a regional myocardial mass of about 7 g, taking for an average a total left ventricular mass of 250 g.
TABLE 3. Mean Cross-sectional Lumen Areas at Specified Vascular Bed Sizes in Left and Right Coronary Arteries Among Normal and CAD Patients

<table>
<thead>
<tr>
<th>Vessel</th>
<th>L (cm)</th>
<th>A1 (cm²)</th>
<th>SD (cm²)</th>
<th>n</th>
<th>A2 (cm²)</th>
<th>SD (cm²)</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCA</td>
<td>1.0</td>
<td>0.007</td>
<td>0.004</td>
<td>17</td>
<td>0.010</td>
<td>0.006</td>
<td>39</td>
<td>0.0384</td>
</tr>
<tr>
<td>LCA</td>
<td>3.0</td>
<td>0.017</td>
<td>0.009</td>
<td>42</td>
<td>0.014</td>
<td>0.008</td>
<td>64</td>
<td>0.0495</td>
</tr>
<tr>
<td>LCA</td>
<td>5.0</td>
<td>0.024</td>
<td>0.014</td>
<td>35</td>
<td>0.017</td>
<td>0.010</td>
<td>53</td>
<td>0.0044</td>
</tr>
<tr>
<td>LCA</td>
<td>7.0</td>
<td>0.030</td>
<td>0.015</td>
<td>27</td>
<td>0.019</td>
<td>0.008</td>
<td>64</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>9.0</td>
<td>0.033</td>
<td>0.015</td>
<td>23</td>
<td>0.024</td>
<td>0.011</td>
<td>56</td>
<td>0.0018</td>
</tr>
<tr>
<td>LCA</td>
<td>11.0</td>
<td>0.041</td>
<td>0.015</td>
<td>30</td>
<td>0.024</td>
<td>0.009</td>
<td>32</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>13.0</td>
<td>0.047</td>
<td>0.013</td>
<td>23</td>
<td>0.035</td>
<td>0.012</td>
<td>26</td>
<td>0.0007</td>
</tr>
<tr>
<td>LCA</td>
<td>15.0</td>
<td>0.049</td>
<td>0.031</td>
<td>22</td>
<td>0.031</td>
<td>0.010</td>
<td>29</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>19.0</td>
<td>0.069</td>
<td>0.017</td>
<td>14</td>
<td>0.038</td>
<td>0.009</td>
<td>9</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>22.0</td>
<td>0.072</td>
<td>0.020</td>
<td>24</td>
<td>0.041</td>
<td>0.017</td>
<td>14</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>26.0</td>
<td>0.068</td>
<td>0.019</td>
<td>7</td>
<td>0.054</td>
<td>0.017</td>
<td>21</td>
<td>0.0364</td>
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<tr>
<td>LCA</td>
<td>30.0</td>
<td>0.106</td>
<td>0.028</td>
<td>3</td>
<td>0.057</td>
<td>0.019</td>
<td>18</td>
<td>0.0005</td>
</tr>
<tr>
<td>LCA</td>
<td>34.0</td>
<td>0.108</td>
<td>0.028</td>
<td>12</td>
<td>0.066</td>
<td>0.025</td>
<td>20</td>
<td>0.0001</td>
</tr>
<tr>
<td>LCA</td>
<td>48.0</td>
<td>0.122</td>
<td>0.023</td>
<td>13</td>
<td>0.066</td>
<td>0.016</td>
<td>14</td>
<td>0.0001</td>
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<tr>
<td>LCA</td>
<td>42.5</td>
<td>0.100</td>
<td>0.013</td>
<td>3</td>
<td>0.078</td>
<td>0.020</td>
<td>17</td>
<td>0.0428</td>
</tr>
<tr>
<td>LCA</td>
<td>47.5</td>
<td>0.122</td>
<td>0.032</td>
<td>5</td>
<td>0.076</td>
<td>0.009</td>
<td>2</td>
<td>0.0498</td>
</tr>
<tr>
<td>LCA</td>
<td>52.5</td>
<td>0.147</td>
<td>0.030</td>
<td>5</td>
<td>0.095</td>
<td>...</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>LCA</td>
<td>62.5</td>
<td>0.142</td>
<td>0.024</td>
<td>3</td>
<td>0.098</td>
<td>0.024</td>
<td>4</td>
<td>0.0307</td>
</tr>
<tr>
<td>LCA</td>
<td>77.5</td>
<td>0.198</td>
<td>0.071</td>
<td>2</td>
<td>0.125</td>
<td>0.022</td>
<td>4</td>
<td>0.0499</td>
</tr>
<tr>
<td>LCA</td>
<td>90.0</td>
<td>0.240</td>
<td>0.027</td>
<td>4</td>
<td>0.116</td>
<td>0.019</td>
<td>3</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

