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Fractal Branchings: The Basis of Myocardial Flow Heterogeneities?

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Introduction

The distribution of myocardial blood flows was found by Yipintsoi *et al*¹ to be surprisingly broad, broader than could be expected from variation in the microsphere technique itself in their studies of anesthetized dog hearts. This was observed by others^{2,3} and was expanded by observations in awake baboons by King *et al.*⁴ who found that the shape of the distribution of regional myocardial blood flows in about 0.2-g pieces was maintained over long periods of time, as estimated by repeated injections of tracer labeled microspheres. In these studies, the microsphere technique variation gave about 8 percent noise, but the heterogeneity of flows had a standard deviation that was about 35 percent of the mean flow, that is, the relative dispersion (RD) or coefficient of variation was 35 percent. The regional flow in a given piece remained almost constant at each of six observation times, spread over many hours, that is, the broad heterogeneity of myocardial blood flows was stable.

More detailed analyses of these data by King and Bassingthwaighe⁵ showed that the temporal fluctuation in regional flows was quite modest compared with the spatial variation. Temporal fluctuations were such that, while flow in a given region showed some apparently random variation with time, local flow in regions with flow less than 50 percent of the mean flow never increased enough to reach the mean. Similarly, regions with flow greater than 150 percent of the mean never diminished to the mean flow. Thus, myocardial regional flows maintained their relative position in the distribution of flows throughout the heart.

These observations gave rise to methodologic and physiological questions. Methodologic questions are: Since there are only four to six observations over time in each of these individual pieces, what could one say about the frequency of temporal fluctuations? Were they rhythmic or not? Which regions of the heart had higher flows vs. lower flows? Were there consistent endocardial and epicardial gradients?

The physiological questions are: What are the implications of having regions that are of consistently high flow or consistently low flow? Is the metabolic rate more in high-flow regions than in low-flow regions? Do high-flow regions have a plethora of flow and

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relatively low oxygen extraction? Are low-flow regions on the verge of becoming ischemic under stress? If the myocardium is stressed and lactate production occurs, is the lactate mainly from low-flow regions whose metabolic demands have now exceeded the supply of substrate and oxygen? Do low-flow regions recruit more under stress than high-flow regions?

The basic question relating to those just posed is one on which many investigators have sought definite information, namely, What is the relationship between metabolism and flow regionally in the heart? Since the organ is essentially monofunctional, and the tissue is reasonably uniform throughout the left ventricular myocardium, this in turn raises the question of why metabolism might be different in one region than another.

But before attempting to answer these methodologic and physiological questions, we had to face a relatively simple methodologic question: What is the appropriate estimate of heterogeneity?

Estimates of Heterogeneity are Dependent on the Size of the Observed Voxels

It is a truism to say that observations of dispersion are dependent on the size of the observed elements. The variance in population density in the United States is modest if one divides the country into four areas, it is greater when one considers it as fifty states, is greater yet when the variance is measured on the basis of populations by county, and greater yet when the observations are population density per square mile. Which is the correct estimate of the variance of the population? We have the same quandary for volume elements, or voxels, in the myocardium, as is illustrated in Figure 1.

It is clear from such observations and from the analogy to population density variation that the relative dispersion (the coefficient of variation or the standard deviation divided by the mean) must increase as the heart is divided more finely. Can any particular shape be expected for this monotonically increasing function? One expectation would be that if there were small functional units that were internally uniform with respect to their local blood flows, then the effect of heterogeneity must plateau when the pieces are as small as these internally uniform regions. Further divisions would cause no further increase in measured heterogeneity.

What we did was to reconstruct the regional myocardial flows at different piece sizes. This could be done because the pieces had been labeled and mapped in three dimensions, so that by putting the heart together numerically, it could then be sliced up in varying numbers of pieces, each composed of sections that were originally adjacent. This is what was done to produce Figure 1.

There are several different ways of dividing the heart into four or eight pieces, and these several different ways were used in the numerical aggregation of neighboring pieces; values of relative dispersion were obtained for each of these ways. Then the average values of the relative dispersion for four, eight, or sixteen, etc., divisions were plotted, as in Figure 2.

