Diameter asymmetry of porcine coronary arterial trees: structural and functional implications

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1Faculty of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa, Israel; and 2Department of Biomedical Engineering, Surgery, and Cellular and Integrative Physiology, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana

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Kaimovitz B, Huo Y, Lanir Y, Kassab GS. Diameter asymmetry of porcine coronary arterial trees: structural and functional implications. Am J Physiol Heart Circ Physiol 294: H714–H723, 2008. First published November 30, 2007; doi:10.1152/ajpheart.00818.2007.—The coronary vasculature is characterized by highly asymmetric diameters at bifurcations, which may be an important determinant of flow distribution. To facilitate accurate reconstruction of the coronary network for hemodynamic analysis, we introduce a statistical data set of the diameter asymmetry at bifurcations based on morphometric data of the porcine coronary arterial and venous trees. The bifurcation asymmetry data were represented by the diameter ratio of the daughters relative to mother vessel and by an area expansion ratio (AER) at each bifurcation. A novel asymmetry ratio matrix was introduced to describe the diameter asymmetry of daughters to mother vessels. The relations between AER and flow velocity, and asymmetry ratio matrix and flow distribution, were considered. The results indicate that the ratio of large daughter to mother vessel has a minimum value at order 5 (mean diameter of ~70 μm), whereas the ratio of small daughter to mother vessel decreases monotonically with increase in order number. The AER was found to be fairly uniform for larger vessels and to increase from order 5 toward the capillaries. At order 5, we observe a transition in asymmetric bifurcation pattern that may mark a hemodynamic transition from transmural to perfusion subnetworks. The functional implications of these structural transitions are considered.

There is significant variability in the coronary anatomy at the level of large epicardial subnetworks, both “globally” (left-right dominance), as well as “locally” at the level of bifurcations (4, 30). The vessel branches are characterized by highly irregular and asymmetric branching patterns (11, 12–15, 28). Due to the fractal nature of the coronary vasculature (31, 32), the number of vessels increases in a geometric fashion toward the capillary vessels. This leads to an overwhelming number of vessels that preclude a deterministic description of the coronary anatomy. For these reasons, a stochastic representation of the anatomy is necessary to facilitate a realistic three-dimensional (3D) reconstruction of the entire coronary vasculature.

The process of obtaining statistical morphometric data from a given tree is unique, provided that we follow a set of rules. Such rules may include the diameter-defined Strahler’s ordering scheme (12) or Weibel’s generation system (29). Alternatively, the process of reconstructing a tree from a statistical database is not unique. One can reconstruct infinitely many trees that are consistent with the statistical database, but not uniquely specified by them. Consequently, a realistic reconstruction of a vascular network requires sufficient constraints or morphometric data to rule out improbable trees. Although the coronary morphology has been described in great detail (12–15), additional morphometric data are required to impose additional bounds and ensure accurate stochastic reconstructions. In particular, a correlation between dimensions of consecutive vessels is an important feature that is absent from the statistical data previously published (12–15, 28). The objective of this study is to fill in the gap.

Of all the morphometric parameters (diameters, lengths, number of vessels, connectivity, etc.), the diameter is arguably the most important hemodynamically. Hence, additional morphometric description of diameters should lead to more accurate anatomical models. The goal of this study is to determine local measures of asymmetry at bifurcations in the context of diameter-defined Strahler’s ordering scheme (12). The diameter ratios and area expansion ratios (AER) are extended to the entire arterial and venous trees in the framework of mother-to-daughter connectivity. It was found that the ratio of large daughter to mother vessels has a statistically significant minimum value at order 5 (mean diameter of ~70 μm). The ratio of small daughter to mother vessels was found to decrease monotonically with order number. The AER remains similar in large vessels of high orders (≥5), but increases toward small orders toward the capillaries. Our results imply a structure-function relation at order 5 that may mark a hemodynamic transition from transmural to perfusion subnetworks.