| RCA    | 1.5    | 0.011    | 0.006    | 50  | 0.008    | 0.003    | 59  | 0.0001 |
| RCA    | 4.5    | 0.017    | 0.012    | 60  | 0.011    | 0.007    | 40  | 0.0056 |
| RCA    | 7.5    | 0.021    | 0.008    | 59  | 0.020    | 0.013    | 116 | NS    |
| RCA    | 12.5   | 0.042    | 0.011    | 28  | 0.026    | 0.012    | 45  | 0.0001 |
| RCA    | 17.5   | 0.048    | 0.016    | 25  | 0.037    | 0.027    | 41  | 0.0347 |
| RCA    | 22.5   | 0.054    | 0.016    | 23  | 0.057    | 0.028    | 24  | NS    |
| RCA    | 27.5   | 0.063    | 0.022    | 18  | 0.056    | 0.024    | 35  | NS    |
| RCA    | 32.5   | 0.054    | 0.019    | 24  | 0.045    | 0.012    | 14  | 0.0490 |
| RCA    | 37.5   | 0.101    | 0.027    | 8   | 0.059    | 0.021    | 29  | 0.0001 |
| RCA    | 42.5   | 0.078    | 0.022    | 13  | 0.067    | 0.019    | 16  | 0.0495 |
| RCA    | 47.5   | 0.083    | 0.012    | 10  | 0.070    | 0.008    | 6   | 0.0173 |
| RCA    | 52.5   | 0.088    | 0.012    | 4   | 0.072    | 0.019    | 16  | 0.0472 |
| RCA    | 60.0   | 0.129    | 0.011    | 3   | 0.053    | 0.029    | 6   | 0.0065 |

CAD, coronary artery disease; L, median values of specified areas of distal summed coronary artery lengths. The upper limit of first specified area of L in the case of LCA is equal to 2 cm and corresponds to a regional myocardial mass of about 7 g (total left ventricular mass = 250 g; total length, Ltotal = 75 cm). A1, A2, mean cross-sectional lumen areas for specified areas of L in group 1 or group 2; n, number of measured values of A; LCA, RCA, left and right coronary artery.

and an average total epicardial coronary artery tree length of 75 cm (see also Table 1).

Cross-sectional lumen area versus length and regional myocardial mass of the right coronary artery. The right coronary artery showed similar relations among cross-sectional lumen area, summed distal lengths, and regional myocardial mass (Tables 3 and 4). For example, arterial lumen area, A, was related to myocardial mass, M, for the normal patients according to the equation A = 0.0041 + 0.0036M0.78; r = 0.83, SEE = 0.0162 cm², n = 325. However, there was a larger variability in these relations as evidenced by the larger SEE. In addition, the slope of area versus length for the right coronary artery was less steep than for the left coronary artery, indicating that for equal distal branch lengths, the right coronary artery lumen size was smaller than for the left coronary artery. In the group of normal patients, this difference between right coronary artery and left coronary artery was statistically significant over the upper 64% of the total range of distal length values; in CAD patients, only half the total range of length showed statistically higher mean cross-sectional coronary artery lumen areas for right coronary artery compared with the left coronary artery. A modified tree analysis was carried out to account for the anatomic requirement of the right coronary artery to act as a long conduit between the aortic root and the vascular bed of the posterior descending coronary artery with few intervening right ventricular branches. The primary area-to-length relations for the right coronary artery were not
changed by excluding from the tree analysis the proximal right coronary artery down to the posterior descending coronary artery (Table 4).

