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Regional myocardial flow heterogeneity explained with fractal networks

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Abstract

There is explain how the distribution of flow broadens with an increase in the spatial resolution of the measurement, we developed fractal models for vascular networks. A dichotomous branching network of vessels represents the arterial tree and connects to a similar venous network. A small difference in vessel lengths and radii between the two daughter vessels, with the same degree of asymmetry at each branch generation, predicts the dependence of the relative dispersion (mean $\pm$ SD) on spatial resolution of the perfusion measurement reasonably well. When the degree of asymmetry increases with successive branching, a better fit to data on sheep and baboons results. When the asymmetry is random, a satisfactory fit is found. These models show that a difference in flow of 20% between the daughter vessels at a branch point gives a relative dispersion of flow of ~30% when the heart is divided into 100–200 pieces. Although these simple models do not represent anatomic features accurately, they provide valuable insight on the heterogeneity of flow within the heart.

Keywords

heart; microspheres; iododesmethylinipramine; fractal model; bifurcating network; branching tree; mathematical model

REGIONAL MYOCARDIAL BLOOD FLOW is very heterogeneous. This has been found by dividing the heart muscle into small sample pieces after an injection of microspheres to measure blood flow to each piece (9, 13, 28). The same has been accomplished using diffusible indicators (28) or the “molecular microsphere” iododesmethylinipramine (IDMI), which is almost completely extracted in one pass and well retained in tissue (4). It turns out that the relative dispersion (RD; mean $\pm$ SD) of the distribution of blood flow increases when the sample pieces into which the heart is divided are made smaller (1, 2). The dependence of RD on the average mass (m) of the samples was found to be well described over a certain range of m by the relation

$$RD(m) = RD(m_0) \cdot \left(\frac{m}{m_0}\right)^{1-D_m} \quad (1)$$

where m_0 is an arbitrary reference mass, $RD(m_0)$ is the RD with sample mass of m_0 , and D_m is a parameter governing the slope of $\log RD$ vs. $\log m$. The dependence on the number of sample pieces (N) into which the ventricle is divided is given by Bassingthwaite et al. (2) using N_0 as a reference number of pieces

$$RD(N) = RD(N_0) \cdot \left(\frac{N}{N_0}\right)^{D_m-1} \quad (2)$$

These equations, describing the relation between a measured quantity and the spatial resolution of the measurement, are also found for mathematical constructs and natural phenomena having a fractal geometry (18, 21, 22). Therefore, D_m is often called the fractal dimension. Although this fractal power law gives a description of the measurement of RD, we believed that vascular networks having fractal characteristics might be useful for explaining the experimental findings. Vascular trees seem to display roughly the same patterns at different levels of scale (24), a property often found in fractal structures (18, 21, 22). Mandelbrot (18) suggested that fractal bifurcating networks mimic the vascular tree. Lefèvre (16) portrayed the pulmonary vasculature as a fractally branching structure, leading to assessment of how well energy expenditure was minimized in delivering blood to the peripheral lung units. West et al. (27) used fractal concepts to describe length and diameter relationships in the bronchial tree. Dichotomous branching tree structures have been considered as algorithmic descriptors of the coronary arterial network by Pelosi et al. (23) and Zamir and Chee (29); those of Pelosi et al. (23) allowed for asymmetry such as was observed in the pial arteriolar microvessels by Hudetz et al. (11).

We have modeled some very simple bifurcating networks of blood vessels and found that such networks nicely describe the dependence of the RD of the flow distribution on the size of the supplied region, although they give overly simple descriptions of the coronary vascular network. The particular contribution that this study makes to understanding myocardial physiology is that the form of the microvascular network is linked to an experimentally measurable variable, local blood flow, and its heterogeneity in the normally functioning organ. How generally this applies to other vascular beds is yet to be seen, but it seems safe to predict that fractal approaches will be useful in describing many different heterogeneous systems.

MODELS

The flow distribution in vascular networks is modeled. The basic element of the network is a bifurcation, whereby a parent vessel generates two daughter branches. The two daughter branches are of different sizes, thereby introducing asymmetry into the networks. The bifurcation is repeated for many generations of branching. At each bifurcation, a fraction (γ_i) of the flow entering the bifurcation enters one branch, the remaining fraction ($1 - \gamma_i$) enters the other (see Fig. 1, *left*). We will discuss four different schemes for determining γ_i and thereby the distribution of flow.

Model I: deterministic constant asymmetrical branching

For the first model we consider an asymmetrically branching network in which the degree of asymmetry is constant for all branch points. We assume that a constant fraction (γ) of the flow entering a bifurcation goes into one daughter branch and the remaining fraction ($1 - \gamma$) enters the other daughter branch (see Fig. 1, *left*).

Thus, in *model I*, the value of γ is assumed not to depend on the branch level. The flows (F) emerging from the network, having flow (F_0) at the origin, after n branchings have the values

$$F = \gamma^k \cdot (1 - \gamma)^{n-k} \cdot F_0 \quad (3)$$

where k assumes integer values from 0 to n . The result is a discrete distribution of flows. The number of occurrences of the k th flow of n discrete levels of flow is $n!/[k!(n-k)!]$ (which is commonly written $\binom{n}{k}$); the fraction of the n th generation of branches having the k th flow is $n!/[k!(n-k)!2^n]$. The average flow (F_{av}) after n branchings is $2^{-n}F_0$. The discrete density distribution of flows for two values of γ are shown in Fig. 2, *top*, and their pseudocontinuous representations in Fig. 2, *bottom*. The distributions broaden and skewness increases as γ deviates further from one-half. Next, we derive the RD (SD/mean) of the flow distribution (see APPENDIX A). The result for *model I* for the relative dispersion, $RD = (\text{Var}(F)/F_{av})$, where $\text{Var}(F)$ is variance of flow, given by Eq. A11 in APPENDIX A

$$RD = \sqrt{2^n [\gamma^2 + (1 - \gamma)^2]^n - 1} \quad (4)$$

The number of arterial endings (N) is 2^n and $n = \log N / \log 2$. Therefore, we find for RD

$$RD = \sqrt{N [\gamma^2 + (1 - \gamma)^2]^{\log N / \log 2} - 1} \quad (5)$$

This expression based on a fractal network cannot be reduced to the form of Eq. 2.