METHODS

Existing data. Our laboratory has previously described in detail the methods of preparation, measurement, and morphometric analysis of the right coronary artery (RCA), left anterior descending (LAD) artery, left circumflex (LCx) artery, and coronary sinus (12, 13). The morphometric data on the coronary vessels of diameters <50 μm were obtained from histological specimens, while the morphometric data on vessels of diameters >50 μm were obtained from cast studies, as described in Kassab et al. (12).

Manual vs. automatic ordering. Our laboratory has previously developed two different schemes for assigning diameter-defined order numbers to the entire coronary arterial and venous trees. We shall refer to these methods as 1) manual (12) and 2) automatic (22). In the former and original approach, the data existed in hard records, and the ordering scheme was carried out manually. In that approach, the assignment of orders was made iteratively, since the coronary vessels were cut at various diameters in the histological sections and casts for reprint requests and other correspondence: G. S. Kassab, Dept. of Biomedical Engineering, Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN 46202 (e-mail: gkassab@iupui.edu).

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(12). Briefly, the capillaries were assigned zero-order number, and the intact segments were assigned order numbers according to Strahler’s system. The derived order numbers were then used to assign order numbers to cut vessels, according to the diameter-defined criterion. This process was continued until the orders of all cut segments of the trees were assigned order numbers. Finally, we required that the order number of any given cut segment fall within the range of diameter criterion for each respective order, i.e., diameter-defined Strahler system (12). This scheme was used to mesh the histological data with those from polymer cast.

In the more recent automatic approach, the hard copy of trees was digitized, and the data were available electronically (22). Briefly, a two-step approach was employed in the reconstruction of the entire coronary arterial tree down to the capillary level. The cast data were reconstructed one bifurcation at a time, while histological data were reconstructed one subtree at a time by “cutting” and “pasting” of data from measured to missing vessels. In this approach, the assignment of orders was done after the entire tree was reconstructed. In the subsequent analysis, we shall use both databases to determine the diameter asymmetry at a bifurcation to rule out the effect of ordering model on the resulting database.

Diameter asymmetry at a bifurcation. The diameter asymmetry at a bifurcation was quantified as a function of the order number of mother vessel for \( D_l/D_m \) and \( D_m/D_m \), i.e., the ratios of the diameters of larger \( (D_l) \) and smaller \( (D_s) \) daughters, respectively, to their mother \( (D_m) \) vessel. The mother vessel order number was selected as the independent variable to partition the data to subgroups, which can then be compared. The raw bifurcation data were based on the morphometric database of Kassab et al. (12, 13) for the arterial and the venous trees and are not dependent on any reconstruction scheme. The classification of the bifurcation data with respect to the order of the mother vessels, however, depends on the reconstruction schemes (either manual or automatic). In addition, a distinction was made between intraelement and interelement segments. For the intraelement case, the branching occurs along the same element, and thus the larger daughter belongs to the element. Accordingly, for this case, the \( D_l/D_m \) statistics were represented as a function of the element order number only (see Figs. 1–3 for the LAD, LCx, and RCA arteries). For the interelement case, each daughter belongs to a different element, and hence the \( D_l/D_m \) ratio was formulated as asymmetry ratio matrix (ARM), where the ratio is a function of order of mother and daughter segments (see Tables 1–3 for the LAD, LCx, and RCA arteries, respectively). The former (intraelement) can be viewed as an index of vessel taper, whereas the latter (interelement) represents branching asymmetry.

Murray’s law states that the \( D_m \) cubed is equal to the sum of the cubes of the daughter vessels (i.e., \( D_m^3 = D_l^3 + D_s^3 \)) (24). Here, we consider a general form of Murray’s law at a bifurcation: \( D_m^3 = D_l^3 + D_s^3 \). The bifurcation exponent \( k \) was determined for each bifurcation of arterial trees.

