Bifurcation asymmetry of the porcine coronary vasculature and its implications on coronary flow heterogeneity

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Submitted 19 April 2004; accepted in final form 30 July 2004

Kalsho, Ghada, and Ghassan S. Kassab. Bifurcation asymmetry of the porcine coronary vasculature and its implications on coronary flow heterogeneity. Am J Physiol Heart Circ Physiol 287: H2493–H2500, 2004; doi:10.1152/ajpheart.00371.2004.—The branching pattern of the coronary arteries and veins is asymmetric, i.e., many small vessels branch off of a large trunk such that the two daughter vessels at a bifurcation are of unequal diameters and lengths. One important implication of the geometric vascular asymmetry is the dispersion of blood flow at a bifurcation, which leads to large spatial heterogeneity of myocardial blood flow. To document the asymmetric branching pattern of the coronary vessels, we computed an asymmetry ratio for the diameters and lengths of all vessels, defined as the ratio of the daughter diameters and lengths, respectively. Previous data from silicone elastomer cast of the entire coronary vasculature including arteries, arterioles, venules, and veins were analyzed. Data on smaller vessels were obtained from histological specimens by optical sectioning, whereas data on larger vessels were obtained from vascular casts. Asymmetry ratios for vascular areas, volumes, resistances, and flows of the various daughter vessels were computed from the asymmetry ratios of diameters and lengths for every order of mother vessel. The results show that the largest orders of arterial and venous vessels are most asymmetric and the degree of asymmetry decreases toward the smaller vessels. Furthermore, the diameter asymmetry at a bifurcation is significantly larger for the coronary veins (1.7–6.8 for sinus veins) than the corresponding arteries (1.5–5.8 for left anterior descending coronary artery) for orders 2–10, respectively. The reported diameter asymmetry at a bifurcation leads to significant heterogeneity of blood flow at a bifurcation. Hence, the present data quantify the dispersion of blood flow at a bifurcation and are essential for understanding flow heterogeneity in the coronary circulation.

Asymmetry ratio; order number; flow heterogeneity; Poiseuille’s resistance; coronary arteries

Myocardial blood flow distribution has been investigated by many authors (see reviews in Refs. 2 and 5). It has been well established that myocardial perfusion is spatially heterogeneous showing a 6- to 10-fold range in normal hearts (2). Bassingthwaighte and colleagues (2) were the first to recognize the fractal nature of coronary flow heterogeneity. They proposed fractal networks to predict the dependence of relative dispersion (SD/mean) on spatial resolution of the perfusion measurements (23). Their model entailed asymmetry of flow distribution in each bifurcation of a fractal tree. It was shown that the simplest fractal model that consists of constant branching asymmetry at each bifurcation predicts the flow data fairly well. If the degree of asymmetry was made to increase with successive branching in the fractal model, however, a better fit to data was obtained. The obvious question is does the coronary arterial tree possess the asymmetry postulated by the fractal models, and, if so, does the asymmetry vary along the bifurcations? The present study was designed to address these issues.

Our hypothesis is that the asymmetry of vascular geometry at a bifurcation is an important determinant of coronary blood flow heterogeneity. We have previously described the branching pattern (connectivity and longitudinal position matrices) and vascular geometry (diameters and lengths) of the coronary vasculature using the diameter-defined Strahler system (7, 10, 22). We found the branching pattern and vascular geometry to be quite asymmetric, which necessitated the use of the diameter-defined Strahler system. The asymmetry was most pronounced for the epicardial vessels that give rise to transmural vessels in “large trunk-small twig” patterns. The asymmetry of the branching pattern was reflected by the pattern of connectivity and longitudinal position matrices and the segments-per-element ratios.

In the present study, we describe the bifurcation asymmetry in terms of local parameters at a bifurcation called asymmetry ratios. For a given mother vessel, we defined the diameter and length asymmetry ratio as the ratio of the daughter diameters and lengths, respectively. The diameter and length ratios were computed for each mother vessel throughout the coronary vasculature (from arteries to arterioles and from venules to veins). The resulting diameter and length asymmetry ratios were used to compute the asymmetry of area, volume, resistance, and flow at various bifurcations throughout the coronary vasculature. These data allow us to predict the flow heterogeneity at a bifurcation along with other important hemodynamic parameters. Furthermore, these data are necessary for the reconstruction of coronary vascular circuits for future hemodynamic analysis.

METHODS

All experiments were performed in accordance with national and local ethical guidelines, including the Institute of Laboratory Animal Resources, National Institutes of Health Guide for the Care and Use of Laboratory Animals, and University of California-Irvine policies regarding the use of animals in research.