We will fit this expression to experimental data on the RD of regional flows measured in the heart of baboons and sheep (see RESULTS). In this network formulation, after n generations in the network, there are N branches, each one supplying one tissue sample. This is a simplification of the in vivo situation in which a piece that is cut will, in general, be supplied by more than one vessel. The effect of such a mismatch between the sample pieces and flow fields is assessed using the model presented in APPENDIX B (see RESULTS). When fitting the data, the total number of branchings was therefore set to $\log N / \log 2$, with N equal to the number of sample pieces. For each data set, three different fits were done. The first fit was produced with γ constant for the entire network. In the second fit, γ_1 for the first generation of branching was fixed at 0.5, but the remaining γ_i s were held constant at γ . For the third fit, γ_1 and γ_2 were fixed at 0.5, with subsequent γ_i s held constant at γ . This means that in some fits the first or the first two generations of branching were assumed to be symmetrical.

A vascular tree consisting of bifurcating cylindrical blood vessels with recursive relationships for radii and lengths of the vessel segments has been described previously (5)

and generates the same flow distribution as found for *model I*. At each bifurcation, the length of the mother vessel is reduced by a factor (f_L) for the first daughter branch and by a factor (f_S) for the second daughter branch. The radius (r) of the mother vessel is reduced to $a \cdot r$ in the first daughter branch and to $b \cdot r$ in the second daughter branch, where a and b are scalars <1 . This network constitutes a complete vascular system, with flows diverging in the arterial tree and flows converging in the venous tree. The flow distribution in this network is exactly equivalent to the distribution in *model I* (5) with

$$\gamma = \frac{f_S \cdot a^x}{f_L \cdot b^x + f_S \cdot a^x} \quad (6)$$

where x is 4 when the resistance is calculated from Poiseuille's law. It can be shown that the pressure is the same at all bifurcation points in any particular generation, but pressure decreases from generation to generation.

Model II: deterministic increasingly asymmetrical branching

In this model, the parameter γ is a function of the i th generation in which i is 1 for the first branching. The law chosen was

$$\gamma_i = \gamma_1 \cdot f^{i-1} \quad (7)$$

where γ_1 is the value of γ for the first branch point, and f is a constant. Here γ_1 was constrained to be in the range of 0–0.5, and f was constrained to the range 0–1. The result is that when f is <1.0 there is a gradual increase in the asymmetry with successive generations. This follows, since flow divides symmetrically at $\gamma_i = 0.5$ and is increasingly asymmetric the further γ_i is from 0.5. The distribution of flow in such a network is depicted by Fig. 1, *right*.

We derived an analytical expression for RD as a function of the number of branch generations n (see APPENDIX A, Eq. A12)

$$RD = \sqrt{2^n \prod_{i=1}^n (2 \cdot f^{2i-2} \cdot \gamma_1^2 - 2 \cdot f^{i-1} \cdot \gamma_1 + 1)} - 1 \quad (8)$$

In this model, the parameter γ_i encompasses all variations of changes in radius and length when a vessel splits at a bifurcation, in accordance with Eq. 6. In *model II*, as in *model I*, the effect of a parent vessel's resistance is carried over down the vascular tree to all generations of vessels fed from the parent.

Model III: asymmetrical branching by random variation (multiplicative model)

In this model the asymmetry parameter γ_i was treated as a random variable. At each branch point, a fraction $\gamma_i = 1/2 + \delta$ of flow goes into one branch, and a fraction $1 - \gamma_i = 1/2 - \delta$ goes into the other (see Fig. 3, *left*). Here δ is a random variable drawn for each branch point from a normal distribution with mean 0 and standard deviation σ . The γ for the first generation was taken to be a deterministic parameter γ_1 . The distribution of flow in this random network was calculated by computer, since we were unable to derive an analytical solution.

The computer program calculating the flows was based on the following principle. The flow entering the network was set to a value of 1. The value of the flows in the daughter branches after the first bifurcation was set to γ_1 and $1 - \gamma_1$, and these values were stored in an array. Each element of the array was then mapped into two elements of a second array, multiplying by γ_i and $1 - \gamma_i$, respectively, after computing γ_i from $\frac{1}{2} + \delta$. After the flow in all vessels had been calculated in this way, the second array was copied into the first array to conserve computer memory space. This procedure of mapping the first into the second array was repeated until the flow distribution in all required generations was obtained. The average flow in the vessels of the i th generation is known to be $F_0 \cdot 1/2^i$. The variance of the flows was determined and the RD obtained.

Model IV: asymmetrical branching by random variation (additive model)

In this model the flow entering a branch at a bifurcation is one-half the flow in the parent vessel plus a random noise term, which depends on the generation via the equation $(\delta/2^{i-1}) \cdot F_0$, where δ is a random Gaussian variable with mean 0 and standard deviation σ . The general scheme is represented in Fig. 3, right.

