Functional hierarchy of coronary circulation: direct evidence of a structure-function relation

Ghassan S. Kassab

Department of Biomedical Engineering, University of California, Irvine, California

Submitted 31 May 2005; accepted in final form 10 August 2005

Kassab, Ghassan S. Functional hierarchy of coronary circulation: direct evidence of a structure-function relation. Am J Physiol Heart Circ Physiol 289: H2559–H2565, 2005. First published August 19, 2005; doi:10.1152/ajpheart.00561.2005.—The heart muscle is nourished by a complex system of blood vessels that make up the coronary circulation. Here we show that the design of the coronary circulation has a functional hierarchy. A full anatomic model of the coronary arterial tree, containing millions of blood vessels down to the capillary vessels, was simulated based on previously measured porcine morphometric data. A network analysis of blood flow through every vessel segment was carried out based on the laws of fluid mechanics and appropriate boundary conditions. Our results show an abrupt change in cross-sectional area that demarcates the transition from epicardial (EPCA) to intramyocardial (IMCA) coronary arteries. Furthermore, a similar pattern of blood flow was observed with a corresponding transition from EPCA to IMCA. These results suggest functional differences between the two types of vessels. An additional abrupt change occurs in the IMCA in relation to flow velocity. The velocity is fairly uniform proximal to these vessels but drops significantly distal to those vessels toward the capillary branches. This finding suggests functional differences between large and small IMCA. Collectively, these observations suggest a novel functional hierarchy of the coronary vascular tree and provide direct evidence of a structure-function relation.

vascular design; coronary vasculature; morphometry; network analysis; blood flow

THE FUNCTION of the coronary circulation is to continually supply blood to meet the continuous requirements of cardiac tissue that is critical to the health of the heart. The coronary arterial system consists of large epicardial coronary arteries (EPCA) that span the surface of the heart and give rise to intramyocardial coronary arteries (IMCA) that penetrate into the inner layers of the heart. The asymmetric branching pattern of the coronary arterial tree is rather complex and gives rise to millions of capillary blood vessels that nourish the myocardium.

The question of functional design of the coronary arterial has been the subject of numerous investigations (2, 3, 7, 31–33). Zamir and Silver (31, 32) have suggested that the arterial system can be classified into “distributing” vessels that remain on the surface of distinct zones of the heart and give rise to “delivering” vessels that penetrate those zones to implement the delivery of blood. As a basis for this classification, Zamir and Silver (31) showed that the distributing vessels have a lower branching rate than the delivering vessels. The delivering vessels were found to divide more profusely and terminate more rapidly than the distributing vessels. Additional evidence for the differences in the branching pattern of EPCA and IMCA came from X-ray studies of Tanaka et al. (28). They found that the self-similar branching pattern of coronary arteries was discrete at the connection between the EPCA and the IMCA (28). Finally, Ritman and colleagues (2, 3) found a similar discontinuity between EPCA and IMCA vessels with micro-computerized tomography.

Although these past studies suggest the existence of anatomic differences between EPCA and IMCA, these differences were not connected to the hemodynamics (flow, velocity, etc.) of the coronary circulation. The hypothesis of the present study is that there exists not only a characteristic variation in cross-sectional area (CSA) that distinguishes EPCA from IMCA but also a similar characteristic pattern of blood flow. An additional hypothesis is that there exists a functional difference between large and small IMCA that demarcates a possible transition from vessels involved in conduction to those vessels involved in transport based on the behavior of flow velocity. To test these hypotheses, a network analysis of coronary arterial blood flow was carried out based on a full set of anatomic data (5, 8, 11, 12). A functional hierarchy of the coronary arterial tree emerges that distinguishes EPCA from IMCA and further distinguishes two functional classes of IMCA. These findings provide direct evidence of a structure-function relation of the coronary circulation.