Using a log plot for the average piece size on the abscissa vs. the log of the mean estimate of the relative dispersion for the given volume element size, the relationships were constructed over the range of sizes available; the range was limited by the resolution with which the heart was originally divided, namely about 170-mg pieces in the baboon heart.

Such straight lines could be regarded as just another log-log regression or power-law relationship, for they are nearly linear over the range from about 16 to 256 pieces. This is a satisfying result because it provides a description of the heterogeneity. It appears that two numbers can define the heterogeneity, these being the relative dispersion at some reference size, for example 1 g, and a slope for the power-law relationship.

The slope of the power-law relationship has meaning, when viewed from a fractal perspective. First, it serves as a summarizing descriptor of the data; the general equation for the microsphere data in Figure 2 is

$$\begin{aligned} \text{RD}(m) &= \text{RD}(m_0) \cdot \left[\frac{m}{m_0} \right]^{1-D} \\ &= 12.1m^{0.3}, \end{aligned}$$

where the reference mass, m_0 , has been taken to be one gram and the relative dispersion (the RD at m_0) at that voxel size is 12.1 percent, and where the mass of the pieces m is in grams. When the observation element sizes, m , are less than one gram, then $\text{RD}(m)$ increases in proportion to the reciprocal of $m^{0.3}$. This allows data from one laboratory to be compared with that from another laboratory where the piece sizes are different. All that is required is that each laboratory report the relative dispersion at one particular partitioning size and the exponent or the fractal dimension D , which is 1.3 in this particular case, but which averaged 1.2 for 11 sheep and 10 baboon hearts.

The second feature of this result, and a prime reason for considering it as a fractal dimension D rather than just as an undesignated power-law relationship, is that the fractal D is bounded. Its maximum is 1.5 for uncorrelated data random numbers, and its minimum is 1.0 for an array of numbers that are either uniform or whose nearest neighbors are so nicely inversely correlated that their mean is uniform. (This implies that it is possible to have a fractal dimension of greater than 1.5 for relative dispersions under special circumstances where inverse correlations become evident. This is outlined by Bassingthwaighe *et al.* 6)

Spatial Correlation is Characterized by the Fractal Dimension

An intriguing and useful feature of the fractal relationship is that it spells out the degree of correlation between neighbors in a spatial domain. In the preceding section, we considered the relative dispersion, or coefficient of variation, of regional flows as a one-dimensional intensity, analogous to a voltage as a function of time. We should really be considering regional flow as the intensity of a property of the myocardium in three-dimensional space, just as we would consider the density of a cloud of chlorine to give a measure of its toxicity at different positions in a three-dimensional domain. In reconstructing the heart from the smallest pieces into larger and larger pieces, we were careful always to group together the

nearest neighbors to form the aggregates of a larger size. When pieces of a given size are cut in half, the increase in apparent variation will then be greater when the two halves of each piece are uncorrelated than when they are correlated. Van Beek worked out a general relationship:⁷

$$\text{Correlation coefficient, } r = 2^{3-2D} - 1.$$

When $D = 1.5$, then $r = 0$, and when $D = 1.0$, $r = 1$, fulfilling expectations. With $D = 1.2$, the average for our sheep and baboon hearts was then $r = 2^{0.6} - 1 = 1.52 - 1 = 0.52$. The effect of doubling the resolving power, cutting pieces in half, for example, increases the RD predictably. If the fractal dimension is 1.2, halving the voxel sizes increases the relative dispersion by only a relatively small factor, $2^{1/5} - 1$ or 15 percent. (This is obtained by $RD(m_2)/RD(m_1) = 1/2^{1-D} = 1/2^{-0.2} = 2^{1/5}$.) The correlation between pieces of a given size is expected to decrease as the distance between the pieces increases; this is analogous to the decay of electrical potential away from a point source of current, but has a form more extended than a single exponential.

The Myocardial Microvascular Unit: A Reference Point?