Available data. We have previously described in detail the methods of preparation, measurement, and morphometric analysis of the right coronary artery (RCA), left anterior descending (LAD) coronary artery, left circumflex (LCx) artery, coronary sinus, and thebesian veins (10, 11). The morphometric data on the coronary vessels of diameters <50 μm were obtained from histological specimens, whereas the morphometric data on vessels of diameters >50 μm were obtained from cast studies as described in Kassab et al. (10). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
morphometric measurements (diameters, lengths, and node-to-node connectivity) of the microvasculature were made by changing the focal plane through the thickness of the histological sections. For cast studies, the trunks of major coronary arteries and veins were sketched, and their segments measured down to ~50 μm in diameter. The raw coronary morphometric data showing node-to-node connectivity, diameters, and lengths are available on http://cvbimtech.eng.uci.edu.

Once the morphometric measurements were completed, we organized the segments and their diameters and lengths in terms of the diameter-defined Strahler’s ordering scheme as described in Refs. 7 and 10. Briefly, the capillary blood vessels are defined as vessels of order 0. The smallest arterioles supplying blood to the capillaries are assigned an order number of 1. The smallest venules draining the capillaries are assigned an order number of -1. When two arterioles of order 1 meet, the confluent vessel is given an order number of 2 if its diameter exceeds the diameters of the order 1 vessels by an amount specified by a set of formulas or diameter criterion (10) or remain as order 1 if the diameter of the confluent is not larger than the amount specified by the formulas. When an order 2 artery meets another order 1 artery, the order number of the confluent is 3 if its diameter is larger by an amount specified by the diameter criterion or remains at 2 if its diameter does not increase sufficiently. This process was continued until all arterial segments were arranged in increasing diameter and assigned the order numbers 1, 2, 3, ..., n. Similarly, the veins are assigned the orders -1, -2, -3, ..., -n. The criterion is a value that is midway between the mean diameter of order n + 1SD and the mean diameter of the order n - 1SD for all n from 1 upward (10).

Asymmetry at a bifurcation. With the existence of a full set of ordered data on the coronary vasculature, we proceeded to define and compute the asymmetry ratios by considering each bifurcation node. The largest and the two smaller vessels meeting at a node are called the mother and daughter vessels, respectively, if the order numbers of these vessels are so arranged that n = m = k with diameters Dn ≥ Dm ≥ Dk. Unlike the coronary arteries, which have cylindrical cross sections and can be quantified by a diameter, the veins have approximately elliptical cross sections. We shall denote the major and minor axes diameters of the coronary veins as Dmaj and Dmin, respectively. For each mother vessel, n, the asymmetry ratio for the major and minor diameters of the daughter vessels, Smin and Smaj, are the ratios defined by

\[ S_{maj} = \frac{D_{maj,m}}{D_{maj,k}} \]

(1a)

and

\[ S_{min} = \frac{D_{min,m}}{D_{min,k}} \]

(1b)

where \( S_{maj} \) ≥ 1, by definition. Analogously, the asymmetry ratio for the length of the daughter vessels, Sn, is the ratio defined by

\[ S_n = \frac{l_n}{l_l} \]

(2)

The asymmetry ratios of the vessel cross-sectional area, A, and volume, V, are similarly defined by

\[ S_A = S_{maj}S_{maj} \]

(3)

and

\[ S_V = S_A S_n \]

(4)

because the cross-sectional area of an elliptical venous vessel is

\[ A = \left( \frac{\pi}{4} \right) D_{maj}D_{min} \]

and the volume of a branch is the product of its cross-sectional area and length (11).

The flow resistance, R, for a vein with an elliptical cross section is computed as follows: assuming that the daughter vessels are long and slender, that the flow is laminar and steady, and that the flow disturbances at the entry and exit sections are negligible, then the resistance to flow in the daughter vessels is given by (Ref. 11)

\[ R = \frac{64\mu l}{\pi} \left[ \frac{(D_{maj}^2 + D_{min}^2)}{(D_{maj}D_{min})} \right] \]

(5)

where \( \mu \) is the apparent viscosity. Hence, we can define an asymmetry ratio of the flow resistance by the equation

\[ S_R = S_A S_{maj} \left[ \frac{S_{maj} + S_{maj}}{S_{maj} + S_{maj}} \right] \]

(6a)

where

\[ S_{maj} = \frac{D_{maj,m} + D_{maj,k}}{D_{maj,k} + D_{maj,k}} \]

(6b)