METHODS

Anatomic model. A flow simulation was carried out in each of the coronary arterial trees, right coronary artery (RCA), left anterior descending coronary artery (LAD), and left circumflex coronary artery (LCx), based on a detailed morphometric database by Kassab et al. (11). Previously, Kassab et al. (11) described in detail the methods of preparation, measurement, and morphometric analysis of the entire coronary arterial tree. Briefly, the morphometric data on the coronary arterial vessels of diameters <40 μm were obtained from histological specimens whereas the data on the coronary arterial vessels of diameters >40 μm were obtained from cast studies. Because it is not possible to obtain a complete cast of the arterial tree down to the capillary vessels, the vessels are invariably “broken” or “missing” at some dimension greater than the capillaries (≥8 μm). Consequently, Mittal et al. (21) developed a growth algorithm to reconstruct the full arterial tree from the partial measured data of Kassab et al. (11). Briefly, a two-step approach was used in the reconstruction of the entire coronary arterial tree down to the capillary level (≤8 μm in diameter). Portions of the arterial tree (RCA, LAD, or LCx) missing from the cast data were computationally reconstructed from anatomic data. Missing components of the tree, from broken vessel segments down to vessels of diameter 40 μm, were reconstructed from the intact cast data. Portions of the tree made up of vessels with diameter <40

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Address for reprint requests and other correspondence: G. S. Kassab, Dept. of Biomedical Engineering, Univ. of California, Irvine, 204 Rockwell Engineering Center, Irvine, CA 92697-2715 (E-mail: gkassab@uci.edu).
μm were reconstructed based on histological data. Reconstructed networks were terminated at segments of diameter ≤8 μm. Any terminal vessel in the cast data with diameter >8 μm was treated as a broken vessel, and the reconstruction algorithm was applied to generate a subtree that branched down to the terminal arterioles of diameter ≤8 μm.

Flow simulation. After the branching pattern and vascular geometry of the full arterial network were generated, a network analysis was performed (6, 14, 20). Briefly, if the cylindrical vessel is considered rigid, long, and slender, under laminar and steady flow, Poiseuille’s law for a Newtonian fluid can be stated as

$$Q = \frac{\pi}{128} \Delta P G$$

where $Q_{ij}$ is the volumetric flow, in a vessel between any two nodes, represented by $i$ and $j$, $\Delta P_{ij}$ is the pressure differential given by $\Delta P_{ij} = P_i - P_j$, and vessel conductance, $G_{ij}$, is given by

$$G_{ij} = \frac{D_{ij}^4}{\mu_{ij}L_{ij}}$$

where $D_{ij}$, $L_{ij}$, and $\mu_{ij}$ are the diameter, length, and viscosity, respectively, between nodes $i$ and $j$. The data on the variation of viscosity with vessel diameter and hematocrit are given by Pries et al. (22) as:

$$\mu_{e, iso} = \left[ 1 + (6 \cdot e^{-0.015D} + 3.2 - 2.44e^{-0.0626D}) \right] \cdot \left( \frac{D}{D - 1.1} \right)^2 \cdot \left( \frac{D}{D - 1.1} \right)^2$$

where $D$ is the vessel diameter. This relationship was used throughout the coronary vasculature for a given vessel diameter $D$ and hematocrit of 0.45.

Two or more vessels emanate from the $j$th node anywhere in the tree, with the number of vessels converging at the $j$th node being $m_j$. By conservation of mass we must have

$$\sum_{j=1}^{m_j} Q_{ij} = 0$$

where the volumetric flow into a node is considered positive and flow out of a node is negative for any branch. From Eqs. 1–3 we obtain a set of linear algebraic equations in pressure for $M$ nodes in the network, namely

$$\sum_{i=1}^{m_j} [P_j - P_i] G_{ij} = 0$$

The set of equations represented by Eq. 4 reduce to a set of simultaneous linear algebraic terms for the nodal pressures once the conductances are evaluated from the geometry and suitable boundary conditions are specified. In matrix form, this set of equations is

$$GP = GB$$

where $G$ is the $n \times n$ matrix of conductances, $P$ is a $1 \times n$ column vector of the unknown nodal pressures, and $GBP_B$ is the column vector of the conductances times the boundary pressures of their attached vessels, respectively. Boundary conditions were prescribed by assigning an inlet pressure of 100 mmHg and a pressure of 25 mmHg at the outlet of the first capillary segment. Because matrix $G$ is a very sparse matrix, it was represented in a reduced form for optimal memory utilization. This system of equations was then solved with a general mean residual algorithm of Saad and Schulter (25) to determine the pressure values at all internal nodes of the arterial tree.