The difference between this model and *model III* will become clear when we examine the flows that result after the second branch point is examined. In the case of *model III*, this is given by $F_0 \cdot (\frac{1}{2} + \delta_{III}) \cdot (\frac{1}{2} + \delta_1)$. This equals $F_0 \cdot [\frac{1}{4} + \frac{1}{2}(\delta_{III} + \delta_1) + \delta_{III} \cdot \delta_1]$. *Model IV* gives the same result except that the last term $\delta_{III} \cdot \delta_1$ is omitted, and because this product is small, there is little difference between *models III* and *IV*. The advantage of *model IV* over *model III* is that an analytical solution has been obtained. The flow after i generations of branching is given by

$$F = F_0 \left[(1/2)^i + (1/2)^{i-1} \cdot \sum_{j=1}^i \delta_j \right] \quad (9)$$

The mean flow after i divisions is $(\frac{1}{2})^i \cdot F_0$. The variance of flow [Var(F)] after i divisions is given by

$$\text{Var}(F) = \text{Var} \left[(1/2)^{i-1} \sum_{j=1}^i \delta_j F_0 \right] = \left[(1/2)^{2i-2} \sum_{j=1}^i \sigma_j^2 \right] \cdot F_0^2 \quad (10)$$

This derivation uses the property that the variance of the sum of random variables is equal to the sum of their variances when the random variables are not correlated and further uses

$\text{Var}(c \cdot \delta_j) = c^2 \cdot \sigma_j^2$, where c is a constant. When we set all σ_j equal at σ we derive

$$RD = \frac{(1/2)^{i-1} \cdot \sigma \cdot \sqrt{i}}{1/2^i} = 2 \cdot \sigma \cdot \sqrt{i} = 2 \cdot \sigma \cdot \sqrt{\frac{\log N}{\log 2}} \quad (11)$$

where N is the number of vessels in the i th generation, with $N = 2^i$. After taking the logarithm of Eq. 11, we find

$$\log RD = \log 2 + \log \sigma + \frac{1}{2} \cdot \log \frac{\log N}{\log 2} \quad (12)$$

As in the case of *model I*, three different fits were done for each data set. The first fit was produced with σ constant for the entire network. In the second fit, γ_1 for the first generation of branching was fixed at 0.5, but the remaining γ_i s were determined by the random drawing of δ . For the third fit, γ_1 and γ_2 were fixed at 0.5, with subsequent γ s determined by the random drawing. Here again, the first one or two generations were assumed symmetrical in some of the fits.

METHODS OF ANALYSIS

Experimental data

The four models were fitted to regional blood flow measurements taken from the left ventricle of conscious baboons and anesthetized openchest sheep. The experimental techniques have been described elsewhere (13, 17). Briefly, in the baboons, radioactively labeled microspheres were injected into the left atrium in ~40 s (13). In sheep (3), microspheres and radioiodinated desmethylinipramine, a molecular flow marker which is ~100% extracted and retained (17), were injected simultaneously. After the animals were killed, the heart was cut out and divided into small samples according to a prefixed scheme (13). The flow to each piece was calculated from the deposition of radioactive tracers. This gives the RD for the highest resolution, i.e., for the largest number of sample pieces. To simulate the RD at lower spatial resolutions, adjacent sample pieces were aggregated to form larger pieces, as described by Bassingthwaite et al. (2). Only the IDMI data were fitted for the sheep, since there is some indication that microsphere depositions give slightly biased estimates of flow (4). In addition to the data for individual animals, we also used RDs derived from composite histograms, one for the baboons and one for the sheep, respectively. These were composed of the normalized local flow measurements of all the individual animals; the normalization was to divide the observed local flow by the mean for the flow for that individual animal (2, 13). The observed RD values were corrected for measurement error by using data from multiple simultaneous injections of differently labeled microspheres or IDMI (2, 13) to yield the unbiased spatial RD (RD_{spatial}).

Fitting the models

We fitted the model to the RD vs. N data using a least-squares criterion. The parameter γ of *model I* and the parameter σ of *model IV* were optimized using a golden section search (8) using the computer routine ZXGSN (IMSL Library, Houston, TX). The optimization was done separately for zero, one, or two generations of symmetrical branching ($\gamma = 0.5$). The least-squares criterion was also used to choose the best fit amongst the number of symmetrical generations. For *models II* and *III*, a Nelder and Mead (20) simplex routine (programmed by J. P. Chandler, Oklahoma State University, 1965) was used for the optimization (8). However, the scheme used to section and aggregate the neighboring samples did not always result in a number N of aggregates that was an integer power of 2. Therefore, for *models II* and *III*, a logarithmic interpolation was done to determine the theoretical data points at the experimental N values.

In the case of *model III*, there were two parameters, γ_1 for the first branching and σ for the next generations, drawing pseudorandom normal deviates z (mean 0, variance 1), using the IMSL-routine GGNML (IMSL) and setting $\delta = \sigma \cdot z$, where σ is chosen by the simplex routine. Because the distributions of flow varied with each formulation of the tree, we generated 10 different trees. Generating 100 trees did not markedly change the estimates. For each σ , exactly the same sequence of random numbers for z was used. When we drew a new set of random z s for each value of σ , this resulted in either very slow or no convergence. The RDs for each of the 10 realizations of the tree were calculated at successive levels of branching and were averaged for the 10 realizations. The residual sum of squares [$\sum (RD_{\text{measured}} - RD_{\text{model}})^2$] was then determined.

The goodness of fit of the model is reported as the coefficient of variation CV

$$CV = \frac{\sqrt{\sum (y_{\text{measured}} - y_{\text{model}})^2 / (n - df)}}{\sum y_{\text{measured}} / n} \quad (13)$$

where y_{measured} are the observed values, y_{model} are the model values of RD, n is the number of points, and df are the degrees of freedom of the model, which in this case is 2 for all four models.

Assessing the effect of mismatch between sample pieces and flow fields

When the heart is divided into sample pieces to measure the deposition of microspheres or IDMI, it is very likely that one cuts across the flow fields of various vessels. This will tend to average out differences in perfusion amongst flow fields. To investigate the extent of this effect, we examined in APPENDIX B the effects of random displacement of the cuts of the tissue relative to the divisions between adjacent cognate supply regions. The result was that the averaging gives a systematic lowering of RD seen as a shift in the curves of RD vs. generation by ~1 generation; however, the estimate of the branching parameter γ in *model I* is basically unaffected.

RESULTS

Figure 4 shows a sensitivity analysis of the parameters of *model II*, γ_1 , and f . The curve with $\gamma_1 = 0.472$ and $f = 0.992$ is the result of the least-squares fit of the model to the data from one baboon. The parameters were varied around these best fit values to exhibit the sensitivity of the model to variations in the parameter values.