\( S_{maj} \) is defined as the apparent viscosity ratio of the two daughter branches (\( \mu_{maj}/\mu_{maj} \)). The data on the variation of viscosity with vessel diameter and hematocrit are given by Pries et al. (19), which was used in our calculations. They proposed a modified viscosity relationship based on a compilation of literature data on relative blood viscosity in tube flow in vitro and in vivo, which reflects the Fahraeus-Lindqvist effect as given by:

\[ \mu_{\text{vivo}} = \left( 1 + \frac{\mu_{maj}}{\mu_{maj}} \right) \left( \frac{D}{D - 1.1} \right)^2 \left( \frac{D}{D - 1.1} \right)^2 \]

(7)

where \( D \) is the vessel diameter. This relationship was used throughout the coronary vasculature for a given vessel diameter D at a hematocrit of 0.45.

For the coronary arteries, the major and minor axes diameters are equal, and hence Eq. 1 reduces to \( S_D = (D_{maj}/D_{maj}) \). Similarly, Eq. 3 becomes \( S_A = S_{maj}r^2 \). Finally, Eq. 5 becomes Poiseull’s resistance (i.e., \( R = 128 \mu l/mD \)), and Eq. 6 reduces to \( SR = S_A S_{maj} \).

Horsfield et al. (6) have previously defined the difference in order \( \Delta = m - k \) to describe the asymmetry at a bifurcation of an airway. Additionally, we shall introduce a parameter \( \varepsilon = (n - m) \), which is the difference between the order of the mother vessel and that of the larger daughter.

Data analysis. All asymmetry parameters were curve fitted by a relation of the form ln(Sa) = a + b ln + c2, where ln is the natural logarithm and x corresponds to diameter (D), length (l), cross-sectional area (A), volume (V), or resistance (R). The empirical constants a, b, and c were determined by a least-squares fit. ANOVA was used to detect differences among different orders for the various parameters (i.e., SD, S, SA, SA, S, S, and ε). Although our data are skewed, it is generally accepted that ANOVA is robust to violations of the normality assumption (4). Statistical significance was accepted at the 0.05 level.

RESULTS

We obtained data from the entire range of orders throughout the coronary arterial and venous trees. A total of 5,082, 4,014, and 1,946 arterial bifurcations of RCA, LAD, and LCx arteries and 13,778 and 4,505 venous bifurcations of coronary sinus and thebesian veins and their branches, respectively, was analyzed. Probability frequency distribution functions were obtained for \( S_D \) and \( S_l \) for each order of the entire coronary vasculature and were found to be right skewed. Tables 1–5 show a summary of the means ± SD of \( S_D \) and \( S_l \) in RCA, LAD, and LCx arteries and sinusal and thebesian veins, respectively. Using ANOVA, we found a significant dependence of \( S_D \) and \( S_l \) on the order number of the mother vessel. We also
found that, at a given order number, the $S_D$ for the venous trees was significantly larger than those of the corresponding arteries (orders 2–10). The $S_I$ was larger for veins of orders 3–6 but smaller for orders 2 and 7–10 compared with arteries. The data on $S_D$ and $S_I$ were represented by a quadratic exponential curve fit and are summarized in Table 6.

Although $S_D \geq 1$, by definition, $S_I$ may be less than or greater than 1. We quantified the fraction of larger daughter vessels that also have longer lengths, i.e., $F_{lm} > l_i = [N(l_m > l_i)/N(l_m > l_i)] + [N(l_m > l_i)]$, where $N(l_m > l_i)$ and $N(l_m > l_i)$ represent the number of bifurcations where the larger daughter diameter vessel has a longer and shorter length, respectively. Figure 1 shows the relationship between $F_{lm} > l_i$ and the order number of the mother vessel throughout the coronary vasculature.

The $S_A$ and $S_C$ of daughter branches of coronary blood vessels of order $n$ were computed from the $S_D$ and $S_I$ as given by Eqs. 3 and 4, respectively. Figures 2 and 3 show the relationship between the mean $S_A$ and $S_C$, respectively, for the entire range of orders. It can be seen that $S_A$ and $S_C$ increase rapidly with the order number for the coronary arteries and veins, becoming very large at highest order numbers. The $S_A$ is significantly larger for the veins compared with the arteries for orders 2–10, which is similar to $S_D$. The $S_C$ for the veins was only significantly larger for orders 2–6. The curve fits of $S_A$ and $S_C$ are summarized in Table 6.

