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Stability of Heterogeneity of Myocardial Blood Flow in Normal Awake Baboons

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SUMMARY

Regional myocardial blood flow has been thought to be relatively uniform, in accord with the singular function of myocardial cells. However, considerable spatial heterogeneity has been observed in the hearts of anesthetized animals and in isolated hearts. Studies were undertaken in a total of 13 baboons. Eleven were awake, healthy animals sitting in chairs at rest or feeding, some performed mild leg exercise (wheel turning), and others were subjected to whole body heating; two were anesthetized, methodological controls. Microspheres ($15 \pm 3 \mu\text{m}$ diameter, $0.5 \times 10^6/\text{kg}$ body weight) were injected via a catheter into the apex of the left ventricle while arterial blood was sampled at a constant rate for calculating cardiac output. Microspheres with different labels were injected at six intervals of 20 minutes to several hours. On sacrifice, the hearts were sectioned into 204 locatable pieces (left ventricle, 168; right ventricle, 27; and atria, 9). Average resting myocardial flow was $2.1 \pm 0.2 \text{ ml/g per min}$ (mean $\pm$ SD, $n = 11$). Left and right ventricles and atria comprised $70 \pm 2\%$ ($n = 13$), $20 \pm 2\%$, and $10 \pm 2\%$ respectively of the total heart mass while receiving $80 \pm 3\%$, $16 \pm 2\%$, and $4 \pm 2\%$ of the total myocardial flow. Thus, mean left ventricular flow was $114 \pm 5\%$ of the average for the whole heart, right ventricular flow was $81 \pm 13\%$, and atrial flow was $41 \pm 13\%$. Myocardial flow heterogeneity was marked; in left ventricle, regional flows ranged from one-third to two times the mean, the relative dispersion (= standard deviation/mean) of regional flows, corrected for methodological scatter and temporal variation, was 0.33 ± 0.06 ($n = 67$) in the whole heart, 0.26 ± 0.07 in left ventricle, 0.32 ± 0.11 in right ventricle, and 0.22 ± 0.19 in the atria. The pattern of regional flows in each heart tended to remain stable with time. In each piece averaged over time, the relative dispersion due to temporal heterogeneity was 0.11 ± 0.03 ($n = 2040$) in the whole heart, 0.09 ± 0.03 in the left ventricle, 0.15 ± 0.05 in the right ventricle, and 0.23 ± 0.06 in the atria. The conclusion is that the degree of spatial heterogeneity of local myocardial flows in conscious primates is similar to that of anesthetized animals and isolated hearts, and is much greater than that due to temporal fluctuations.

Keywords

Flow distribution; Coronary arteries; Septal perfusion; Tracer-labeled microspheres; Awake primates; Spatial variation in flow; Temporal variation in flow

With the increasing refinement of biochemical and physiological observations, the variations that occur throughout the myocardium in rates of metabolism (Griggs et al., 1972), in

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oxygenation (Gamble et al., 1974; Schubert et al., 1978; Weiss and Sinha, 1978), and in flow (Domenech et al., 1969; Yipintsoi et al., 1973) have become quite evident. It is no longer sufficient either in concept or in practice to regard the heart as a simple, homogeneous organ, even in the normal state.

The primary objectives of this study were, first, to provide information on the distribution of myocardial blood flow (MBF) by repeatedly measuring microsphere distributions in small regions of the myocardium, and, second, to estimate the overall myocardial heterogeneity of MBF in several situations where mean MBF and its distribution might change. Primates were chosen because of their similarity to humans. We studied conscious baboons conditioned to sit quietly for long periods in neutral (resting control) and hot environments (heat stress), with and without added feeding activities, and to perform mild leg exercise (wheel turning).

The data will lead to the conclusion that there is a stable spatial pattern of regional flows in each heart, around which the “twinkling” (Yipintsoi et al., 1973) of temporal fluctuations is small. Methodological error also contributes to the observed variation in regional flows and must be accounted for separately. The heterogeneity observed at any “snapshot” in time depicted by the local deposition-densities of microspheres from a single injection can usefully be summarized by the variance of the distribution. When the various factors contributing to the observed variance are independent of one another, then the observed total variance, SD_{obs}^2 , is the sum of the contributing variances:

$$SD_{obs}^2 = SD_{spatial}^2 + SD_{twinkling}^2 + SD_{method}^2.$$

So that the spatial heterogeneity might be examined, the contributions of temporal variation and methodological noise had also to be assessed.

Secondary objectives were to test whether or not the heterogeneity of myocardial blood flow was changed as total coronary blood flow or cardiac output changed, and to relate these changes to mass transport through the myocardial circulation. Previous studies by Knopp et al. (1976) and by Yipintsoi and Bassingthwaite (1970) have shown that albumin, an indicator limited to the vascular space, and iodoantipyrine, whose exchange with myocardial water space is so rapid that it is flow-limited, undergo similar degrees of dispersion relative to their mean transit times for transcortical passage. This is the case even over a wide range of myocardial flows (Bassingthwaite et al., 1972). This result could be obtained if myocardial flow in each region changed in proportion to the total myocardial blood flow. The present microsphere studies provide a test to indicate whether such an explanation is reasonable.

