Scaling of myocardial mass to flow and morphometry of coronary arteries

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There is no doubt that scaling relations exist between myocardial mass and morphometry of coronary vasculature. The purpose of this study is to quantify several morphological (diameter, length, and volume) and functional (flow) parameters of the coronary arterial tree in relation to myocardial mass. Eight normal porcine hearts of 117–244 g (mean of 177.5 ± 32.7) were used in this study. Various coronary subtrees of the left anterior descending, right coronary, and left circumflex arteries were perfused at pressure of 100 mmHg with different colors of a polymer (Microfil) to obtain rubber casts of arterial trees corresponding to different regions of myocardial mass. Volume, diameter, and cumulative length of coronary arteries were reconstructed from casts to analyze their relationship to the perfused myocardial mass. Volumetric flow was measured in relationship with perfused myocardial mass. Our results show that arterial volume is linearly related to regional myocardial mass, whereas the sum of coronary arterial branch lengths, vessel diameters, and volumetric flow show an ~3/4, 3/8, and 3/4 power-law relationship, respectively, in relation to myocardial mass. These scaling laws suggest fundamental design principles underlying the structure-function relationship of the coronary arterial tree that may facilitate diagnosis and management of diffuse coronary artery disease.

METHODS

Animal preparation. All animal experiments were performed in accordance with national and local ethical guidelines, including the Institute of Laboratory Animal Research guidelines, Public Health Service policy, the Animal Welfare Act, and an approved Indiana University Purdue University Indianapolis protocol regarding the use of animals in research. The choice of the present animal model was based on the similarities between human and swine coronary vessels (6, 8, 9).

Eight hearts from normal Yorkshire swine of either sex with body weight of 25.1–38.8 kg (mean of 30.9 ± 4.2) were used in this study. The animals were fasted overnight. Surgical anesthesia was induced with TKX (Telazol 500 mg, Ketamine 250 mg, Xylazine 250 mg) and maintained with isofluurane 1–2%. Ventilation with 100% O2 was provided with a respirator to maintain PO2 and PCO2 at ~100 and 35 mmHg, respectively. The chest was opened through a midsternal thoracotomy, and an incision was made in the pericardium to reach the heart. The animals were then deeply anesthetized followed by an injection of a saturated potassium chloride (KCl) solution through the jugular vein to arrest the heart in diastole. The aorta was clamped to keep air bubbles from entering the coronary arteries, and the heart was excised and placed in a cold saline solution.

Heart preparation. To delineate various myocardial regions perfused by different coronary arterial trees, multiple cannulations with different cast colors were made. Two cannulations were made at different points (proximal and distal) along the main trunk of the left anterior descending (LAD) artery, three in the right coronary artery...
(RCA), and two in the left circumflex (LCX) artery. All vessel segments were cannulated under saline to avoid air bubbles and perfused with cardioplegic solution to flush out the blood. The seven vessel segments were individually perfused at pressure of 100 mmHg with cardioplegic solution, and the corresponding flows were measured by a flowmeter (Transonic Systems). The seven vessel segments were then perfused at pressure of 100 mmHg with seven different colors of a liquid polymer (Microfil, Flow Tech, Carver, MA) mixed with Cab-O-Sil M-5 (Cabot) to block the capillaries, resulting in the perfusion of the entire arterial tree down to precapillary levels. After the Microfil was allowed to harden for 45–60 min, the cannulas were removed, and the hearts were kept in the refrigerator for 2–3 days in saline solution to increase the strength of the silicone rubber before maceration (14).

Optical measurements of branching coronary arterial tree. After the cast material was completely hardened, the myocardium was cut in seven regions delineated by each color of the microfil compound (Fig. 1). Each region was weighted and macerated in 30% potassium hydroxide (KOH) solution for 5–7 days to remove the cardiac tissue and obtain a cast of the coronary arteries and their branches (Fig. 2). The cast was then rinsed several times in water until all macerated tissue was washed away. Each cast corresponding to the arterial tree segment was weighted, dissected into smaller pieces, and photographed using a stereomicroscope (SMZ 660, Nikon) and a color digital camera (STC 620, Sentech). The coronary arterial segments were reconstructed completely with the proximal lumen diameters, and the cumulative lengths of the tree were measured using an image analysis software (SigmaScan Pro 5.0). The volume (V) corresponding to each arterial tree was calculated from the weight (m) of the casts and the density ($\rho$) of the microfil compound ($V = m/\rho$).