The ratio of the Poiseuille’s resistance of the daughter branches, $S_R$, was computed from the diameter (major and minor), length, and viscosity ratios as given by Eq. 6. The relationship between $S_R$ and the order number of the mother vessel is shown in Fig. 4. We found a significant effect of the mother vessel, such that as the order of the mother vessel increases, both the arteries and veins show a significant increase in asymmetry. The $S_R$ was significantly larger for the veins of orders 4–8 compared with arteries. Furthermore, the $S_R$ was significantly smaller (more asymmetric) for the thebesian compared with sinusual veins for orders −6 to −10. Table 6 summarizes the empirical constants of $S_R$ for a particular curve fit.

The asymmetry can be described with respect to the order numbers at a bifurcation. The order asymmetry ratio between daughter vessels is given by $\Delta = (m - k)$, as shown in Fig. 5. The deviation from symmetry ($\Delta = 0$) is largest for the larger vessels. The value of $\Delta$ was significantly larger for the veins compared with arteries for orders 3 and 5–11. The order asymmetry between mother and larger daughter vessel is given by $\epsilon = (n - m)$ and is shown in Fig. 6. Similarly, it is clear that $S_{maj} > S_{min}$ major diameter asymmetry ratio of daughter vessels.

### Table 1. Asymmetry ratios of diameters and lengths of daughter vessels in each order of mother vessels in the RCA and its branches of the pig

<table>
<thead>
<tr>
<th>Mother Vessel, µm</th>
<th>$S_D$</th>
<th>$S_I$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>9.57 ± 1.03</td>
<td>1.34 ± 0.33</td>
</tr>
<tr>
<td>2</td>
<td>13.2 ± 1.73</td>
<td>1.39 ± 0.36</td>
</tr>
<tr>
<td>3</td>
<td>19.0 ± 2.85</td>
<td>1.55 ± 0.46</td>
</tr>
<tr>
<td>4</td>
<td>29.6 ± 4.14</td>
<td>1.73 ± 0.70</td>
</tr>
<tr>
<td>5</td>
<td>70.1 ± 15.1</td>
<td>1.74 ± 0.80</td>
</tr>
<tr>
<td>6</td>
<td>139 ± 30.6</td>
<td>2.41 ± 1.43</td>
</tr>
<tr>
<td>7</td>
<td>259 ± 45.4</td>
<td>3.69 ± 2.68</td>
</tr>
<tr>
<td>8</td>
<td>422 ± 62.0</td>
<td>4.77 ± 3.77</td>
</tr>
<tr>
<td>9</td>
<td>712 ± 133</td>
<td>5.61 ± 5.24</td>
</tr>
<tr>
<td>10</td>
<td>1,399 ± 386</td>
<td>6.56 ± 4.92</td>
</tr>
<tr>
<td>11</td>
<td>2,327 ± 258</td>
<td>7.50 ± 6.64</td>
</tr>
</tbody>
</table>

RCA, right coronary artery; $S_D$, diameter asymmetry ratio of daughter vessels; $S_I$, length asymmetry ratio of daughter vessels.

### Table 2. Asymmetry ratios of diameters and lengths of daughter vessels in each order of mother vessels in the LAD artery and its branches of the pig

<table>
<thead>
<tr>
<th>Mother Vessel, µm</th>
<th>$S_D$</th>
<th>$S_I$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>9.22 ± 0.95</td>
<td>1.42 ± 0.36</td>
</tr>
<tr>
<td>2</td>
<td>12.8 ± 1.76</td>
<td>1.47 ± 0.42</td>
</tr>
<tr>
<td>3</td>
<td>18.5 ± 2.55</td>
<td>1.52 ± 0.46</td>
</tr>
<tr>
<td>4</td>
<td>29.2 ± 3.55</td>
<td>1.69 ± 0.60</td>
</tr>
<tr>
<td>5</td>
<td>80.4 ± 17.4</td>
<td>1.84 ± 1.16</td>
</tr>
<tr>
<td>6</td>
<td>156 ± 36.2</td>
<td>2.35 ± 1.93</td>
</tr>
<tr>
<td>7</td>
<td>305 ± 53.0</td>
<td>4.05 ± 3.42</td>
</tr>
<tr>
<td>8</td>
<td>468 ± 56.6</td>
<td>4.75 ± 4.10</td>
</tr>
<tr>
<td>9</td>
<td>713 ± 118</td>
<td>5.06 ± 3.72</td>
</tr>
<tr>
<td>10</td>
<td>1,532 ± 367</td>
<td>3.85 ± 4.36</td>
</tr>
<tr>
<td>11</td>
<td>3,369 ± 1,055</td>
<td>7.12 ± 3.43</td>
</tr>
</tbody>
</table>

LAD, left anterior descending.