Comparison Between Observed and Theoretically Determined Data

Cross-sectional area ratio between parent and daughter vessels. The mean lumen cross-sectional area ratio of parent-to-daughter vessel at 50 bifurcations in left coronary artery trees among 12 normal patients (Table 2) showed a mean value of 1.647±0.06, which equals $2^{0.72}$, where $a=0.72$ in the term $2^a$ of Equation 11. This observed value is significantly different from $2^b$ ($p<0.005$) predicted by the constant mean velocity principle, which makes it unlikely that this principle characterizes vascular tree structure of the coronary artery system. However, the observed value of 1.647 is not significantly different from the theoretical value of 1.588 derived from the $\frac{2}{3}$ power principles ($2^{0.72} = 2^{0.67} = 1.588$, where $a=0.67$ in the term $2^a$) as shown in Table 2. Therefore, the observed data on parent-to-daughter ratios fit the principles of minimum energy loss, of limited/adaptive wall shear stress, and of minimum vascular volume at bifurcations but do not fit the

FIGURE 3. Graph showing relation of left coronary artery lumen area ($A$, cm$^2$; y axis) measured at 314 locations in the left coronary arteries of 12 patients with normal coronary arteriograms to the corresponding summed ($\Sigma$) coronary artery branch lengths ($L$, cm; x axis) distal to the sites where $A$ was measured down to a vessel diameter of about 0.5 mm. n, Number of measured points; SEE, standard error of estimate for values of $A$; x-sectional, cross-sectional.

FIGURE 4. Graph showing relation of left coronary artery lumen area ($A$, cm$^2$; y axis) measured at 314 locations in the left coronary arteries of 12 patients with normal coronary arteriograms to the corresponding distal regional mass of myocardium ($M$, g; x axis) calculated according to Equation 13. n, Number of measured points; SEE, standard error of estimate for values of $A$; x-sectional, cross-sectional.

FIGURE 5. Graph showing relation of left coronary artery lumen area ($A$, cm$^2$; y axis) measured at 490 locations in the left coronary arteries of 17 patients with coronary artery disease (CAD) on coronary arteriograms to the corresponding summed ($\Sigma$) coronary artery branch lengths ($L$, cm; x axis) distal to the sites where $A$ was measured down to a vessel diameter of about 0.5 mm. Heavy line represents the curve fitting of $A$ vs. $L$ in normal patients from Figure 4. n, Number of measured points; SEE, standard error of estimate for values of $A$; x-sectional, cross-sectional.

FIGURE 6. Graph showing relation of left coronary artery lumen area ($A$, cm$^2$; y axis) measured at 490 locations in the left coronary arteries of 17 patients with coronary artery disease (CAD) on coronary arteriograms to the corresponding distal regional mass of myocardium ($M$, g; x axis) calculated according to Equation 13. Heavy line represents the curve fitting of $A$ vs. $M$ in normal patients from Figure 4. n, Number of measured points; SEE, standard error of estimate for values of $A$; x-sectional, cross-sectional.
principle of mean coronary blood flow velocity. The observed parent-to-daughter ratio of 1.647 and the corresponding \( a = 0.72 \) are slightly higher than the theoretically derived values of 1.588 and \( a = 0.67 \) for symmetrical trees, probably because of a modest degree of asymmetry in the coronary vascular tree.

The observed parent-to-daughter ratio of mean lumen area at bifurcations (\( A_0/A \)) of 1.647 indicates that the daughter-to-parent ratio of lumen area (\( A/A_0 \)) is the inverse of 1.647, or 0.607. Therefore, the total combined lumen area of both daughter arterial branches at every arterial bifurcation from proximal to distal (\( 2A/A_0 \)) increases by a factor of 1.214. Because blood mass and volume blood flow proximal and distal to the bifurcation are conserved, the mean blood flow velocity has to decrease by the same factor of 1.214, and therefore, the principle of mean blood flow velocity is not likely to characterize the coronary artery tree structure.