The composite data for the baboons are plotted in Fig. 5, with the best fits resulting from the four models. The composite data for sheep are plotted in Fig. 6. The results for the estimation of the parameters of the four models are given in Table 1 for baboons and in Table 2 for sheep, together with the resulting CVs. For both *models I* and *IV*, the fits were very sensitive to the number of generations with symmetrical bifurcations. This resulted in changes of the CVs by 37–323% with number of symmetrical generations for *model I* and by 23–218% for *model IV*.

A general overview of the results in Tables 1 and 2 reveals that the best-fitting descriptors are not very asymmetrical. For *model I*, γ is ~ 0.46 , not far off the symmetrical 0.5. For *model II*, the product $\gamma_1 \cdot f$ is also ~ 0.46 . For *model III*, the operative γ is likewise ~ 0.45 , that is, 0.5–0.05. Likewise for *model IV*, σ is ~ 0.045 , giving a similar asymmetry nearly equivalent to a γ of 0.455. In general, the sheep show slightly greater asymmetry than do the baboons.

In 14 of the 21 individual animals, *model II* had the lowest residual sum of squares, whereas *model III* had the lowest residual sum of squares in 6 of the 21 animals. For the composite data, *model II* had the lowest residual sum of squares in both the baboons and sheep. When goodness of fit was compared with an F test between pairs of models, *model II* did fit significantly better ($P < 0.05$) than *model III* in 6 of 21 animals, whereas *model III* was significantly better than *model II* in 2 animals. For the deterministic models, *model I* was never significantly better than *model II*, but *model II* was significantly better than *model I* in 9 of the 21 animals. For the stochastic models, *model IV* was never significantly better than *model III*, but *model III* was significantly better than *model IV* in 9 of the 21 animals. We can conclude that the randomized or noisy recursions of *model III* did provide almost as good fits as did *model II*. We further conclude for the stochastic models that *model IV* has curvature in Figs. 5 and 6, similar to *model I*, but did not fit as well as *model III*, and we conclude for the deterministic models that *model I* did not fit as well as *model II*.

Figure 7, *left*, shows how the relationship between RD and the number of sample pieces is changed when flow fields and sample pieces do not correspond exactly. The RD is diminished at each value of N . The overall effect of the mismatch between sample and flow fields is that the curve is shifted to the right by slightly more than one generation of branching. We examined the mismatching for various values of γ and found when fitting the shifted data points that the discrepancy between sample and flow fields was compensated for by fixing γ_1 at 0.5 in *model I*.

DISCUSSION

In this study we have explored four models based on a dichotomous branching pattern. Four ways of defining the asymmetry between the two daughter vessels at each branch site have been used. All models show considerable simplification with respect to the real coronary vasculature. Despite this, the models fit the relation between the RD of the flow distribution and the spatial resolution of the flow measurement rather well, with only two parameters in each model.

We have not yet attempted to exactly fill up the three-dimensional space of the wall of the heart with the flow fields supplied by the various vessels in the network model. When trying to do this, one would have to decide in exactly which directions vessels run after they branch from a bifurcation. This is not specified in any of the four models. The myocardium can be supplied by the model networks in many ways. These models do not account for the branch angles of the bifurcations, curvature in the vessel segments, or other rheologically important factors.

A major simplification in the modeling lies in the assumption that the sample pieces into which the heart is cut correspond exactly to the region supplied by one particular vessel. In reality, a sample piece will contain part of the flow fields of a few different vessels. This will result in an RD that is lower than that predicted by the model. This effect was investigated by the ring simulation of APPENDIX B. Because it can be argued that the network models give a reasonable approximation to the existing neighbor-to-neighbor correlation between flow fields (see below), this ring model is appropriate for estimating the effect of mismatch between sample pieces and flow fields. The simulation showed that the effect of mismatched sample pieces and flow fields was accounted for in *model I* by making the first bifurcation symmetrical. In the majority of cases, the fit of *model I* to the data was indeed better when one generation of branching was symmetrical. This suggests that the estimates for γ in these cases are not biased by the mismatch between flow and sample fields. When symmetrical branching is not available in the first generation, as for *models II* and *III*, the deviation of γ from 0.5 will probably be somewhat underestimated (see Fig. 7, *right*).

Microspheres may preferentially be deposited in the regions with higher flow. However, comparison with the molecular microsphere IDMI (3, 4) has shown that such a bias is minor. Furthermore, the sheep data were obtained directly with the molecular microsphere IDMI. The data used in this study, therefore, reflect myocardial flow with sufficient accuracy to justify the analysis with these fractal models.

The experimental data do show that a sample with high flow tends to have a neighbor that also has a relatively high flow, and low flow regions tend to have low flow neighbors. This is implied by the fractal law in Eq. 1, as will be shown below. When two adjacent pieces are taken together ($Y_1 + Y_2$), the expectation (E) for the combined flow is

$$E(Y_1 + Y_2) = 2\mu \quad (14)$$

where μ is the average flow to each piece. Mendenhall and Scheaffer (19) show the expected variance of $Y_1 + Y_2$ to be

$$Var(Y_1 + Y_2) = Var(Y_1) + Var(Y_2) + 2 \cdot Cov(Y_1, Y_2). \quad (15)$$

where Cov is the covariance. Because it is assumed that $Var(Y_1) = Var(Y_2) = Var(Y)$, we find

$$RD(Y_1 + Y_2) = 2^{-0.5} \cdot \frac{\sqrt{Var(Y) + Cov(Y_1, Y_2)}}{\mu} \quad (16)$$