### Table 3. Asymmetry ratios of diameters and lengths of daughter vessels in each order of mother vessels in the LCx artery and its branches of the pig

<table>
<thead>
<tr>
<th>Mother Vessel, µm</th>
<th>$S_D$</th>
<th>$S_I$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>9.21 ± 0.95</td>
<td>1.43 ± 0.37</td>
</tr>
<tr>
<td>2</td>
<td>12.8 ± 1.76</td>
<td>1.47 ± 0.42</td>
</tr>
<tr>
<td>3</td>
<td>18.5 ± 2.55</td>
<td>1.52 ± 0.46</td>
</tr>
<tr>
<td>4</td>
<td>27.5 ± 3.58</td>
<td>1.67 ± 0.50</td>
</tr>
<tr>
<td>5</td>
<td>83.6 ± 17.1</td>
<td>1.70 ± 0.70</td>
</tr>
<tr>
<td>6</td>
<td>149 ± 30.5</td>
<td>1.74 ± 0.80</td>
</tr>
<tr>
<td>7</td>
<td>290 ± 58.1</td>
<td>2.61 ± 1.60</td>
</tr>
<tr>
<td>8</td>
<td>467 ± 75.4</td>
<td>3.39 ± 2.05</td>
</tr>
<tr>
<td>9</td>
<td>1,011 ± 268</td>
<td>4.30 ± 3.39</td>
</tr>
<tr>
<td>10</td>
<td>2,560 ± 323</td>
<td>5.84 ± 4.61</td>
</tr>
</tbody>
</table>

LCx, left circumflex.
Table 5. Asymmetry ratios of major diameters and lengths of daughter vessels in each order of mother vessels in the Thebesian veins and their branches of the pig

<table>
<thead>
<tr>
<th>Mother Vessel, μm</th>
<th>$S_{D_{maj}}$</th>
<th>$S_l$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>11.7 ± 2.12</td>
<td>1.38 ± 0.37</td>
</tr>
<tr>
<td>2</td>
<td>18.8 ± 3.22</td>
<td>1.71 ± 0.65</td>
</tr>
<tr>
<td>3</td>
<td>27.1 ± 5.20</td>
<td>1.90 ± 0.81</td>
</tr>
<tr>
<td>4</td>
<td>56.6 ± 14.5</td>
<td>2.13 ± 1.48</td>
</tr>
<tr>
<td>5</td>
<td>111 ± 24.6</td>
<td>3.03 ± 2.46</td>
</tr>
<tr>
<td>6</td>
<td>189 ± 41.1</td>
<td>4.14 ± 3.55</td>
</tr>
<tr>
<td>7</td>
<td>302 ± 83.2</td>
<td>5.60 ± 4.85</td>
</tr>
<tr>
<td>8</td>
<td>408 ± 81.1</td>
<td>6.99 ± 6.24</td>
</tr>
<tr>
<td>9</td>
<td>586 ± 98.3</td>
<td>7.36 ± 7.70</td>
</tr>
<tr>
<td>10</td>
<td>766 ± 123</td>
<td>11.8 ± 9.51</td>
</tr>
</tbody>
</table>

The asymmetry (deviation from ε = 1) is greatest for the larger vessels.

The coefficient of variance (CV = SD/mean) was determined for the various asymmetry quantities for each order number of mother vessel. Figure 7 shows the CV of $S_D$ for the arterial and venous trees. The CV for the $S_D$ is significantly larger for the venous trees compared with the arterial trees.

**DISCUSSION**

Asymmetry at a bifurcation. Circuitry asymmetry has many measures. In this study, we described vascular asymmetry at a bifurcation with the use of ratios of diameter and length of daughter vessels ($S_D$ and $S_l$, respectively). Our data show that the largest mean $S_D$ is ~10 and 12 for the largest arterial and venous bifurcations (Tables 1 and 5), respectively, which implies that the larger daughter vessel is on the average 10 and 12 times greater than its sister vessel.

As we have previously stated, $S_D \geq 1$ by definition. $S_l$, on the other hand, is not bound in this way because a larger diameter daughter vessel may be shorter than the smaller daughter vessel. The fraction of larger diameter daughter vessels that have longer lengths than the smaller vessels is shown in Fig. 1. It is interesting to note that for the smallest five orders, ~50% of the daughter vessels with larger diameters also have longer lengths. For the larger mother vessels, however, a higher percentage of daughter vessels of larger diameter have longer lengths.

Knowledge of $S_D$ and $S_l$ allows the determination of $S_A$, $S_v$, and $S_0$ of the two daughter branches of each mother vessel. The $S_A$ is simply the square of $S_D$. However, the $S_A$ is not simply the square of mean $S_D$ because of the skewed shape of the distribution. The $S_0$ is the product of $S_A$ and $S_l$. The $S_A$ and $S_v$ are greatest for the larger vessels and decrease toward the order number of the mother vessel of the coronary vasculature.