Comparison between observed and theoretically derived coronary size-to-regional mass relations. The theoretical relation of coronary artery lumen area to regional myocardial mass derived from the area-flow equations of each physical principle were converted to theoretical lumen area–mass relations for comparison with observed area–mass relations by dividing flow in the theoretical equations by an assumed, theoretical, average resting myocardial perfusion of 0.8 cm³/min/g. Figures 7 and 8 compare the observed and theoretical data. The theoretical relations between area and mass are within the 95% confidence intervals of measured area-to-mass relations for those theoretical relations derived from the principles of minimum bifurcation volume and minimum energy loss at resting but not maximum flow. These results suggest that the principles of minimum bifurcation volume and minimum energy loss at resting coronary flow levels characterize the coronary artery tree structure in man. However, the principles of minimum bifurcation volume and minimum energy loss at maximum flow do not fit observed data.

The theoretical area–mass relations also fit observed area–mass relations for the principle of limited and adaptive shear stress at maximum coronary flow rate.
The observed arterial lumen sizes are about two times larger than the theoretical sizes (limited shear principle), which would cause shear forces destructive to the endothelium at acutely increased, maximum flow rates (shear stress around 200 dynes/cm²). The observed arterial lumen sizes would be able to maintain normal endothelial shear forces of approximately 30 dynes/cm² (adaptation) at chronically increased, maximum flow rates. Therefore, the limited shear stress principle is consistent with arterial size observed by establishing a biologically relevant shear stress limit, but the chronic adaptive shear stress principle more closely approximates the observed data. Thus, the two intuitively important principles—minimum energy loss and adaptive shear stress—both closely fit observed data in humans. Because the observed parent-to-daughter mean artery size ratio does not fit the theoretical principle of mean coronary blood flow velocity (Table 2), the lumen area–to–regional mass relation derived on the basis of this principle is not plotted with the observed data.

For the normal reference group 1, there was a close direct relation between total left ventricular mass and total left coronary artery length as shown in Figure 9, plotting one point for each subject (n=12). These results in humans parallel a similar observation for the canine coronary artery tree reported by Freiman et al.9

Discussion

Measures of percent stenoses and current quantitative coronary arteriography may fail to account for true normal coronary artery size in assessing severity of segmental or diffuse CAD because the "normal" reference segment may also be narrowed. To address this problem, we have developed the theoretical basis and methodology for analyzing the entire coronary epicardial arterial tree, including observed arterial lumen size and expected true normal arterial size for the size of the dependent coronary vascular bed on clinical coronary arteriograms. Results in patients without and with segmental CAD on clinical arteriograms document the following: 1) Observed left and right coronary artery lumen area at each point along the length of the artery and its branches closely correlates with the summed arterial branch lengths and regional myocardial mass distal to each point. 2) Coronary artery lumen area in patients with CAD is on the average nearly one third to one half smaller than the normal size for the dependent branch lengths and regional mass. 3) The observed relations among coronary artery lumen area, summed distal branch lengths, and distal regional mass in left and right coronary arteries is closely approximated by a ½ power relation. 4) The parent-to-daughter mean lumen area ratio at normal left coronary artery bifurcations is also closely approximated by a ½ power relation between lumen area and regional mass, not a linear relation. 5) The observed data fit the theoretical ½ power-law principles of minimum energy loss and minimum vascular volume at bifurcations at resting flow and the principles of limited/adaptive wall shear stress. Thus, these principles are consistent with the arteriographic data of the entire coronary artery tree as well as with its local structural element, the bifurcation.