But, it has been empirically found (see Eq. 1) that

$$RD(Y_1 + Y_2) = RD(Y) \cdot 2^{1-D} \quad (17)$$

where, by definition

$$RD(Y) = \sqrt{Var(Y)/\mu} \quad (18)$$

By inserting Eq. 18 into Eq. 17 and then Eq. 17 into Eq. 16 we get

$$1 + \frac{Cov(Y_1, Y_2)}{Var(Y)} = 2^{3-2D} \quad (19)$$

Because the correlation coefficient r is equal to $Cov(Y_1, Y_2) / \sqrt{Var(Y_1) \cdot Var(Y_2)}$, it follows that

$$r = 2^{3-2D} - 1 \quad (20)$$

This little expression is an important statement because it summarizes the whole situation. If there is no spatial correlation, $r = 0$, so that when the local flows are completely randomized, the fractal dimension $D = 1.5$. This gives a maximal slope in the plots of RD vs. the number of generations N or vs. the mass of the region supplied at each generational level. At the opposite extreme, with perfect correlation, $r = 1$, flows are uniform and the fractal dimension D is 1.0. Where the dispersion is to the power $1 - D$, as in the linear higher resolution upper segments of the data in Figs. 5 and 6, which are well described by Eq. 2, there is no change in correlation with a change in spatial resolution or generation.

Because D for the dispersion in regional blood flows is frequently ~ 1.15 , it follows that the correlation coefficient for the flow in adjacent pieces is $\sim r = 0.63$. This is true for the correlation of flow between adjacent pieces over all of the range that Eq. 1 holds. It should be noted that the fractal laws of Eqs. 1 and 2 can be derived by assuming that the correlation coefficient r is the same for all scales of the piece sizes Y_1 and Y_2 (see Eqs. 14 and 15).

The structures of the model networks do define the correlation between flows in neighboring vessels. The correlation between “sister” vessels results in correlation existing in the network. When aggregating neighboring flows in the model, as was done with sample pieces in the experimental data, we only combined the flows of sister vessels. Although this approach oversimplifies reality, the fits to the experimental data are good, and we conclude that the spatial correlation properties of the primitive models are reasonable first approximations to the myocardial flow distribution.

A minor problem is that our hypothetical networks do not account for flow variation in time. In the real vascular tree, fluctuations of flow may occur at a range of frequencies. The mechanical action of contraction of the heart on the blood in the vessels causes a cyclical flow variation synchronous with the heart beat. Because the microspheres in the baboons were given over 40 s and in the sheep the IDMI was injected over 2–4 s, we can safely say that the parameter γ represents the distribution of flow in a bifurcation averaged over many heart beats. When there is vasomotion with a period on the same order as the duration of the injection, the snapshot picture we get from the injection underestimates the dispersion of flow found at any one “sharp” moment in time. When there are slow variations in vasomotor tone in the coronary tree, which take much longer than the injections for the flow

measurement, γ reflects a snapshot “frozen” picture of the coronary tree at that moment. However, variations of flow over periods of 4 min to 27 h were small relative to spatial variation (12, 13). This latter finding indicates that a model for the spatial distribution of flow, not incorporating temporal variation, is of value.

The models, when given in terms of radii and lengths of vessels, do not take entrance effects and radius-dependent changes in viscosity (Fahraeus-Lindqvist effect) into account. These can be incorporated by defining suitable relationships between flow, lengths, radii, hematocrits, and so on written into a more complex version of Eq. 6. Expressed alternatively, one can interpret our estimates of γ in terms of other rheological situations. Hudetz et al. (11) assumed for their network model that the fraction of flow entering a daughter vessel at a bifurcation is proportional to the radius to a power n . They found a minimum dispersion of terminal pressures in their model of the pial arterial tree for values of the exponent $n \sim 2.5$. Our calculations for the dispersion of flow apply to Hudetz's power law (11), with $\gamma = a^n/(b^n + a^n)$ and f_s and f_L equal. When f_L is proportional to parameter a and f_s is proportional to parameter b , the value of n becomes 3. For the comparison of Hudetz's study (11), it should be remarked that the dispersion of terminal pressures in our deterministic models is zero.

The predictions the models have here been tested against the RD of the flow distribution only. The RD reflects the second central statistical moment of the distribution of the data. Voss (26), in his Fig. 1.17, showed that the same fractal D holds for all normalized moments, so presumably the same D would be found for skewness and kurtosis.

One should obtain anatomic measurements on the coronary vessels to get realistic data for incorporation into a model of the vascular network. When measurements are done in a cast of the circulation, there is certainly a possibility of distortion of radii, which has an exaggerating effect due to the r^n dependence, with $n = 4$ for Poiseuille's law. Another fundamental problem arises from the fact that flow into a vessel segment does not only depend on the segment's dimensions but usually much more on the dimensions of the whole vascular network fed by that vessel. Therefore, to predict flow into a vessel accurately, one has to know much about the vessel network supplied by it, and measurements on only the first few generations of vessels are not sufficient. Anatomic measurements would yield valuable information on the actual parent-daughter relationship, as has been shown in the data of Suwa and Takahashi (25) and Suwa et al. (24). All fractal vessel networks presented here imply that a range of scales for lengths and radii is found at each generation. The same is true of the fractal description by West et al. (27) for the bronchial tree. Anatomic measurements of the coronary bed show the same feature (29). The fractal network also complies with the finding that vessels with smaller diameters deeper in the coronary tree tend to supply smaller volumes of the myocardium (14).

The models do not strictly presume that capillary density is homogeneous. Because the resistance of the capillaries supplied by a terminal arteriolar branch are assumed to be proportional to the resistance of this branch (5), capillary density can vary. However, capillary density is probably not an important determinant of local flow. This is emphasized by the findings that capillary density is lower in the subendocardium than in the

subepicardium (10), whereas in contrast, perfusion might be slightly higher in the subendocardium (7, 28). On the other hand, the distribution of resistance in the arterial tree is of major importance when examining the distribution of flow.