Tree models. Two vascular circuits were considered. One, called the truncated tree model, was an actual reconstruction of the coronary arterial tree down to $\sim 1$ mm in diameter. This model corresponds to what would typically be observed in an angiogram (spatial resolution of $\sim 1$ mm), and hence has obvious clinical implications. The other model, called an extrapolated full tree model, is an idealization of the entire tree down to the capillary level. This model was generated using a combination of data obtained from the arterial casts and the extrapolation of data from the terminal diameters of the casts based on previously established tree growth algorithms of coronary arteries (19). Since it is impossible to experimentally obtain a complete cast of the entire vascular tree down to the capillary vessels, we used the data on those parts of the tree that were measured previously on the same size animals to extrapolate the data on those parts that were missing (19). The proximal branches obtained from casts were measured, while the microvessels were reconstructed using a computer algorithm (19). The full extrapolated model is useful to explore basic design principles of coronary arterial trees.

RESULTS

A scaling model of the form $Y = Y_0 m^b$, was fitted to the data where $Y$ is the cumulative volume, length, branch diameter, or flow; $Y_0$ is a normalization constant, and $b$ is the power-law exponent. The findings are summarized along with a least square fit model in Table 1.

Volume-mass relation. A significant linear relation was found between coronary arterial volume and myocardial mass in both models, as shown in Fig. 3. A least square fit exponent in the truncated tree model ($n = 4$) was $0.97 \pm 0.04$ with a correlation coefficient of 0.99, as shown in Fig. 3, top. In the full tree model ($n = 8$), the exponent was $1.05 \pm 0.06$ with a correlation coefficient of 0.99 (Fig. 3, bottom). The regression values were also compared with a scaling model that shows a significant fit (Table 1).

Length-mass relation. The relationship between normalized cumulative arterial lengths and myocardial mass for the truncated tree model is shown in Fig. 4, top. We found a power-law relation between these two parameters with an exponent of $0.76 \pm 0.07$ and a correlation coefficient of 0.98. Figure 4,
bottom, shows the relationship between normalized cumulative arterial lengths and myocardial mass for the full tree model. There was also a power-law relation with an exponent of 0.81 ± 0.12 ($r^2 = 0.93$). The means (±SD) of the exponents determined by curve fits of measurements and those predicted from the scaling model are shown in Table 1.

**Diameter-mass relation.** The relation between normalized proximal arterial diameters and myocardial mass for different segments of LAD, LCX, and RCA is shown in Fig. 5. The power-law relation observed between these two parameters has an exponent of 0.41 ± 0.05 ($r^2 = 0.87$). Table 1 also shows a comparison between the least-squares fit of the data and the values predicted by the scaling model fit for the full extrapolated model.

**Flow-mass relation.** The relationship between normalized arterial flow and myocardial mass for different segments of LAD, LCX, and RCA is shown in Fig. 6. We found a power-law relation with an exponent of 0.74 ± 0.04 ($r^2 = 0.97$). The regression values compared with the scaling model are shown in Table 1. The mean flow per mass (perfusion) for all the territories was 1.05 ± 0.16 ml min$^{-1}$ g$^{-1}$.

We also determined the V-L, V-D, and L-D relations based on the experimental data. A least-square fit of the V-L relation yields an exponent of 1.24 ± 0.21 ($r^2 = 0.93$) for the full extrapolated model. Therefore, the myocardial mass and coronary flow can be predicted by the scaling model.

### Table 1. A least-square fit as well as a scaling model fit (Y = Y$_0$ln$^b$) of the morphometry-mass data

<table>
<thead>
<tr>
<th></th>
<th>Least-Squares Fit</th>
<th>Scaling Model Fit</th>
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<tbody>
<tr>
<td></td>
<td>$Y_0$</td>
<td>b</td>
</tr>
<tr>
<td><strong>Full Extrapolated Model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V, ml</td>
<td>0.013±0.002</td>
<td>1.05±0.06</td>
</tr>
<tr>
<td>L, cm</td>
<td>49.4±30.2</td>
<td>0.81±0.12</td>
</tr>
<tr>
<td>D, mm</td>
<td>0.72±0.13</td>
<td>0.41±0.05</td>
</tr>
<tr>
<td>Q, ml/min</td>
<td>0.64±0.03</td>
<td>0.74±0.04</td>
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<tr>
<td><strong>Truncated Model</strong></td>
<td></td>
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<tr>
<td>V, ml</td>
<td>0.013±0.001</td>
<td>0.97±0.04</td>
</tr>
<tr>
<td>L, cm</td>
<td>0.89±0.18</td>
<td>0.76±0.07</td>
</tr>
</tbody>
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Values are means ± SE. Y represents the arterial vascular volume (V), cumulative vessel lengths (L), proximal diameter (D), or volumetric flow (Q). The truncated model represents data proximal to 1 mm in diameter while the full extrapolated model represents a fully extrapolated model down to the capillary vessels.
extrapolated model, and 1.32 ± 0.15 ($r^2 = 0.97$) for the truncated model. On the basis of the hypothesized scaling relations, we would expect an exponent of 4/3 or 1.33, which is verified by the data. Similarly, an exponent of 2.51 ± 0.19 ($r^2 = 0.97$) is obtained for the $V-D$ relation, which compares to an 8/3 law (2.66). Finally, a 1.90 ± 0.30 ($r^2 = 0.92$) exponent is obtained for the $L-D$ relation which compares well with the expected $L \alpha D^2$.