Statistical analysis. To determine statistical significance of differences, especially the minimum for the \( D_l/D_m \) ratio found at mother vessel of order 5, we carried out various statistical analyses. The tests included both order-independent and order-dependent tests. The order-independent test was based on a polynomial fitting of the \( D_l/D_m \) ratio as function of the \( D_m \). For this purpose, a linear regression was made for the \( D_l/D_m \) ratio as function of the logarithm of the \( D_m \). ANOVA test was performed to validate the significance of the polynomial coefficients. To evaluate the significance of the minimum of the polynom (the “dip”), a \( t \)-test was performed on a population of samples of \( D_l/D_m \) ratios located in the vicinity of the minimum to test the hypothesis that the mean of the population around the minimum location and the mean value of the entire population are identical. The “dip” population sample size was varied between 2.5 and 25% of the entire population size. The order-dependent analysis tested the significance of the differences in the \( D_l/D_m \) ratio between each group and the entire population and included Wilcoxon-Mann-Whitney, Kolmogorov-Smirnov, and Kruskall-Wallis nonparametric tests, as well as \( T \)-test.

RESULTS

Figure 1, A and B, shows the relationship between \( D_l/D_m \) and order number for manual and automatic tree data, respectively, of LAD, LCx, and RCA arteries. Similar to previous studies (3, 10), the data can be classified in three regimes: 1) epicardial (vessel orders 8–11, which mainly exist in the epicardium), 2) transmural (orders 5–8, which perforate the myocardium), and 3) perfusion subnetworks (orders 1–5, which are within the sheets of myocardium to provide local perfusion). The diameter ratio in the epicardial regime is relatively constant (no statistically significant change). There is a significant decrease and increase in diameter ratio, however, in the transmural and perfusion vessels, respectively. Figure 2 depicts the relationship between \( D_l/D_m \) and order number, which shows a monotonic trend where the larger orders are more asymmetric than lower orders. Figure 3 shows the relationship between AER and order number for both schemes. The data can be subdivided into two subregimes: epicardial and...
transmural subnetworks (orders 5–11) and perfusion subnetworks (orders 1–5). In the former, the AER is relatively uniform (no significant change) but increases significantly in the latter. Corresponding to Figs. 1–3, Supplemental Tables S5–S7 (the online version of this article contains supplemental data) list the mean ± SD values for the \( D_l/D_m \) (for interelements) and the corresponding \( D_s/D_m \) ratios and the AER (AER = \([D_l^2 + D_s^2]/D_m^2\)) for LAD, LCx, and RCA trees, respectively. Finally, the mean and SE of the bifurcation exponent \( k \) for various vessel order of the LAD, LCx, and RCA trees are depicted in Fig. 4.

The \( D_l/D_m \) data for the interelements are represented using the ARM for the LAD, LCx, and RCA trees in Tables 1–3, respectively. Tables 1–3 show the \( D_l/D_m \) ARM for the LAD, LCx, and RCA arteries in the manual scheme, and similar data are shown in Supplemental Tables S1–S3 for the automatic scheme. It is found that the manual (raw) tree data agree well with the automatic tree data, which suggests that the automatic scheme faithfully reconstructs the morphometric data.

**Order-independent statistical analysis.** The polynomial fit of the \( D_l/D_m \) ratio as a function of the mother diameter for the LAD, LCx, and RCA branches is depicted in Fig. 5. The entire data were initially fitted by a polynomial of orders 4–8. Up to this order polynomial, all curve-fit coefficients were found to be significant (\( P < 0.001 \)), based on ANOVA test as well as \( t \)-test for the coefficients. It can be seen in Fig. 5 that the minimum for the \( D_l/D_m \) ratio occurs at \( D_m \) approximately equal to 70–80 μm, which corresponds to mother vessel order 5 for the coronary arterial branches.

The hypothesis that the mean of the population of samples around the minimum location (the “dip population”) is a random sample of the entire population was rejected (\( P << 0.001 \)). This was found to be the case in a series of \( t \)-tests performed for a variable size of dip populations ranging (symmetrical relative to the dip location) over 2.5–25% of the entire population size.