Agreement Between Observed Data and Theoretical Principles

The relation between arterial lumen cross-sectional area at each point along the artery and the sum of branch lengths or regional myocardial mass distal to each point can be theoretically derived from each of several basic physical principles: 1) minimum energy dissipation at resting flow conditions, 2) adaptive/limited wall shear stress, and 3) minimum vascular volume at arterial bifurcations. This relation is described by Equation 4, in which the constant a is theoretically derived as ⅔ or 0.67. The observed value for the constant a determined from measurements on clinical arteriograms of parent-to-daughter mean lumen area ratios is 0.72 and determined from lumen area–summed branch lengths is 0.82. The observed values for the constant a closely approximate the theoretical values but are slightly higher.

These observations raise two questions. First, are the observed values for the constant a slightly higher than the theoretical values because of biological and measurement variability, or is some other factor playing a role?

The present study shows that the observed parent-to-daughter ratios of mean artery lumen area at coronary
bifurcations \((A_0/A)\) is equal to 1.647, which equals \(2^{0.72}\), where \(a=0.72\) in the term \(2^a\) of Equation 11. In other words, the observed daughter-to-parent lumen area ratio \((A/A_0)\) is 0.607, and the observed lumen area at every arterial junction from proximal to distal \((2A/A_0)\) increases by a factor of 1.214. The higher observed values of the constant \(a\) compared with theoretical data can be partially explained by the fact that the theoretical principles assume a symmetrical coronary tree, in which the parent-to-daughter lumen area \((A_0/A)\) is 1.588. The daughter-to-parent ratio is the inverse of 1.588, or 0.630, and the total combined lumen area of two daughter branches is 1.260. Therefore, symmetry means that the lumen sizes of the two daughter branches will be equal, with both having 63% of the cross-sectional lumen area of the parent artery \((1.260/2)\).

Asymmetry of the coronary tree refers to regional differences in the parent-to-daughter and also daughter-to-parent lumen relation at branching points. Consequently, one daughter branch \((A')\) meeting with the second at, for example, the first-generation bifurcation level is, on average, smaller than the other. For an asymmetrical coronary vascular tree, \(A_0/A'=1.588\), or \(A_0/A'=2^{0.72}\). The observed ratio of 1.647 and the observed constant \(a=0.72\) compared with values of 1.588 and 0.67 for a symmetrical arterial tree suggest that the human coronary vascular tree has a slight degree of asymmetry. Factors suggesting that the slightly higher observed values for the constant \(a\) compared with those theoretically predicted for a symmetrical vascular tree are real and indicate some asymmetry rather than being a result of biological or measurement variability include 1) the strong correlation between lumen area, summed lengths, and regional mass with a large number of points with highly significant probability values and 2) the similar observed values for the constant \(a\) determined from different independent measurements of lumen areas at bifurcations and from measured lumen area-summed lengths relations.

The second question arising from these observations is, in a sense, a philosophical question. What are the implications of the observed lumen area-summed lengths–mass relations and the observed parent-to-daughter lumen area ratios fitting several different physical principles: those of minimum energy dissipation at resting flow conditions, minimum volume at arterial bifurcations, and also adaptive/limited shear stress? The first two of these three principles are not actually independent but rather reflect the same concept of minimum energy loss, one developed by considering the entire coronary vascular tree and the other by considering arterial bifurcations. For either starting point, the principle is minimum energy loss.

However, the principle of minimum energy loss is independent of and unrelated to the principle of adaptive/limited shear stress, being based on different physical concepts and derived by different equations. Nevertheless, both principles predict the same lumen area, summed branch lengths, and regional myocardial mass relations by a \(1/2\) power equation (Equations 4 and 8). Although they are derived from different physical concepts and are derived differently mathematically, we believe that these different principles are linked biologically through the properties of blood viscosity, associated viscous shear, and viscous energy loss, which are the mechanisms by which the physical principles are expressed biologically. Viscous wall shear is the mechanism for linking flow phenomenon to behavior of the arterial wall by shear-sensitive receptors of coronary vascular endothelium. Stimulation of these shear-sensitive receptors or lack thereof regulates a variety of biovascular mediators for vasomotion, reorientation of endothelial cells, and cellular proliferation.35–37 In short-term observations (months), fluid dynamic factors appear to play a role in reshaping the coronary artery experimentally1,38 and in humans at sites of coronary artery stenoses.1