Statistical analysis. The parameters of interest are reported as means ± SD, and log-log plots of the data were made. A least-squares regression was performed and product-moment correlation coefficients were calculated using Microsoft Excel Software. Group comparisons were made using ANOVA, and significance was determined using $t$-test.

DISCUSSION

There is no doubt that fundamental design principles underlie the relation between structure of the coronary arterial tree and the respective perfused myocardial region. Our study found a linear relation between coronary arterial volume and myocardial mass. We also found a power-law relation between myocardial mass and cumulative length ($L \alpha m^{3/4}$), arterial diameters ($D \alpha m^{1/8}$), and flow ($Q \alpha m^{3/4}$). This is the first time that several morphometric-flow-mass relationships have been established in the heart based on direct measurements.

The dependence of many biological variables on body mass is characterized by allometric scaling laws related to metabolism of an organism (1, 15). Many biological phenomena scale as quarter powers of body mass (30, 31). Scaling laws arise from the interplay between physical and geometric constraints implicit in three axioms: 1) a space-filling, fractal-like branching network is required to supply the entire volume of the organism; 2) the final branch of the network is a size-invariant unit; and 3) the energy required to distribute resources is minimized. The 3/4 and 3/8 power laws for length and diameter, respectively, arise in the simple case of the classic rigid-pipe model, where the branching is assumed to be area preserving (i.e., the sum of the cross-sectional areas of the daughter branches equals that of the parent). This model, proposed by West and colleagues (30, 31), predicts structural and functional properties of vertebrate cardiovascular and respiratory systems, plant vascular systems, insect tracheal tubes, and other distribution networks.

Anatomic design of the coronary arterial tree. The anatomic structure of the coronary arterial tree can be described in terms of lumen diameter, branch lengths, branching patterns, volume, and myocardial mass. The relation between these parameters can be observed from clinical arteriograms (26, 27) and can be derived based on one or more design principles (35, 36). Since 1926, numerous investigators have made attempts to explain the design rules underlying the anatomic structure of the coronary arterial tree based on the principles of minimum work (21, 22), optimal design (25), minimum blood volume (10), and minimum total shear force on the vessel wall (33, 34). Murray (21, 22) was the first who derived a relationship between the diameter of the mother and daughter vessels at a bifurcation. He proposed a cost function that is the sum of the friction power loss and the metabolic power dissipation proportional to blood volume. By minimizing the cost function, Murray (21) derived an optimal condition for a vascular bifurcation, referred to as Murray’s law, which states that the cube of the radius of a parent vessel equals the sum of the cubes of the radii of the daughter vessels. Mittal and colleagues (20) also found a power-law relation between flow and diameter, as suggested by Murray’s law. The value of the exponent, however, is not 3, as predicted by Murray but rather 2.2, 2.1, and 2.1 for RCA, LAD, and LCX, respectively. The differences in the exponent have been clarified by Kassab and colleagues (13).

Several studies (26, 27, 35, 36) have suggested a systematic correlation between coronary artery lumen size at any point in the arterial tree, the sum of arterial branch lengths distal to that point, the volumetric flow in the entire arterial tree, and regional myocardial mass. Kassab (12) reported a linear relationship between flow and length for the LAD, RCA, and LCX, and a 3/4 power-law relation between flow and volume as predicted here. Those results also indicate that the distribution of regional flow becomes broader as the stem diameter or crown length becomes smaller. This behavior is similar to a previously reported relationship between flow and regional myocardial mass where it was observed that the dispersion in flow was increased as the size of the myocardial mass decreased (4, 32). Seiler and colleagues (26, 27) reported a power-law relationship between the cross-sectional area of the feeding vessel and the cumulative length of the tree perfusing a myocardial region. The power-law relationship was shown to be comparable in both canine and human studies, thereby confirming the fundamental physical principles underlying the structure of the coronary arterial tree in different species. Kassab (13) demonstrated that different vascular trees (coronary, pulmonary, vascular systems of various skeletal muscles, mesentery, omentum, and conjunctiva) in various species (rat, mouse, monkey, and human) scale as $L \alpha D^2$.
hamster, cat, rabbit, pig, and human) obey a set of design rules or scaling laws. The present findings are consistent with the previous morphometric scaling relation. The major contribution here is to relate the morphometric data to myocardial mass, which remains consistent with previous findings.