**Order-based statistical test.** The order-based statistical test was implemented for the LAD branches, which relates to the vessel order as the independent variable. It depends on the model by which orders were assigned to the vessels. Hence,
the same hypothesis tested in the order-independent test was retested based on the vessel order. The results are summarized in Table 4. The distribution of the population of the $D_l/D_m$ ratio is found to be nonnormally distributed for orders 7–9, based on Kolmogorov-Smirnov, and for orders 4 and 7–9, based on the Lilliefors tests (Table 4). The hypothesis that adjacent populations have the same mean is rejected for orders 1 and 4–7 based on all of the nonparametric tests, i.e., Wilcoxon-Mann-Whitney, Kruskall-Wallis, and the Kolmokorov-Smirnov, indicating that the minimum found at order 5 has a statistical significance.

Flow distribution. Using the flow analysis in Ref. 8, the distribution of flow was calculated in the entire coronary arterial tree. Figure 6 shows the relation between the flow ratio ($Q_l$ and $Q_s$ are flows in large and small vessel, respectively) and mother order number in the entire arterial tree of LAD, LCx, and RCA from the automatic scheme. Figure 7 shows the corresponding relation between the velocity and order number. It is clear that the flow ratio remains fairly uniform in the perfusion subnetworks and increases significantly in the epicardial and transmural vessels. In comparison, the velocity ratio is about two orders of magnitude smaller than the flow ratio in all three networks. Furthermore, the transmural subnetwork has a velocity ratio approximately equal to unity and increases toward higher and lower orders in epicardial and perfusion subnetworks, respectively.

DISCUSSION

In the present study, we determined the bifurcation asymmetry for intra- and interelement segments. A novel ARM was introduced to describe the diameter asymmetry of daughter to mother vessels. Several new findings emerged as 1) the ratio of large daughter to mother vessels has a minimum value at vessel order 5 (mean diameter of ~70 μm), depicting a functional hierarchy for epicardial, transmural, and perfusion subnetworks; 2) the ratio of small daughter to mother vessels decreases monotonically with order number, with the larger vessels being more asymmetric than smaller vessels; and 3) the AER has values near unity in orders 6–11 and monotonically increases toward order 1, which again reflects a functional hierarchy between perfusion and transmural and epicardial subnetworks. We will elaborate on the hemodynamic significance of each of these findings below.

Structure-function relation. Our laboratory has previously developed the diameter-defined Strahler model, connectivity, and longitudinal position matrices to quantify the anatomy of the arterial and venous trees (12, 13). In this study, we introduce the bifurcation asymmetry to further quantify the constraints of morphometry of the coronary vasculature with emphasis on the diameters. It was found that the $D_l/D_m$ ratio has a minimum value at order 5, as shown in Fig. 1 for arterial trees (both manual and automatic tree data). The statistical tests (Table 4 and Fig. 5) were carried out to indicate that the minimum value found at order 5 is statistically significant. The $D_l/D_m$ ratio (Fig. 1) reveals a functional hierarchy for the coronary arterial tree, depicting epicardial, transmural, and perfusion subnetworks. This is consistent with a previous study that showed an abrupt change in cross-sectional area and blood flow that demarcates the transition from epicardial (orders 8–11) to intramyocardial coronary arteries (transmural and perfusion vessels) (17). The $D_l/D_m$ ratio was found to decrease with order number, as shown in Fig. 2. This implies that the larger vessels (higher orders) are more asymmetric than the smaller vessels. If we define $S_D = D_l/D_s$ (ratio of $D_l/D_m$ and $D_s/D_m$), $S_D$ remains uniform in orders 1–5 and increases for orders $>5$ (data not shown), consistent with previously published data (11).

Our laboratory has previously shown several structure-structure and structure-function relationships for the coronary arterial trees (18, 19, 33). To determine the hemodynamic consequence of bifurcation asymmetry, we consider the approximate relations: $R_l/R_s = S_D^2$ and $Q_l/Q_s = S_D^3$, as determined in the APPENDIX (Eqs. A8 and A9, respectively), where $R_l$ and $R_s$ are the equivalent resistances of distal tree to large and
### Table 1. $D_s/D_m$ (ARM for raw data) for the LAD artery