The slopes of the power-law relationships differed from animal to animal, but in each set of observations, in baboons, sheep, and rabbits, there was a consistent phenomenon. Those animals that exhibited large relative dispersion at the one-gram reference size had lower fractal dimensions or slopes than did those that had small relative dispersions. From this we surmised that the data for a given species might be represented by a family of lines intersecting at a common point. This idea was applied by Roger *et al.*,⁸ as illustrated for the sheep data in Figure 3.

The point of intersection, at RD = 102 percent at a volume element size of 75 μg is shown in Figure 3. The lines through the sets of data have the common equation

$$RD_s = 102\% \cdot \left(\frac{m}{75 \mu\text{g}} \right)^{1-D_s}.$$

The fractal dimension then gives the individual lines; each animal has a separate and distinct fractal D , which can be calculated from the RD observed with 1-g pieces:

$$D = 1 - \frac{\log [RD(1)/1.02]}{\log [75 \times 10^{-6}]}$$

This relationship then gives a common representation of all of the data for the 10 baboons and 11 sheep shown in Figure 4.

This point of intersection at a 75- μg piece size might suggest that the common microvascular unit is about 75 μg or 75 nl in volume. This would in turn suggest that there might be about 13 arteriolar inflow points into 1 mm^3 of tissue, a number compatible with those from Eng *et al.*,⁹ Kaneko,¹⁰ and Bassingthwaighte *et al.*,¹¹ but larger than those of Batra and Rakusan.¹² The apparent heterogeneity at this projected microvascular unit size, however, was too large at 102 percent compared with the direct observations of Stapleton *et al.*,¹³ who obtained estimates of RD under 50 percent, from high-resolution measurements in hamster hearts. They used autoradiography to assess flow heterogeneity in element sizes of greater than 100 cubic microns, using the “molecular microsphere” iododesmethylinipramine developed by Bassingthwaighte *et al.*¹⁴ While the fractal relationships were not well determined in Stapleton's observations, due to limitation in the statistical assessment, this provoked a reassessment. After all, the projection of the data on the sheep and baboons was an extrapolation from the smallest observed pieces of about 100 mg down to pieces of less than 100 μg , a three order of magnitude extrapolation, leaving a lot of room for doubt.

Van Beek *et al.*⁷ sought a combination of an explanation for the flow heterogeneity and a reasonable projection. They found that small asymmetries in a dichotomously branching system could give rise to the appropriate relative dispersions. Two variations on a branching algorithm, each a fractal recursion, are shown in Figure 5.

The network was described on the basis that at each branch point a fraction γ of the apparent flow went to one branch, while a fraction $1 - \gamma$ went to the other branch. The fraction γ could be used as a constant, or modified in each generation, as in the right panel of Figure 5, or could be slightly random, around 0.5. No matter which version of deterministic or random γ was used, the degrees of asymmetry that gave fits to the data were small, that is, values of γ differed from 50 percent by only 3–4 percent. The relative dispersion at the n th generation in such a network, for example, with an unchanging γ , was

$$\text{RD} = \sqrt{2^n (\gamma^2 + (1 - \gamma)^2)^n - 1},$$

where the number of arterial endings is 2^n . The plots of relative dispersion vs. number of branchings or piece size from such networks are curvilinear, not straight, even though their basis is perfectly fractal. More interestingly, it turned out that these curvilinear relationships gave slightly better fits to the data on the individual sheep and baboons than did the straight-line relationships. Furthermore, these curvilinear relationships could also be extrapolated, in the same fashion as were the straight lines, to their intersection at a common point surmised to be the functional microvascular unit.