Other models with fractal or regular geometry could be considered. One such model begins with a larger vessel that has many side branches that are of the same dimensional order and considerably smaller than the parent vessel, as seen in the pattern of a fern. Although this can to some extent be approached by a bifurcating model like *model I*, with the parameters for the radii a and b , for instance, 0.98 for the main vessel and 0.05 for the side branch (see Fig. 1), the assumption that the small side branch and the large main trunk supply an equal volume of tissue would also have to be modified (14). Therefore, this type of fern-like pattern, which seems to occur in tissue, calls for a qualitatively different model in which the volumes supplied are defined with respect to the terminal branches rather than the bifurcations.

It is remarkable that a relatively small deviation from a symmetrical distribution of flow explains the marked differences in local perfusion. In *models I* and *II* this is reflected by γ , which is ~ 0.45 . In *models III* and *IV* this is reflected by σ , which is ~ 0.05 . The repetitive action of the mildly asymmetrical distribution of flow results in the marked heterogeneity of flow found with small tissue samples. The structure of *models I, II, III, and IV* implies a strong correlation down the vascular tree between the resistances of vessels derived from a given parent vessel. This can be seen from the derivation of the distribution of flow from *model I* in which all dependent vessels have the multipliers f_L and a for vessels depending on one daughter branch and f_S and b for the other daughter branch. The same principle of correlation applies to the other models. A physiological interpretation of this correlation might be that when a region requires much flow the local vessels increase in size and that this size increase is transmitted upward to the supplying vessels in the course of development, as Langille (15) has found for the renal artery.

A second way of using the mathematical models might also be appropriate for the description of flow measurements with microspheres and IDMI. One may consider the heterogeneous distribution of any quantity in space, e.g., the amount of water in a cloud or blood flow in the myocardium. On dividing the space into two halves, a fraction γ_1 of the total amount is found in one half and the remaining fraction $1 - \gamma_1$ in the other half. Now each half is divided again into two halves, and a fraction γ_2 of the total present in one half is now allotted to one quarter and the remainder $1 - \gamma_2$ to the other. This process is repeated over and over again to generate a fractal heterogeneous distribution of the quantity over space. The distribution generated obeys exactly the same mathematics and shows the same relation between spatial resolution and RD. Although this interpretation of the mathematics provides no explanation of the flow distribution in terms of a vessel network, it might be a useful tool for describing spatial heterogeneity, without the need for any simplifying assumptions necessary for the vessel networks.

The fractal description expressed in Eqs. 1 and 2 does not fit the relations between number of pieces and RD derived from the four fractal network models. Eqs. 1 and 2 imply that the correlation between flows in neighboring sample pieces is the same across all length scales

(see Eq. 20). However, when the pattern of branching is the same across all scales as in *models I–IV*, the log RD vs. log N relation is curved. The latter notion fits the experimental data better for the range of spatial resolutions over which experimental data are available at present.

The fractal dimension D , defined by the slope of the log RD vs. log N plot, is getting smaller as the spatial resolution of the measurement increases. The slope diminishes faster for *models I* and *IV* than for *models II* and *III*. The value of D for *model II* for the highest spatial resolution in the data is 1.17 for the baboons and 1.14 for the sheep.

Asymmetry was introduced into the network in four different ways. All four bifurcation models provide good descriptions of the heterogeneity of flow found experimentally in the myocardium. The data analysis indicates that *model II*, wherein the degree of asymmetry increases on subsequent branching, and *model III*, in which the asymmetry is stochastic, provide the best fits to the data. Preliminary studies with a modified version of *model I*, in which no generations are assumed to be symmetrical but the first generation has a different asymmetry parameter γ_1 , yielded in just over half the cases an improvement over *model I*. Because in almost half the cases this gives also an improvement over *model II*, this suggests that the improvement of *model II* over *model I* results from the fact that γ_1 for the first generation can be estimated independently of the γ for the second and following generations. However, when this model with parameters γ_1 and γ_2 was extended further, by deriving γ_i for i greater or equal to 3 from $\gamma_i = \gamma_2 \cdot i^{-2}$, the CV was further improved in more than half of the cases. Thus a progressive decrease in γ_i with generation i tends to improve the model fit to the data, tending to straighten the curve of log RD vs. log m .

In conclusion, we developed models of the coronary circulation based on a bifurcating network of blood vessels. The models described the spread of the distribution of flows found in the myocardium rather well. Further research will require developing branching models that approximate the branching of the coronary vasculature and should account for spatial correlation in regional flows.

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APPENDIX A

Derivation of the Relative Dispersion for Deterministically Branching Networks

Here we will give a derivation for the formula of relative dispersion RD of flow as a function of the number of pieces in the network depicted in Fig. 1, *left*. The derivation is for the general case in which γ_i varies amongst branch generations but is constant across the branches of a particular generation. The flows through the branches of such a network, after n generations of branching, are given by $\beta_j \cdot F_0$, where j takes on values from 1 to N , and $N = 2^n$ is the number of branches after n generations. The β_j for such a network is given by

$$\beta_j = \prod_{i=1}^n \alpha_i \quad (\text{A1})$$

where α_i is equal to either γ_i or to $(1 - \gamma_i)$. This can be formalized by defining α_i as

$$\alpha_i = \gamma_i \cdot h_\gamma(i, j) + \{(1 - \gamma_i) \cdot [1 - h_\gamma(i, j)]\} \quad (\text{A2})$$

where $h_\gamma(i, j)$ is a binary function on the indexes i and j , which has the property that its value is either 0 or 1. No series of $h_\gamma(i, j)$ values with i going from 1 to n is exactly the same for two values of j . Each permutation of 0 and 1 in such a series occurs once and only once for all j .

The branches with α_1 equal to γ_1 are represented by j values between 1 and $(N/2)$, whereas the branches with α_1 equal to $(1 - \gamma_1)$ are represented by j values between $(N/2) + 1$ and N . The branches with α_2 equal to γ_2 are represented by j values between 1 and $(N/4)$ and between $(N/2) + 1$ and $3/4N$, whereas the branches with $(1 - \gamma_2)$ have j values between $(N/4) + 1$ and $(N/2)$ and between $3/4N + 1$ and N . This pattern is repeated recursively.