<table>
<thead>
<tr>
<th>Daughter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.663±0.132 (295)</td>
<td>0.511±0.106 (68)</td>
<td>0.347±0.113 (10)</td>
<td>0.181</td>
<td>0.067±0.013 (3)</td>
<td>0.670±0.091 (106)</td>
<td>0.515±0.063 (36)</td>
<td>0.342±0.031 (3)</td>
<td>0.151±0.033 (15)</td>
<td>0.085±0.023 (13)</td>
<td>0.485±0.069 (36)</td>
</tr>
<tr>
<td>1</td>
<td>0.670±0.091 (106)</td>
<td>0.640±0.090 (47)</td>
<td>0.587±0.126 (20)</td>
<td>0.240±0.104 (106)</td>
<td>0.640±0.090 (47)</td>
<td>0.463±0.125 (455)</td>
<td>0.321±0.078 (112)</td>
<td>0.321±0.078 (112)</td>
<td>0.453±0.130 (213)</td>
<td>0.579±0.160 (53)</td>
<td>0.453±0.130 (213)</td>
</tr>
</tbody>
</table>

Values are means ± SD for $D_s/D_m$ [asymmetry ratio matrix (ARM) for raw data] for the left anterior descending (LAD) artery, where $D_m$ and $D_s$ are the diameters of the mother and smaller daughters, respectively. The intersection of row $n$ and column $m$ represents the mean ± SD values (averaged over the total number of mother vessels, as indicated in parentheses at the intersection) of the ratio of $D_s$ (in order $n$) to $D_m$ (in order $m$).

### Table 2. $D_s/D_m$ (ARM for raw data) for the LCx artery

<table>
<thead>
<tr>
<th>Daughter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.663±0.132 (295)</td>
<td>0.511±0.106 (68)</td>
<td>0.347±0.113 (10)</td>
<td>0.181</td>
<td>0.067±0.013 (3)</td>
<td>0.670±0.091 (106)</td>
<td>0.515±0.063 (36)</td>
<td>0.342±0.031 (3)</td>
<td>0.151±0.033 (15)</td>
<td>0.085±0.023 (13)</td>
<td>0.485±0.069 (36)</td>
</tr>
<tr>
<td>1</td>
<td>0.670±0.091 (106)</td>
<td>0.640±0.090 (47)</td>
<td>0.587±0.126 (20)</td>
<td>0.240±0.104 (106)</td>
<td>0.640±0.090 (47)</td>
<td>0.463±0.125 (455)</td>
<td>0.321±0.078 (112)</td>
<td>0.321±0.078 (112)</td>
<td>0.453±0.130 (213)</td>
<td>0.579±0.160 (53)</td>
<td>0.453±0.130 (213)</td>
</tr>
</tbody>
</table>

Values are means ± SD for $D_s/D_m$ (ARM for raw data) for the left circumflex (LCx) artery. The intersection of row $n$ and column $m$ represents the mean ± SD values (averaged over the total number of mother vessels, as indicated in parentheses at the intersection) of the ratio of $D_s$ (in order $n$) to $D_m$ (in order $m$).
Table 3. \( D_l/D_m \) (ARM for raw data) for the RCA artery

<table>
<thead>
<tr>
<th>Order</th>
<th>Mother</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.079 ± 0.018 (271)</td>
<td>0.080 ± 0.010 (90)</td>
</tr>
<tr>
<td>2</td>
<td>0.236 ± 0.013 (30)</td>
<td>0.255 ± 0.017 (2)</td>
</tr>
<tr>
<td>3</td>
<td>0.425 ± 0.016 (12)</td>
<td>0.515 ± 0.040 (5)</td>
</tr>
<tr>
<td>4</td>
<td>0.631 ± 0.014 (5)</td>
<td>0.631 ± 0.014 (5)</td>
</tr>
<tr>
<td>5</td>
<td>0.720 ± 0.012 (4)</td>
<td>0.720 ± 0.012 (4)</td>
</tr>
<tr>
<td>6</td>
<td>0.768 ± 0.013 (2)</td>
<td>0.768 ± 0.013 (2)</td>
</tr>
</tbody>
</table>

Values are means ± SD for \( D_l \) (in mm) and \( D_m \) (in mm) in each order. The \( D_l/D_m \) ratio was calculated as the total number of mother vessels, as indicated in parentheses at the intersection of row \( n \) and column \( m \).