Comparison with other studies. Evaluation of the coronary arteries to localize stenosis, measure severity, and assess the distal vessel is important in the diagnosis and management of coronary artery disease (CAD) and is essential before any revascularization procedure is performed. There is no established standard, however, for assessing the severity of diffuse CAD (DCAD) for routine clinical evaluation to which the various available assessment methods can be compared. To evaluate the severity of DCAD and the myocardial mass at risk, it is important to know the normal arterial lumen size in the absence of atherosclerosis at each branch of coronary artery relative to the distal vascular bed size distal to each of those points. Several studies (27, 28, 31) have indicated that relations between morphological parameters and myocardial mass measurements may exist. For example, the close correlation between ventricular mass and the cross-sectional area of the main stem of coronary arteries (16) or the close correlation between coronary size and regional myocardial mass (3). Our current study provides experimental data that relates the total distal regional coronary arterial lumen volumes, diameters, lengths, and flow to regional myocardial mass in the normal bed.

Clinical implications. DCAD, a common form of atherosclerosis, is difficult to diagnose because the arterial lumen is usually diffusely reduced along the length of the vessel (5, 18, 23, 24, 29). Coronary arteriography is the current gold standard for evaluation of severity of coronary artery stenosis, which is commonly measured as percent diameter stenosis or narrowing relative to the normal lumen size adjacent to the stenotic segment. There are well known limitations, however, to the subjective visual grading of the severity of coronary artery stenosis because atherosclerosis is often diffuse and the normal reference segment is also narrowed (7, 18, 26). This is particularly important in the case of an intermediate coronary lesion (30–70% diameter stenosis), where coronary arteriography is very limited in identifying if a lesion is significantly important to produce myocardial ischemia. Furthermore, it is also known that vulnerable plaques with superimposed occlusive thrombosis, underlying acute coronary syndromes or sudden death, often occur at sites of <50% diameter stenoses (2, 17). Therefore, information on seemingly milder obstructive or nonobstructive lesions may frequently be missed and their prognostic importance underestimated.

A major challenge in cardiology is to develop diagnostic methods for identifying early atherosclerotic disease that can allow the physician to target aggressive preventive measures to avoid vessel occlusion or plaque rupture. It is essential to establish morphometric relationships for the coronary arterial tree in the normal heart. One important application of the morphometric relationships for the truncated model is the assessment of DCAD. As previously stated, CAD is usually quantified by the percentage stenosis of arterial diameter, which is an important index of coronary lesion. Using this index to evaluate DCAD, however, has been seriously questioned (18). The most obvious problem is that the normal reference segment does not exist in the case of DCAD. Therefore, it is essential to establish morphometric relationships for the coronary arterial tree in the normal heart. The proposed morphometric-mass relationships for the truncated model are a first step toward developing a quantitative estimate in the assessment of DCAD. Pathological changes may alter these relationships where the deviations from normal curves can then be used to diagnose DCAD. The exponent may serve as an index of the normal coronary arterial tree, where deviations from this index may quantitatively establish the extent of DCAD using angiographic techniques.

In summary, our present study shows that the $V^{-1/3}$, $L^{-1/4}$, $D^{-m_{3/4}}$, and $Q^{-m_{3/4}}$ relationships provide insight into the design of the coronary arterial tree and may be of great value in the assessment and diagnosis of DCAD. The determination of the deviations of these relations as a measure of extent of DCAD remains a laudable objective for future studies. The present study establishes the “signature” of a normal porcine heart.

Future studies. The long-term objective is to develop a diagnostic rationale for the assessment of DCAD. To accomplish this goal, a number of future studies are needed. For example, we must establish the applicability of the design rules found for the pig coronary arteries in healthy humans and then examine the deviations of these relations in human hearts with DCAD. This will provide a rationale for implementing a diagnostic technique in patients with DCAD.

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GRANTS

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