The pressure drops as well as the corresponding flows were then calculated. The mean velocity, $U_{ij}$, was computed as

$$U_{ij} = \frac{4}{\pi D_{ij}^4} Q_{ij}$$

The velocity in Eq. 6 corresponds to a vessel segment between nodes $i$ and $j$.

Relation between vessel diameter and order number. Kassab et al. (11) have previously documented the relationship between diameter and order number. They used a diameter-defined Strahler system to assign order numbers to the entire coronary arterial tree starting with capillary vessels (order 0). Briefly, when two order 0 vessels meet, the conflu ent vessel is assigned order 1. When two order 1 vessels meet the confluence was assigned order 2 if its diameter exceeded the diameters of the order 1 vessels by an amount specified by a set of formulas or the diameter criterion (11) or remained as order 1 if the diameter of the confluence was not larger than the amount specified by the formulas. When an order 2 artery met another order 1 artery, the order number of the confluence was 3 if its diameter was larger by an amount specified by the diameter criterion or remained at 2 if its diameter did not increase sufficiently. This process was continued until all arterial segments were arranged in increasing diameter and assigned the order numbers 1, 2, 3, . . . , $n$, . . . .

RESULTS

Ten anatomic reconstructions of the porcine RCA, LAD, and LCx arterial trees were performed. Because the pattern of data was very similar, we present typical data from one simulation. Figure 1A shows the variation of CSA along the length of the main trunk and the primary branches of the RCA tree. The main trunk begins at the root (most proximal segment) and is defined by the path corresponding to the largest vessel at each bifurcation down to the capillary segment. Similarly, the trunk of each primary branch begins at the segment that arises directly from the main trunk and descends to the capillaries along the path of the larger diameter at each bifurcation. Because the path lengths for the main trunk and the primary branches vary, the axial position of each path is normalized with respect to the length of the main trunk (normalized cumulative length, NCL). The variation of the CSA shows a "knee" or an abrupt change in trend (Fig. 1A). The knee occurs at a diameter (mean ± SD for the 10 simulations) of 404 ± 114 μm (order 8 vessels), where proximal to the knee are EPCA and distal to the knee are IMCA. The main trunk can be seen as having relatively constant CSA or diameter compared with other EPCA because the trunk of the RCA maintains a uniform CSA proximal to the posterior descending artery.

Figure 1B shows the flow corresponding to each of the vessels whose CSA is shown in Fig. 1A. The flow remains fairly constant for the EPCA and suddenly drops at the IMCA. The shape is nearly identical to the CSA curve, with the location of the knee occurring at approximately the same NCL, which corresponds to the same diameter (order 8 vessels). Hence, both CSA and flow remain relatively constant throughout the larger EPCA but decrease drastically in the smaller IMCA. The main trunk flow can be easily recognized in comparison with other EPCA, similar to the CSA. Similarly, the flow in the epicardial primary branches can be distinguished from that in the intramyocardial branches.

Similar data are shown for the LAD and LCx coronary arterial trees in Figs. 2, A and B, and 3, A and B, respectively. The knee is also clearly seen, similar to the RCA. The knee
Fig. 1. A and B: relationship between segment cross-sectional area (A) and segment flow (B) and the normalized cumulative length of the segment from the root of the trunk and the primary branches of the right coronary artery (RCA) tree. The solid line denotes the main trunk. C: isodensity plot showing 5 layers of frequency between the velocity in a vessel segment and the corresponding diameter of the vessel for the RCA tree. The total number of data points shown are 754 (A and B) and 1,716,705 (C).