Fig. 5. Polynomial fit for the \( D_l/D_m \) ratio as a function of \( D_m \) in the manual (raw) tree data of LAD, LCx, and RCA arteries. The entire data are fitted by polynomials of orders 4–8.

The significance of the ratio \( D_l/D_m \) may be related to the “distributing” vessels that remain on the surface of distinct zones of the heart, compared with the “delivering” vessels that penetrate the respective zones to implement the delivery of blood (17). The former constitute the epicardial vessels, whereas the latter constitute the transmural and perfusion subnetworks. The distributing arteries tend to maintain their diameter and, consequently, their flow fairly uniformly, so that the various regions of the heart can receive a similar source of blood supply (17). This is achieved when the vessels maintain their diameters, i.e., small tapering rate, and, accordingly, large \( D_l/D_m \) (17).
symmetric), which is reflected in the decrease of $D_l/D_m$ value toward $D_s/D_m$.

The wall shear stress, $\tau$, can be related to the exponent $k$, as shown in the APPENDIX (Eq. A14); namely, $\tau \sim D^{k-3}$. If $k = 3$ (Murray’s law), the wall shear stress is uniform over different size vessel. If $k = 2$ (AER = 1), the velocity is uniform, but the shear stress increases inversely with a decrease in diameter, i.e., amplifies in the microcirculation. The variation in $k$ for different size vessels is shown in Fig. 4 and reflects the transitions for changes in shear stress (8).

Comparison with other works. VanBavel and Spaan (28) reported a mean AER of $1.12 \pm 0.302$ (mean $\pm$ SD) in the entire porcine coronary arterial tree. A linear regression of AER as a function of log($D_m$) yields a correlation coefficient of 0.024 (28). Here, we determined the AER for each order number of arterial trees (Fig. 3). Our data (Figs. 3) show an interesting transition at orders 5 for the arterial trees, which was not previously observed. As shown in Ref. 28, the considerable spread of the data was mainly due to measured variability of diameters, which was confirmed in the present study.

VanBavel and Spaan (28) reported the bifurcation exponent ($k$) to be 2.82 for $D_m < 40 \mu m$, 2.50 for $40 < D_m < 200 \mu m$, and 2.35 for $200 \mu m < D_m$ in the Murray-type relation ($S_l + S_s = 1$), where $S_l$ is $D_l/D_m$ ratio, and $S_s$ is $D_s/D_m$ ratio. The values of $k$ for each order number of the arterial trees are shown in Fig. 4. Again, there is a drastic change at order 5 for the arterial trees. In summary, there appears to be a structural and functional transition at the microvasculature.

Many researchers (24, 25) used the minimum work principle and uniform shear stress to understand the design of arterial bifurcations. It was postulated that an exponent $k$ of 3 represented an optimized design. Numerous studies (26, 27), however, showed significant scatter in the exponent. Our previous studies (18, 19) found an exponent of $\sim 2.2$ for the entire coronary arterial tree, which deviates from Murray’s prediction.

### Table 4. Statistical test results for $D_l/D_m$ for the LAD tree

<table>
<thead>
<tr>
<th>Order of Mother Vessel</th>
<th>$H_0$: the Ratio $D_l/D_m$ is Normally Distributed</th>
<th>$H_0$: Mother and Daughter Population Have the Same Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kolmogorov-Smirnov Test</td>
<td>Lilliefors Test</td>
</tr>
<tr>
<td></td>
<td>Result</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.35</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.51</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0.89</td>
</tr>
</tbody>
</table>

$D_h$ diameter of the larger daughters. $H_0$ accepted $= 0$.