![Fig. 1. Relationship between the fraction of larger daughter vessels that also have longer lengths than the smaller daughter vessels and the order number of the mother vessel of the coronary vasculature.](http://ajpheart.physiology.org/)

![Fig. 2. Relationship between the cross-sectional area ratio of daughter vessels and the order number of the mother vessel of the coronary vasculature.](http://ajpheart.physiology.org/)
smaller vessels. The mean asymmetry ratios of area and volume at the highest orders are \(150\) and \(560\) (RCA) and \(180\) and \(360\) (sinus vein), as shown in Figs. 2 and 3, respectively. The enormity of the asymmetry is remarkable. Finally, the \(S_R\) considers the \(S_D, S_l, \) and \(S_m\) as expressed by Eq. 6 and shown in Fig. 4. The \(S_R\) is \(< 1\) because a larger vessel has a lower resistance than a smaller vessel. The \(S_D\) dominates over the \(S_l\) because of the fourth power exponent.

Comparison with other studies. Kassab et al. (9, 13) have previously described the bifurcation asymmetry of the right ventricular branches in normal and hypertensive right ventricles. They found that the \(S_D\) and \(S_l\) increase significantly with order number for both control and hypertensive hearts. As expected, the control data on the right ventricular branches were similar to the present data for the RCA tree.

Horsfield et al. (6) introduced the concept of \(\Delta\) to describe the branching asymmetry at a bifurcation. They showed that a fixed value of \(\Delta\) implies a property of self-similarity, i.e., each succeeding bifurcation having the branching pattern and relative dimensions of the parent vessel but on a smaller scale. In the present study, we found that the value of \(\Delta\) varies with order number. It is interesting to note that the first six orders of arterial trees have a fairly uniform value of \(\Delta\) of \(\sim 1\) but increase with higher orders (Fig. 5). We have added a new parameter, \(\epsilon\), which describes the order asymmetry between mother and larger daughter vessel (Fig. 6). The collective data on \(\Delta\) and \(\epsilon\) can be used to reconstruct the order connectivity of the vascular tree.

Relation of asymmetry ratios to design rules. We have previously predicted several structure-structure and structure-function relationships for coronary arterial trees (29). In the process, a vessel segment was defined as a stem that perfuses a tree or a crown (25). The crown includes all vessels proximal to the stem including the first segment of capillary vessels. If \(A\) and \(Q\) represent the mean cross-sectional area and blood flow of a stem, respectively, and \(V\) and \(L\) represent the cumulative

Fig. 3. Relationship between the volume ratio of daughter vessels and the order number of the mother vessel of the coronary vasculature.

Fig. 4. Relationship between the Poiseuille’s resistance ratio of daughter vessels and the order number of the mother vessel of the coronary vasculature.

Fig. 5. Relationship between the difference in the order between the two daughter vessels, \(\Delta\), and the order number of the mother vessel of the coronary vasculature.

Fig. 6. Relationship between the difference in the order between the mother and larger daughter vessel, \(\epsilon\), and the order number of the mother vessel of the coronary vasculature.
The asymmetry ratio for the crown length increases with $S$ length $S$ of the entire tree. The values of volume of the entire tree of interest, and the cumulative arterial and flow of the most proximal stem to the arterial tree, the predicted the following relationships:

$$D_{\text{max}} = \left( \frac{L}{L_{\text{max}}} \right)^{\gamma}$$

$$V_{\text{max}} = \left( \frac{L}{L_{\text{max}}} \right)^{\beta}$$

$$Q_{\text{max}} = \left( \frac{D}{D_{\text{max}}} \right)^{\delta}$$

where $D_{\text{max}}$, $Q_{\text{max}}$, $V_{\text{max}}$, and $L_{\text{max}}$ correspond to the diameter and flow of the most proximal stem to the arterial tree, the volume of the entire tree of interest, and the cumulative arterial length of the entire tree. The values of $\gamma$, $\beta$, and $\delta$ have been previously reported as 0.41, 1.35, and 2.42 (RCA); 0.41, 1.37, and 2.45 (LAD); and 0.40, 1.38, and 2.47 (LCx) for the arterial trees, respectively (29). These relationships have been determined and validated in the following three ways: 1) a hemodynamic analysis of coronary arterial blood flow based on detailed anatomic data yields these relationships over the entire arterial network (12); 2) a generalization of Murray’s cost function and conservation of energy predict the same result over the entire tree (29); and 3) in vivo data on flow, length and volume using digital subtraction angiography (28) verified the relationships for vessels proximal to 0.5 mm in diameter as observed in an angiogram.