This is illustrated in Figure 6 for the data on 10 baboons, where the curved relationships extrapolate to an estimated microvascular unit size of 50 μg . This extrapolation gives an estimate of the projected overall heterogeneity of a distribution of flows at a standard deviation of 55 percent of the mean. It seems much more compatible with the direct observations on the hamster hearts using the molecular flow marker, but data on larger

hearts have not been obtained at this level of observation. The observation and projection also raise the issue of whether the heterogeneity in larger hearts is, for any given unit size, larger than in small hearts. It would seem reasonable that it might be, since there must be a larger number of generations of branching to supply a given unit size in a large heart than in a small heart. An argument against this is that the metabolic requirements of a given unit size might in fact be the same in all hearts, or at least when normalized for the fact that small animals normally have higher metabolic rates than large animals, but there are also large variations in the ratios of heart mass to body mass among species, dog hearts being about 1 percent of the body mass, while sheep hearts are only 0.3 percent. Such differences in ratios of heart mass to body mass presumably reflect the metabolic activity of the heart and the maximum ability of the animal to exercise.

Conclusion

The use of fractals for discussing flow heterogeneity in the myocardium is at three levels. The first level is simply descriptive, giving a common relationship for flow heterogeneity over a large range of sizes of the observed tissue samples. The second level is one of explanation, namely that fractally branching arterial networks can give rise to the observed heterogeneity. Whether the dichotomous networks giving the fits shown here are close approximations to the real arterial networks is as of yet unknown, since sufficient data have not yet been acquired on coronary arterial branching patterns. The third use of the fractals was in projecting the heterogeneity to the functional microvascular unit size. The extrapolation is over three orders of magnitude, an uncomfortably large range, but nevertheless the estimated dispersions are compatible with those obtained by making observations in another species in pieces within the range of the expected microvascular unit sizes. Verification is not secure if it is from another species, and so the question remains, and needs to be resolved by observations in larger hearts made with pieces ranging from many grams down to pieces of microgram or at least 100- μ g sizes.

While it cannot be said that fractal relationships are proved as the basis of flow heterogeneity in the myocardium, it can be said that the use of fractal approaches gives rise to some ways of making observations and asking questions that would seem useful in the field. Further studies need to be accomplished before the assessment is complete.

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Figure 1.

The effect of sample size on the apparent dispersion of regional blood flow in the left ventricle of 11 sheep hearts. Data were obtained using the “molecular microsphere” iododes-methylmipramine. The average mass of the pieces, $\bar{m}_i$, are in the order of the peak heights of the distributions and the RD's increase with finer division. (From Bassingthwaighe *et al.* 6 Reprinted with permission from the American Heart Association.)

Figure 2.

The apparent relative dispersions of regional flows, the standard deviations divided by the mean at each level of division, are plotted against the average masses of the pieces for seven different sample sizes of the heart of one sheep. The estimates of RD were obtained by forming aggregates of adjacent pieces in three to eight different ways, except for the smallest pieces. Data were from simultaneous injection of microspheres (*open circles*) and IDMI (*closed circles*). (From Bassingthwaighe *et al.*⁶ Reprinted with permission from the American Heart Association.)

Figure 3.

Projection of the fractal relationships for the relative dispersions of regional flows for 11 sheep through a common point. The best fit was obtained with the intersection point at $m = 75 \mu\text{g}$ and $\text{RD} = 102\%$ ($r = 0.975$). (From Roger *et al.*⁸ Reprinted with permission from Microvascular Research.)

Figure 4.

Scatter plot of the fractal dimension vs. the relative dispersion of regional flows (at $m = 1g$). The line is the best fitting for the data from 10 baboons and 11 sheep (the coefficient of variation is 0.032) using the equation for a common point of intersection of the fractal relationship. (From Roger *et al.*⁸ Reprinted with permission from Microvascular Research.)

Figure 5.

Recursive relations for branch flows in a dichotomously branching network. Two generations only are shown. **Left panel:** Model I, all $\gamma_i = \gamma$ at all generations. **Right panel:** Model II, all γ_i for the i th generation are the same, but decrease from generation to generation when $f_i < 1$. (From van Beek *et al.*⁷ Reprinted with permission from American Journal of Physiology.)

Figure 6.

Projection of a dichotomously branching fractal arterial network model to fit the data from the hearts of 10 baboons. The common point of intersection shows a relative dispersion of 50 percent at a common unit size of $50 \mu\text{g}$ (coefficient of variation = 0.045). (From Roger *et al.*⁸ Reprinted with permission from Microvascular Research.)