Fig. 2. A and B: relationship between segment cross-sectional area (A) and segment flow (B) and the normalized cumulative length of the segment from the root of the trunk and the primary branches of the left anterior descending coronary artery (LAD) tree. The solid line denotes the main trunk. C: isodensity plot showing 5 layers of frequency between the velocity in a vessel segment and the corresponding diameter of the vessel for the LAD tree. The total number of data points shown are 859 (A and B) and 1,872,027 (C).
occurs at 503 ± 40.3 (order 8 vessels) and 434 ± 102 (order 8 vessels) μm, respectively. Hence, the first three largest orders are EPCA, whereas the remaining orders are IMCA (10). Unlike the RCA, the LAD and LCx arterial trees lack a distinct main trunk (Figs. 2, A and B, and 3, A and B). This is reasonable because the main trunks of the LAD and LCx taper gradually, unlike the RCA, which remains fairly uniform.

The relation between the velocity in each vessel segment and the diameter for all vessels >8 μm is shown in Fig. 1C (nearly 2 million vessels for the RCA tree). Because of the enormity of the number of vessels, the figure is represented as an isodensity plot showing five layers of frequency. The velocity appears relatively uniform for the larger vessels and abruptly decreases distal to ~12.7 ± 0.38 μm (mean ± SD for the 10 simulations). The characteristic decrease in velocity can also be seen in Figs. 2C and 3C for the LAD (at 13.3 ± 0.34-μm vessels) and LCx (at 13.1 ± 0.69-μm vessels) arterial trees, respectively.

DISCUSSION

In a recent study (20), our group carried out an analysis of blood pressure and flow distribution through the entire coronary arterial tree. In that study, we focused on the flow-diameter relation, longitudinal pressure distribution, pressure-flow relation, transit time distributions, and capillary flow heterogeneity. In the present study, we focus on the transition of CSA and flow from EPCA to IMCA and on the transition of flow velocity from large to small vessels as outlined below.

Transition from distributing to delivering vessels. The relationships between the CSA plotted against the NCL for the main trunk and primary branches exhibit a knee or abrupt change in trend (Figs. 1A, 2A, and 3A). Interestingly, the transition of branching pattern for the CSA occurs at order 8 vessels (~400–500 μm in diameter). Typically, orders 11, 10, and 9 are epicardial whereas orders ≤8 are intramural (11). Hence, the transition demarcates EPCA from IMCA. This difference in design of EPCA and IMCA vessels is interesting. The EPCA tend to maintain their CSA fairly uniform and serve to spread the larger branches over the surface of the heart to reach the entire surface area of the ventricles. These vessels were coined as distributing by Zamir and Silver (31). Furthermore, the EPCA seem to maintain relatively uniform flow (Figs. 1B, 2B, and 3B) so that the various regions of the heart can receive a similar source of blood supply. The observation that the EPCA and IMCA have different branching patterns in terms of the decrease in segment CSA with increasing distance from the proximal artery has been reported by Zamir (32) in humans, by Tanaka et al. (28) in dogs, and by Beighley et al. (2, 3) in rats. The observation that the flow pattern is similar to the CSA pattern with the same EPCA-IMCA transition has not been previously reported. This novel finding illustrates a direct connection between structure (CSA) and function (flow).

Transition from “conduction” to “transport.” An additional interesting pattern can be seen for the flow velocity of the entire coronary arterial tree as shown in Figs. 1C, 2C, and 3C. The velocity is relatively uniform throughout the larger vessels and abruptly decreases in the microcirculation. The transition corresponds to the diameter of order 2 vessels (~13 μm in diameter). This is a novel observation that demarcates the functional significances of various intramyocardial or deliver-
ing vessels. This may mark the transition from conductive to transportive flow. The conduction vessels (orders 3–8) are nearly area conserving (i.e., the exponent of flow-diameter relation is 2). Their function is to conduct blood without reduction in velocity. In the smaller arterioles and capillaries (orders ≤2), however, the velocity must be reduced to ensure sufficient transit time in the capillaries and consequently sufficient transport of oxygen and nutrients. Hence, the exponent must become >2; the larger the exponent, the greater is the reduction in velocity. In the entire coronary arterial tree, the exponent is only 2.2, but this is sufficient to reduce the flow velocity by nearly a factor of 1,000 at the precapillary arteriole (Figs. 1C, 2C, and 3C).