To relate the asymmetry ratios of stem quantities (diameter, cross-sectional area, and flow) to crown quantities (crown length and volume), we combined Eq. 8 with Eq. 1 for an artery to yield

$$S_L = S_D^{\delta/\gamma}$$

or

$$S_L = S_D^{\delta/\gamma}$$

since $\gamma \delta = 1$, as shown previously (29). $S_L$ is the crown asymmetry length compared with the segment asymmetry length $S_r$. The exponent of $Eqs. 11$ has a value of $\sim 2.5$. Hence, the asymmetry ratio for the crown length increases with $S_D$ raised to the power of 2.5. Similarly, the $S_V$ and $S_Q$ (Eqs. 9 and 10) can be expressed in terms of $S_D$ as:

$$S_V = S_D^{\delta/\gamma}$$

and

$$S_Q = S_D^{\delta/\gamma}$$

respectively. The exponents of $Eqs. 12$ and 13 are $\sim 3.4$ and 2.5, respectively. Murray’s law predicts a fixed value of 3 for $\delta$ irrespective of the organ of interest based on the minimum energy hypothesis (18).

We have also previously verified a form for the crown resistance ($R_c$), i.e., equivalent resistance of vessels in a crown, as

$$R_c = k_R \frac{L^3}{V_2 - V_1}$$

where $k_R$ and $\varepsilon$ are constants determined from experimental data (10). The reported value of $\varepsilon$ was approximately $-0.55$ (29). The asymmetry ratio of the crown resistance can be expressed as

$$S_{R_c} = \frac{S_D^{3+\delta-2\beta}}{S_V^2}$$

Equations 11 and 12 can be combined with Eq. 15 to yield

$$S_{R_c} = S_Q^{\frac{3+\delta-2\beta}{4\gamma}}$$

The exponent is numerically equal to approximately $-1.3$, i.e., $S_{R_c}$ is $< 1$, similar to $S_R$. We can relate the asymmetry of flow to that of crown resistance if we combine Eqs. 13 and 16 and use $\gamma \delta = 1$ as

$$S_{R_c} = S_Q^{\frac{1+\delta}{1+\delta}}$$

Because $\delta$ is $\sim 2.5$, the exponent of Eq. 17 is $-0.52$. Hence, for the coronary arterial tree, $Eq. 17a$ can be reduced to

$$S_{R_c} = \frac{1}{\sqrt{S_Q}}$$

which is a remarkably simple relationship between flow asymmetry at a bifurcation and the crown asymmetry.

A relation between $S_{R_c}$ and $S_R$ can be determined if we combine Eq. 16 with Eq. 6 for a cylindrical vessel, i.e.,

$$S_{R_c} = \left( \frac{S_{R_c}}{S_R} \right)^{3+\delta-2\beta}$$

The exponent of $Eq. 17$ is obviously $-0.32$. Again, this can be simplified as

$$S_{R_c} = \left( \frac{S_R}{S_{R_c}} \right)^{1/3}$$

In the microcirculation, at the site of vascular resistance, $S_L$ and $S_{\mu}$ are $\sim 1$ (Tables 1–5) and hence $S_{R_c} \sim S_{R_c}^{1/3}$. This remarkably simple relation implies that the crown resistance ratio at a bifurcation can be determined from the resistance ratio of the daughter vessels for coronary microvessels. In summary, the conclusion of the above analysis is that the crown ratios (Eqs.
Implications of $S_D$ on flow heterogeneity. The bifurcation asymmetry of resistance may not be directly proportional to the flow asymmetry because the flow distribution depends on the total distal resistance (crown resistance) of the two daughter vessels, as shown in Eq. 17. Hence, it is desirable to have a more direct relationship between the geometric asymmetry ratios and the flow distribution. Such relationship is expressed by Eq. 13, which shows a power-law dependence of flow asymmetry on the diameter asymmetry. The implication of Eq. 13 is that a small increase in diameter asymmetry ratio can cause a large increase in flow asymmetry. Hence, the heterogeneity of flow at a bifurcation is very sensitive to the diameter ratio of daughter vessels.