Similarly, viscous shear determines viscous energy losses along an artery and therefore the energy balance of flowing blood cumulatively throughout the entire length of an artery. The major difference of these principles related to viscous shear in blood is that the adaptive shear equation describes the fluid dynamic phenomenon at small local segments of the vascular tree, whereas the minimum energy principle describes the fluid dynamic phenomenon integrated over the entire length of coronary arteries and arterial tree. These two principles are therefore essentially the same conceptually, but one reflects a macro view of the entire coronary epicardial arterial tree and the other a micro view of small segments of coronary arteries. That they give similar answers from independent starting points adds further credence to these conclusions.

**Limitations of the Study**

In this study, the primary data measured on coronary arteriograms were lumen area and summed lengths, which were observed to follow a 0.82 power relation. A modest limitation of this study is that the “observed” values of regional mass were calculated on the basis of the experimental observation by Freiman et al that summed lengths and regional mass were linearly related. However, this experimental observation is supported by our observation of an essentially linear relation between the total summed lengths and total left ventricular mass in humans (Figure 9) based on clinical coronary arteriograms of the normal group 1. Because there is no way of independently measuring regional mass for a coronary arterial branch in humans, these two observations are the best established regional mass–summed lengths relation for analyzing clinical arteriograms.

Three of the 17 patients in the group with CAD (group 2) had no evidence of significant segmental CAD. They had angina pectoris, ST segment depression on exercise testing, and positive thallium scans, indicating ischemia. These patients could be judged to have diffuse CAD and were therefore included in group 2. An alternative explanation would have been that these patients had syndrome X and thus no coronary atherosclerosis. Any bias by including them in group 2 would be against our hypothesis; therefore, including them in group 2 was scientifically conservative.

**Clinical Implications**

There are several clinical implications from this study. It demonstrates the conceptual basis, methodology, and application of an approach to analyzing the entire coronary vascular tree on clinical arteriograms.
for the purpose of assessing diffuse coronary artery narrowing with and without segmental narrowing. By determining what the true normal cross-sectional arterial lumen area would be for its distal vascular bed size, we demonstrated that arterial lumen size in patients with CAD is 30–50% smaller than what it should or would normally have been in the absence of atherosclerosis. Finally, this approach and the anatomic structure of the human coronary epicardial arterial tree can be explained by basic physical principles.

Although carried out on clinical coronary arteriograms, two additional developments are necessary before this approach can be routinely applied clinically. The first is the development of completely automated software for analyzing each entire artery along its length on an arteriogram independent of operator intervention other than choosing a cine arteriographic frame and the origins of the left and right main coronary arteries. The second is to develop the methodology for determining coronary flow reserve of each entire artery and its branches by integrating the pressure drop along each coronary artery and/or branches using fluid dynamic equations incorporating the expected normal lumen size for size of the distal bed, the observed lumen size, and cumulative effects of sequential and/or parallel stenoses in branching arteries. These two steps in quantitative coronary arteriography will require further work based on the fundamental concepts documented here.

Acknowledgment
We gratefully acknowledge the technical assistance of Yvonne M. Stuart, RT.

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\begin{figure}
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\includegraphics[width=\textwidth]{figure9.png}
\caption{Graph showing relation of total left ventricular mass ($M_{LV}$; $g$; $y$ axis) to total left coronary artery tree branch length ($L_{tot}$; cm; $x$ axis) in 12 patients with normal coronary arteriograms. $n$, Number of patients; SEE, standard error of estimate for values of $M_{LV}$.}
\end{figure}
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Basic structure-function relations of the epicardial coronary vascular tree. Basis of quantitative coronary arteriography for diffuse coronary artery disease.
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doi: 10.1161/01.CIR.85.6.1987

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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