The relative uniformity of velocity in the large epicardial circulation has been documented experimentally. Stepp et al. (27) measured the velocity of canine epicardial coronary arteries in the range of 50–450 μm in diameter. They showed that the velocity varies from ~10 (450-μm vessels) to 6 (50-μm vessels) mm/s. The corresponding variations in flow velocity in the adenosine-dilated state were 20 to 12 mm/s, respectively. Unfortunately, the measurements were limited to vessels >50 μm.

The relatively abrupt transition in velocity demands an explanation. Naturally, there are two opposing determinants of velocity: 1) the decrease in CSA from larger to smaller vessels and 2) the increase in number of vessels. An analytical explanation can be realized if we consider an idealized symmetric circuit such that the flow, \( q_n \), at each level is given by

\[
q_n = \frac{Q_n}{N_n}
\]

where \( Q_n \) is the inlet flow and \( N_n \) is the total number of vessels at order \( n \). Conservation of mass implies that the mean velocity

\[
U_n = \frac{Q_n}{A_nN_n}
\]

where \( A_n \) is the average CSA of each vessel at order \( n \). The change in velocity from a higher to a lower order is given by

\[
\frac{U_{n+1}}{U_n} = \frac{A_n}{A_{n+1}} \frac{N_{n+1}}{N_n}
\]

where the numerator and denominator are the CSA and branching ratios, respectively. The velocity is maintained uniform (velocity ratio is 1) when the CSA ratio increases in proportion to the branching ratio, i.e., the decrease in CSA from larger to smaller vessels occurs in proportion to the increase in number of vessels. This seems to be the case for orders ≥3. When the increase in number of vessels is more rapid than the decrease in CSA, however, the velocity ratio becomes <1 and hence the velocity decreases toward the smaller vessels (orders ≤2). It should be noted that distal to the order 1 and 2 arterioles are capillary vessels (order 0a) that undergo further branching into smaller capillaries (order 00 vessels), which further branch and anastomose (9).

A close inspection of previously published data (11) on the diameter and hence CSA indeed reveals a decrease in the diameter ratio at order 2 (mean diameter of 12 μm). The mean CSA ratio (square of diameter ratio) is 3.58 (for orders 3–11) and 1.97 (orders 0a–2) for the RCA. There is a similar significant difference in the mean area ratio in the same range of orders for the LAD (3.61 and 1.98) and LCx (4.07 and 1.98) arterial trees. No such difference was found in the branching or number ratio throughout the range of orders for the RCA, LAD, and LCx arterial trees. In conclusion, the diameters decrease more slowly distal to order 3 (lower CSA ratio) and hence the total CSA (product of CSA and total number of vessels) increases as reported previously by Kassab et al. (11). Consequently, the velocity decreases more rapidly in those vessels.

The relatively flat velocity distribution followed by an abrupt decrease in velocity of small arterioles may be unique to the heart. In the bat wing, Mayrovitz et al. (18) reported a linear drop in flow velocity from 80-μm arterioles to the capillary vessels. In the pial arteries of cat, Kobari et al. (16) reported a roughly linear decrease from 200- to 50-μm arterioles. Similar conclusions were made in the human retinal vessels, where the velocity varied nearly linearly with diameters in the range of 40–140 μm (24). In the cat and human pulmonary vasculature, the increase in CSA toward the capillary vessels is exponential (4, 26, 30). These data imply that the velocity will decrease exponentially toward the capillary vessels. The heart may indeed be different in that the flow velocity is decreased significantly during each cardiac cycle because of the vessel-muscle interaction such that the anatomic increase in CSA toward the capillaries does not need to be as large as in other organs.

Global design of coronary circulation. Kassab and colleagues (7, 35) showed previously that the structure (diameter, length, and volume) and function (flow) of the coronary vasculature obey a set of scaling laws that are based on the hypothesis that the costs of construction of the tree structure and operation of fluid conduction are minimized. It was shown that the design of coronary circulation can be deduced on the basis of the minimum-energy hypothesis and conservation of energy under steady-flow conditions. This hypothesis was tested with an anatomically based analysis of coronary arterial blood flow (35) and in vivo measurements of morphometry and flow by digital subtraction angiography (34). Globally the coronary circulation appears to minimize the energy of construction and operation, whereas locally it serves the specific function of the heart in relation to distribution, conduction, and transport as documented in the present study. Hence, the functional hierarchy obeys the minimum-energy hypothesis and the resulting scaling laws.