The CV can be estimated for the asymmetry of flow. If we take the differential of Eq. 13 and divide it by Eq. 13, we obtain

$$\frac{\partial S_Q}{S_Q} = \delta \frac{\partial S_D}{S_D} \quad (19a)$$

or

$$CV(S_Q) = \delta CV(S_D) \quad (19b)$$

Hence, the $CV(S_Q)$ is proportional to the $CV(S_D)$ with $\delta$ (a value of 2.5) as the proportionality constant. We found that $CV(S_Q)$ of veins was significantly larger than that of arteries. Hence, the CV($S_Q$) at a venous bifurcation is expected to be greater than that at an arterial bifurcation. This result has important implications for coronary venous retroperfusion where blood supply to the ischemic myocardium may be provided by making an arterial anastomosis with the coronary venous system (15). It suggests that the flow delivery to the capillary vessels will be more heterogeneous than antegrade flow. We have previously shown that the capillary network homogenizes the blood flow supplied by the arterial tree (14).

Critique of methods. Although the coronary arterial tree is dominated by bifurcations (98% bifurcations, 2% trifurcations) (10), the coronary veins consists of 86%, 12.8%, 1%, and 0.2% bifurcations, trifurcations, quadrisacations, and quintiurcations, respectively (11). The present data apply only to the bifurcations but can be easily extended to trifurcations, etc. Furthermore, although the arteries have a fairly uniform diameter along their segment (i.e., diameters only change upon branching), the veins have more complex variations within segments. Because the measurement of venous diameter represents an average over the segment, the asymmetry ratio for the vein also represents an average in that sense. Finally, the asymmetry ratios may change with pressure because the coronary vessels are distensible. The present data correspond to a particular distribution of pressure through the diastolic state.

The present asymmetry ratios were expressed in terms of order numbers as determined by the diameter-defined Strahler system. Numerious ordering schemes exist, however, which may result in somewhat different asymmetry ratios. The Strahler’s scheme was used because it handles the asymmetry of the system very well (22). The diameter-defined modification was proposed to eliminate the overlap in the diameters between successive orders (7, 10). In a previous study (9), we considered the diameter of the mother vessel as an independent variable regardless of the order number. We found that the diameter asymmetry ratios were similar in both cases.

The asymmetry in diameters also affects the asymmetry of bifurcation angles. This issue has been examined in detail by Zamir and colleagues (27). Zamir (26) showed that in a nonsymmetrical bifurcation, the branching angle that the larger branch makes relative to the parent vessel decreases with an increase in asymmetry ratio. The angle data affect the optimality of vascular junctions as flow conduits and dictate the spatial position of the vessels relative to the myocardium.

Although asymmetry at bifurcation is an important determinant of flow distribution, it is unlikely to be the only determinant of flow heterogeneity. In the beating heart, a heterogeneous distribution of stresses can affect the perfusion pattern (1). The addition of coronary tone plays a major role in modulating regional flow (1). Although the present anatomy was obtained under dilated state, this case is applicable when the heart is stressed physiologically or in the presence of coronary artery disease. Although the coronary anatomy establishes the potential distribution of coronary flow, mechanical, metabolic (3, 21), neural (24), and signal transduction (20) dictate local perfusion of myocardium.

Significance of study. The present study shows that the large asymmetry at a bifurcation can result in significant asymmetry of flow and potentially large spatial heterogeneity of blood flow. We have previously shown that such geometric asymmetry can remodel in right ventricular hypertrophy during flow overload (9, 13). Hence, the asymmetry parameters may be important indices of flow distribution in the heart in health and disease.

The lumen cross-sectional area and length of coronary arteries and their blood volume and flow rate can be determined from an angiogram using digital subtraction angiography (8, 16, 17). Hence, the $S_P$, $S_L$, $S_V$, and $S_Q$ can be quantified and their relationships (Eqs. 11–13) can be established as signatures of normal patients where coronary disease can be studied in relation to changes in these relationships. Furthermore, knowledge of $S_P$ or $S_Q$ allows the determination of $S_R$ through Eqs. 16 or 17, respectively. The assessment of ratio of total arterial or crown resistance in a normal region compared with that in an ischemic or infarct region has obvious clinical significance.

An additional significance of the asymmetry ratios relates to the reconstruction of the full vascular arterial tree for blood flow analysis. The process of obtaining statistical morphometric data from a tree is unique, given that the same set of rules are followed each time (e.g., the diameter-defined Strahler system). The creation of a circuit from morphometric data, however, is a nonunique process. An infinite number of circuits can be created corresponding to a set of morphometric data but not uniquely specified by them. In addition to the connectivity and longitudinal position matrices and the diameters, lengths, and number of vessels previously reported, the proposed asymmetry ratios impose additional constraints on the reconstruction of tree circuits.

ACKNOWLEDGMENTS

We thank Winny Tan and Marli Amin for excellent technical assistance.
REFERENCES