The variance of the flows is given by (19)

$$\text{Var}(F) = E(F^2) - F_{av}^2 \quad (\text{A3})$$

The term $E(F^2)$ can be expressed as

$$\begin{aligned} E(F^2) &= \frac{F_0^2}{2^n} \cdot \sum_{j=1}^N \beta_j^2 = \frac{F_0^2}{2^n} \sum_{j=1}^N \left(\prod_{i=1}^n \alpha_i \right)^2 \\ &= \frac{F_0^2}{2^n} \cdot \sum_{j=1}^N \prod_{i=1}^n \{ \gamma_i \cdot h_\gamma(i, j) + (1 - \gamma_i) \cdot [1 - h_\gamma(i, j)] \}^2 \end{aligned} \quad (\text{A4})$$

inserting Eq. A2. Because $h_\gamma(i, j)$ assumes only the values 0 and 1, it follows that

$$E(F^2) = \frac{F_0^2}{2^n} \sum_{j=1}^N \left(\prod_{i=1}^n \{ \gamma_i^2 \cdot h_\gamma(i, j) + (1 - \gamma_i)^2 \cdot [1 - h_\gamma(i, j)] \} \right) \quad (\text{A5})$$

Because for $j = 1$ to $(N/2)$ the value of $h_\gamma(i, j) = 1$ and for $j = (N/2) + 1$ to N the value of $h_\gamma(i, j) = 0$, this can be written

$$E(F^2) = \frac{F_0^2}{2^n} \cdot [\gamma_1^2 + (1 - \gamma_1)^2] \cdot \sum_{j=1}^{N/2} \left(\prod_{i=2}^n \{ \gamma_i^2 \cdot h_\gamma(i, j) + (1 - \gamma_i)^2 \cdot [1 - h_\gamma(i, j)] \} \right) \quad (\text{A6})$$

because the product $\prod_{i=2}^n$ is the same for $j = 1$ to $(N/2)$ with γ_1 as is the product for $j = (N/2) + 1$ to N with $(1 - \gamma_1)$. Following the same type of reasoning, we “pull out” γ_2 and $(1 - \gamma_2)$

$$E(F^2) = \frac{F_0^2}{2^n} \cdot \prod_{i=1}^2 [\gamma_i^2 + (1 - \gamma_i)^2] \cdot \sum_{j=1}^{N/4} \left(\prod_{i=3}^n \{ \gamma_i^2 \cdot h_\gamma(i, j) + (1 - \gamma_i)^2 \cdot [1 - h_\gamma(i, j)] \} \right) \quad (\text{A7})$$

and after repeating this process for n steps we get

$$E(F^2) = \frac{F_0^2}{2^n} \cdot \prod_{i=1}^n [\gamma_i^2 + (1 - \gamma_i)^2] \quad (\text{A8})$$

The variance of the flow is thus according to Eq.A3 given by

$$Var(F) = \frac{F_0^2}{2^n} \left[\prod_{i=1}^n [\gamma_i^2 + (1 - \gamma_i)^2] - \frac{1}{2^n} \right] \quad (\text{A9})$$

and the RD is given by

$$RD = \frac{\sqrt{Var(F)}}{F_0 \cdot 2^{-n}} = \sqrt{2^n \cdot \left\{ \prod_{i=1}^n [\gamma_i^2 + (1 - \gamma_i)^2] \right\} - 1} \quad (\text{A10})$$

For *model I*, all γ_i are constant at γ , and it follows

$$RD = \sqrt{2^n [\gamma^2 + (1 - \gamma)^2]^n - 1} \quad (\text{A11})$$

For *model II*, $\gamma_i = f^{i-1} \cdot \gamma_1$ from which follows

$$RD = \sqrt{[2^n \cdot \prod_{i=1}^n (2 \cdot f^{2i-2} \cdot \gamma_1^2 - 2 \cdot f^{i-1} \cdot \gamma_1 + 1)] - 1} \quad (\text{A12})$$

These analytical solutions give the same results as those obtained by numerical simulation, in which the flows and quent RD of flows in the end branches of the network are calculated.

APPENDIX B

Ring Model to Evaluate Effect of Mismatched Sample Fields and Flou Fields

The sample pieces into which a heart is sliced and the areas that are supplied by a blood vessel will not match in general. To investigate the effect of this mismatching, we examine a very simple model. A slice of the left ventricle, forming a ring, is supplied with blood by the bifurcating network of Fig. 1, *left*. Each of the N end vessels supplies one segment of the ring, and flows are assigned to adjacent pieces according to the pattern of Fig. 1. The ring is then cut into N sample pieces with an offset with respect to the boundary of the flow fields such that a fraction x of the flow in each segment is added to a fraction $(1 - x)$ of the flow in the adjacent piece in the clockwise direction (see Fig. 7, *left, inset*). Therefore, when $x = 0$, the boundaries of the sample pieces and flow fields coincide exactly. The RD of flows is calculated for $x = 0$ through $x = 0.99$ at 0.01 intervals. The RD of flow in the offset sample pieces is averaged over these 100 offset positions. The result of the simulation for *model I* is shown in Fig. 7, *left*. Data points are derived from this simulated data set and fit with the original model. The estimated γ s from the fits are plotted against the γ s that were used in the model calculations in Fig. 7, *right*. Because the ordering of flows in the vessel networks gives a reasonable first approximation to the correlation of flows in the myocardium (see the

DISCUSSION), the ring model might provide a reasonable first approximation for evaluating the problem of the mismatch between sample pieces and flow fields.

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Fig. 1.

Recursive relations for branch flows in a dichotomously branching network. Two generations only are shown. *Left*: in *model I*, all $\gamma_i = \gamma$ at all generations. *Right*: in *model II*, all γ_i for the i th generation are the same but decrease from generation to generation. In *models III* and *IV*, γ_i is a random variable.

Fig. 2.