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**Fig. 6.** Relation between the flow ratio ($Q_l$ and $Q_s$ are flows in large and small vessel, respectively) and mother vessel order number in the entire arterial tree of LAD, LCx, and RCA for the automatic scheme.
of 3. The present study further confirms that the exponent varies with different orders. This may be caused by reduced loss coefficients at bifurcations when the value of exponent is approximately equal to 2 (7, 21). When AER increases in the lower orders, large loss coefficients, coupled with other factors (e.g., the increase of total cross-sectional area, vessel number, and bifurcations due to the fractal nature of the coronary vasculature) may contribute to large energy losses. This loss of energy is necessary to reduce flow velocity to ensure sufficient transit time for transport of oxygen and nutrients in the capillaries.

Our laboratory previously studied the bifurcation asymmetry in coronary arterial vessels of porcine hearts (7, 11, 16). We found a power-law dependence of flow distribution on the diameter asymmetry at a bifurcation. This implies that a small increase in diameter asymmetry ratio may cause a large increase in flow asymmetry at a bifurcation. In the present study, it was found that the ratio of $D_l$ to $D_m$ remained uniform for the epicardial vessels, but changed significantly for the transmural and perfusion subnetworks. This implies that the flow distribution for the epicardial vessels is relatively uniform.

**Anatomical reconstructions.** In a previous 3D reconstruction of the entire coronary arterial tree (10), the bifurcation asymmetry data were required to reproduce a faithful reconstruction of the coronary vascular tree. Briefly, the reconstruction procedure began with the most proximal segment. The diameter for the vessel was generated using a uniform random number generator. Once the diameter of the first segment was determined, the diameters for the rest of the segments that belong to the same element were generated using a normal random number generator with parameters that conformed to the intrainelement $D_l/D_m$ mean and SD statistics for the corresponding order. Next, the diameters of the segments that branch from the first element were generated based on the $D_l/D_m$ interelement statistics, namely the ARM. The $D_l/D_m$ interelement statistics were used for the segments that stem from the distal segment in the mother element. The diameter assignment for the rest of the segments for each of the elements followed the same scheme as described above. This procedure was repeated for all segments in a top-down manner to the capillaries. The outcomes were reconstructions of the entire coronary arterial trees, consistent with measurements. The data provided here are expected to provide further realism to future coronary vascular reconstructions.

**Critique of methods.** Although the bifurcation asymmetry is an important factor for flow distribution, it is unlikely the only determinant. The flow distribution can be affected by many factors, such as the myocardial contraction (1), pulsatile flow (7, 9), vascular tone (5), duration of systole (5), and so on (Ref. 2, 20 and unpublished observations). Hence, an integration of morphometric, rheological, and mechanical factors is needed to fully understand flow distribution at a bifurcation.

Although the relative flow distribution at a bifurcation can be captured by this analysis, the spatial heterogeneity of myocardial perfusion cannot be studied by the present data alone. This would require knowledge of the volume of myocardium perfused by a particular vessel, which is not provided in this study. Although heterogeneous distribution of flow along the arterial branches can be computed from the present data, the perfusion/unit volume of myocardium perfused by those branches may still be homogeneous. A full analysis of flow heterogeneity requires the present data, along with 3D data on the vessel/tissue relation (Ref. 10 and unpublished observations).

Although a local minima exists for $D_l/D_m$, as determined from a model-dependent (Fig. 1) and -independent analysis (Fig. 5), the exact location may be uncertain due to the relative scarcity of data in that region (Fig. 5). As reported previously, the smaller vessels (approximately <40 mm) are measured from histology, while larger vessels (>40 mm) are determined from casts (12). The overlap of the data seems to occur in the region of local minima. Despite the relative scarcity of data in
this region, there are many overlapping data points. The manual (raw) data of LAD, LCx, and RCA trees encompass 11,201 measurements, in which there are 246 measurements in the regions of mother diameter in the range of 35–60 μm. Clearly, this is sufficient data to statistically define the character of the curve and confirm the existence of a local minimum.

Significance of study. The present study indicates that the arterial vessels in order 5 demarcate an interesting transition in structure and function. These findings may further support the role of microvasculature as a regulatory module or unit. In addition to the functional implications, the data are essential for faithful reconstructions of the coronary vasculature. Since the diameter is the most significant hemodynamic parameter, the present data on the local diameter asymmetry can be used to physically constrain the reconstructions of full coronary vascular networks and improve previous 3D reconstructions.