Possible mechanisms for functional hierarchy. Metzger and Kasnow (19) proposed a common genetic mechanism for all branching structures, including blood vessels independent of organ region. Furthermore, because EPCA and IMCA are formed from the same extracardiac source of endothelial cells, it is unlikely that the differences are embryological (1). A possible explanation for the differences in EPCA and IMCA is dictated by local demand. In the inner layers of the heart, angiogenesis is stimulated as the local tissue oxygen gradient increases during postnatal growth of myocardium. The EPCA, on the other hand, only grow in diameter or CSA in response to increased flow or wall shear stress (13). There is evidence that capillary density and the number of small arterioles increase during the postnatal period (17, 23). The larger vessels, however, only increase in CSA and segment length (29). Similar observations (increase in diameter and length of larger
vessels and increase in number of smaller vessels) were made in a swine model of flow overload-induced remodeling of the right ventricular branches in right ventricular hypertrophy (15).

Critique of model. Although our analysis is based on detailed measured morphometric data of the entire coronary arterial tree, there are still a number of assumptions that warrant discussion. For example, the vessels are assumed to be rigid, which is untrue in reality. This issue becomes particularly important when considering the flow in a contracting myocardium because the elasticity of vessels gives rise to the vessel-muscle interaction. If we consider the diastolic state of the heart, however, the elasticity of the vessels is relatively small (10) and does not affect the diastolic pressure-flow relation significantly (6). Furthermore, all vessels in the present model are assumed to be in a vasodilated state where coronary flow reserve is substantially reduced. Although it is important to eventually include vasoregulatory mechanisms to investigate many clinically relevant phenomena that relate to coronary flow reserve, it is unlikely that this will change the CSA and flow pattern of large vessels because the effect of tone is small.

The major assumption of the above analysis is that blood flow is steady and fully developed. This assumption holds when both the Reynolds (ratio of inertial to viscous forces) and Womersley (ratio of transient inertia to viscous forces) numbers are sufficiently small. The first parameter marks the transition to turbulence (Reynolds number \(>2,500\)), whereas the latter parameter is an index of pulsatility that becomes significant for Womersley number \(>4\). We verified that the Reynolds number is \(<100\) for all vessels and hence justifies the quasi-steady state assumption. The Womersley number, on the other hand, is \(<1\) for vessels \(<700\ \mu m\). Hence, although the inertia of larger blood vessels should be taken into account, it is unlikely this will change the conclusions of the present study.

Significance of study. The structure-function relation is one of the oldest paradigms in biology and medicine. The present study provides direct evidence of the structure-function relation in the coronary circulation. The transition from EPCA to IMCA is evident in the CSA (structure) and flow (function) curves. The structure of the EPCA vessels is suited for distribution of blood flow to various regions of myocardium without significant diminishment of blood flow. Furthermore, the transition from conductive to transportive flow further demarcates the functional hierarchy of the IMCA. The proximal portion of the IMCA, whose role is flow delivery, maintains a constant velocity of conduction, whereas the distal vessels significantly reduce the velocity to ensure ample transit time for transport of oxygen and nutrients. Collectively, these observations lead to a functional hierarchal model of the coronary arterial tree in normal hearts. This functional model will serve as a reference state for understanding coronary circulatory dysfunction. Clearly, coronary artery disease will affect both the CSA and flow patterns and hence cardiac function. Hence, the present CSA, flow, and velocity profiles may represent the signatures of normal coronary circulation, and deviations from these patterns may indicate perfusion abnormalities.

ACKNOWLEDGMENTS

The author acknowledges Sonky Ung and Nishant Mittal for technical expertise.

GRANTS

This research was supported in part by National Heart, Lung, and Blood Institute Grant 2-R01-HL-055554-06.

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