TOP: discrete density of frequency of occurrence of a certain flow value (relative to mean flow) after 8 generations. Sum of heights of bars is 1. *Bottom:* “pseudocontinuous” representation of density given in *top*. This was obtained by dividing frequency at each flow by range of flow axis in which points were closer to that particular flow than to its neighbors. For highest and lowest flow, distance to nearest flow was used to divide frequency.

Fig. 3.

Scheme for distribution of flow at consecutive bifurcations for *model III* (left) and *model IV* (right). Roman numeral subscripts refer to different drawings of random numbers for each bifurcation.

Fig. 4. Sensitivity of *model II* to its parameters. *Left*: results of model fits to *baboon 5* with γ_1 varied and f held constant at 0.992. *Right*: results of model fits to *baboon 5* with f varied and γ_1 held constant at 0.472.

Fig. 5. Relative dispersion (RD) vs. number of pieces (N). Composite data for baboons. Deterministic *models I and II* are on *left*; stochastic *models III and IV* are on *right*. Fits for *models I and IV* virtually overlap. Parameters are given in bottom line of Table 1.

Fig. 6. Relative dispersion (RD) vs. number of pieces (N). Composite data for sheep. Deterministic models I and II are on left; stochastic models III and IV are on right. Fits for models I and IV virtually overlap. Parameters are given in bottom line of Table 2.

Fig. 7.

Effect of mismatched flow and sample fields on relative dispersion (RD). *Left*: RD vs. number of sample pieces (N) from ring model (APPENDIX B). Dotted line represents a direct match; solid line represents average shift when 2 fields are offset, as depicted in *inset*. *Right*: comparing change in γ due to offsetting flow and sample fields. Dotted line represents fits done on the lower curve on the *left* with *model I*, having 0 symmetrical branch points. Solid line represents fits done with first generation of branching being symmetrical.

TABLE 1

Baboons: parameter estimates and coefficient of variation for models I–IV

Expt	Model I		Model II		Model III		Model IV		Coefficients of Variation			
	n_{sym}	γ	γ_1	f	γ_1	σ	n_{sym}	σ	Model I	Model II	Model III	Model IV
1	1	0.453	0.462	0.996	0.465	0.0480	1	0.0479	0.031	0.027	0.028	0.028
2	1	0.459	0.474	0.990	0.484	0.0470	1	0.0417	0.065	0.034	0.019	0.068
3	1	0.457	0.474	0.989	0.484	0.0485	1	0.0428	0.081	0.045	0.044	0.084
5	1	0.459	0.472	0.992	0.478	0.0445	1	0.0412	0.041	0.028	0.028	0.043
6	0	0.448	0.449	0.999	0.449	0.0548	0	0.0527	0.047	0.046	0.053	0.049
7	1	0.458	0.472	0.992	0.477	0.0455	1	0.0422	0.072	0.031	0.050	0.074
8	1	0.466	0.481	0.990	0.487	0.0391	1	0.0344	0.121	0.047	0.083	0.0123
9	1	0.470	0.478	0.996	0.482	0.0322	1	0.0304	0.026	0.018	0.012	0.027
10	1	0.471	0.483	0.993	0.489	0.0329	1	0.0290	0.081	0.014	0.035	0.082
11	1	0.465	0.476	0.994	0.479	0.0372	1	0.0352	0.082	0.047	0.060	0.083
Mean $\pm$ SD	0.9	0.461	0.472	0.993	0.477	0.0430	0.9	0.0398	0.065	0.034	0.041	0.066
		0.0074	0.0099	0.0032	0.0120	0.00735		0.00751	0.029	0.012	0.021	0.030
All	1	0.460	0.472	0.993	0.477	0.0430	1	0.0402	0.040	0.016	0.024	0.042

Parameter n_{sym} gives number of symmetrical branchings which gave best least-squares fit. For meaning of other parameters, see text.

TABLE 2

Sheep: parameter estimates and coefficient of variation for models I-IV

Expt	Model I		Model II		Model III		Model IV		Coefficients of Variation			
	n_{sym}	γ	γ_1	f	γ_1	σ	n_{sym}	σ	Model I	Model II	Model III	Model IV
230186	0	0.447	0.449	0.999	0.449	0.0561	0	0.0534	0.051	0.049	0.057	0.053
010586	0	0.463	0.463	1.000	0.462	0.0378	0	0.0371	0.047	0.047	0.053	0.047
220586	1	0.474	0.488	0.991	0.500	0.0311	1	0.0261	0.145	0.045	0.058	0.146
290586	1	0.467	0.484	0.989	0.495	0.0393	1	0.0334	0.157	0.035	0.093	0.159
050686	1	0.477	0.486	0.995	0.493	0.0262	1	0.0228	0.089	0.062	0.054	0.090
90686a	0	0.411	0.411	1.000	0.396	0.0863	0	0.0920	0.049	0.049	0.053	0.040
190686b	0	0.429	0.429	1.000	0.404	0.0604	0	0.0724	0.098	0.097	0.072	0.090
080886a	1	0.448	0.460	0.994	0.463	0.0530	1	0.0525	0.050	0.024	0.022	0.050
080886b	1	0.464	0.473	0.995	0.476	0.0373	1	0.0360	0.039	0.012	0.019	0.040
300487	1	0.424	0.441	0.992	0.446	0.0770	1	0.0774	0.034	0.029	0.031	0.031
060587	0	0.454	0.455	0.999	0.454	0.0475	0	0.0460	0.033	0.032	0.036	0.034
Mean		0.451	0.458	0.996	0.458	0.0502	0.545	0.0499	0.072	0.044	0.050	0.071
± SD		0.022	0.025	0.004	0.034	0.0189	0.522	0.0224	0.044	0.023	0.022	0.045
All	1	0.452	0.462	0.996	0.464	0.0476	1	0.0481	0.038	0.026	0.030	0.035

Parameter n_{sym} gives number of symmetrical branchings which gave best least-squares fit. For meaning of other parameters, see text.