**APPENDIX**

Several scaling laws have been determined for the coronary arterial tree (18, 19), which can be written as follows:

\[
\frac{Q}{Q_{\text{max}}} = \left( \frac{D}{D_{\text{max}}} \right)^b \tag{A1}
\]

\[
\frac{D}{D_{\text{max}}} = \left( \frac{L}{L_{\text{max}}} \right)^x \tag{A2}
\]

\[
V = \left( \frac{L}{L_{\text{max}}} \right) \tag{A3}
\]

\[
\frac{Q}{Q_{\text{max}}} = \left( \frac{V}{V_{\text{max}}} \right)^\beta \tag{A4}
\]

\[
R^c (= \frac{\Delta P^c}{Q}) = \left( \frac{U}{U_{\text{max}}} \right)^{3-\varepsilon/\chi} \tag{A5}
\]

where \(D\) and \(Q\) represent diameter and mean blood flow of a stem, respectively, and \(L, V, R^c,\) and \(\Delta P^c\) represent the cumulative length and volume of a crown, crown resistance, and the pressure drop, respectively. A stem was considered as a vessel segment that perfuses a tree or a crown (a subtree proximal to the stem). The subscript “max” represents the corresponding parameters at the inlet of the entire arterial tree. From Eqs. A1–A5, we can obtain the relationship between crown resistance and diameter of the stem, which can be written as:

\[
R^c = \frac{\Delta P^c}{Q} = \left( \frac{D}{D_{\text{max}}} \right)^{3-\varepsilon/\chi} \tag{A6}
\]

We define the parameter \(\alpha\) as \((3 - \varepsilon/\chi)/\chi\), which is numerically equal to approximately \(-2\) (see Table 1 in Ref. 18). From Eq. A6, we obtain the approximate relation:

\[
R^c = \left( \frac{D}{D_{\text{max}}} \right)^{3-\varepsilon/\chi} \tag{A7}
\]

where \(R^c\) and \(R^s\) are the resistance of crown proximal to large and small daughter vessels, respectively; and \(D_l\) and \(D_s\) are the diameter of large and small daughter vessels, respectively. If we define \(S_D = D_l/D_s\) as in Ref. 10, Eq. A7 can be written as:

\[
R^c = S_D^{3-\varepsilon/\chi} \tag{A8}
\]

The exponent \(\delta\) in Eq. A1 is numerically equal to \(-2\) (see Table 1 in Ref. 18). Hence, Eq. A1 is written as:

where \(Q_l\) and \(Q_s\) are mean blood flow in the large and small daughter vessels, respectively. Equations A8 and A9 relate the resistance and flow asymmetry to the diameter asymmetry at a bifurcation. These relations reflect structure-function relations.

A hemodynamic connection to the AER can be made as follows. From mass conservation, we have:

\[
Q_m = Q_l + Q_s \tag{A10}
\]

where \(Q_m\) is mean blood flow in the mother vessel. Equation A10 can be written as:

\[
U_m A_m = U_l A_l + U_s A_s \tag{A11a}
\]

or

\[
U_m = \frac{U_l A_l + U_s A_s}{A_m} \tag{A11b}
\]

where \(U_l, U_s,\) and \(U_m\) are the mean velocities, and \(A_l, A_s,\) and \(A_m\) are the corresponding cross-sectional areas. If we assume \(U_l \equiv U_s,\) Eq. A11 can be written as:

\[
\frac{U_m}{U_l} = \frac{A_l + A_s}{A_m} = \frac{D_l}{D_m}^2 + \frac{D_s}{D_m}^2 = \text{AER} \tag{A12}
\]

For a Murray-type relation \(Q \sim D^3\) (24), we can express the wall shear stress \(\tau\) as:

\[
\tau = \frac{3\mu Q}{\pi D^4} \sim D^{3-\varepsilon/\chi} \tag{A13}
\]

where \(\mu\) is blood viscosity. Equations A13 shows the relation between wall shear stress and exponent \(\varepsilon/\chi\).

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**REFERENCES**