The results show that in healthy, awake, active baboons, there is marked heterogeneity of regional myocardial blood flows. The flow distributions are nearly symmetrical about the mean flow for the heart and have a standard deviation of 36% of the mean. Even in the left ventricle (LV) alone, there is a 5- to 6-fold range of flows. The heterogeneity is due to a stable spatial variation; temporal fluctuations account for less than one-tenth of the variance. There are normal myocardial regions in which the flow is only 30–40% of the mean, and which should not be considered ischemic.

Methods

Animals

We studied 13 male adolescent baboons (*Papio anubis*) weighing 8.2–15.5 kg. Seven of these were animals in which the effects of heat stress on the whole body distribution of cardiac output has been reported by Hales et al. (1979). The animals were adapted over a period of several weeks to living in primate chairs and to spending up to 10 hours at any one time seated quietly in an acoustically isolated booth. They sat upright in the chair, with the torso and the limbs free to move. Three or more days before experimental observation, catheters and other probes were inserted under general anesthesia (halothane in oxygen); sterile procedures were observed. A polyethylene catheter was passed via the left common carotid artery to the apex of the left ventricle for the injection of microspheres. Vinyl catheters (0.8 mm i.d., 1.2 mm o.d.) with 6-cm-length tips of Silastic attached were placed in an axillary artery for the monitoring of arterial pressure and in one or both of the femoral arteries for the blood sampling necessary for microsphere measurements. No major blood vessels were ligated. To prevent closing of the catheters, each was perfused with heparinized isotonic saline (approximately 250 IU heparin per catheter per 24 hours). Arterial blood pressure (pulse and mean) and heart rate were recorded on a Beckman polygraph, via a Statham P23dB strain gauge. Arterial blood samples were drawn into chilled heparinized syringes and the P_{CO_2} , P_{O_2} , and pH were directly measured with electrodes (BMS3 MkII, Radiometer); analyses were made at 37°C and were corrected to the animal's body core temperature.

Experimental Procedure

Three hours or more before we began the experimental measurements, the animal was placed in the acoustic booth and continuous monitoring of arterial pressure and heart rate was begun: Ambient temperature was 18–21°C in the control state. When monitored functions were steady, control measurements were made: the first blood sample was taken for blood gas analysis, followed immediately by the first microsphere injection and withdrawal of the systemic arterial blood sample to provide measures of cardiac output and tissue blood flow rate. In some animals, this procedure was repeated approximately 15 minutes later.

Heat Stress and Exercise—Our intent was to impose two stresses that might raise cardiac output and myocardial blood flow so that regional heterogeneity might be examined under these circumstances. However, none of the seven animals exposed to heat stress under the conditions reported previously (Hales et al., 1979) showed large increases, nor did those performing mild leg exercise (three animals). Because of the absence of significant changes in coronary blood flow, distinction between the “test” or “stress” and “control” states is not warranted from the physiological point of view, although the tables provide separately the “test” and “control” data.

Microsphere Injections—Hales and Cliff (1977) observed directly, in a rabbit ear chamber preparation, that 15- μ m microspheres lodged in precapillary sphincter regions and capillaries and did not stop the flow of erythrocytes. Bassingthwaighe and Carlson (unpublished data) showed that, in the heart, they lodge mainly in capillaries. The conclusion is that microspheres provide a measure of regional capillary blood flow at the level of resolution of the cognate bed supplied by one terminal arteriole or smaller, about 1 mm³ or less, according to the estimates of Bassingthwaighe et al. (1974).

The technique used by us has been more fully described by Hales (1974), Hales et al. (1979), Yipintsoi et al. (1973), and Heymann et al. (1977). We will present here only particular details.

Radioactive microspheres nominally 15 μm in diameter were obtained from the 3M Company, with six different labels: ^{141}Ce , ^{51}Cr , ^{113}Sn , ^{85}Sr , ^{95}Nb , and ^{46}Sc . Microsphere doses were injected over approximately a 40-second period into the left ventricle or atrium (in two control animals) so that many cardiac cycles were encompassed. The injection was made by hand with a 2-ml syringe, followed by a quick and then a slower 5-ml flush of non-tracer-containing saline solution into the catheter system. We calibrated the dose by measuring the activity of the syringe containing the injectate before injection, and of the syringe and related connectors after injection.

Doses contained approximately 0.5×10^6 microspheres/kg body weight. This is a greater number than commonly used, and based on prior experience with sheep was necessary to obtain an acceptable degree of precision in organs (e.g., skin) with relatively low rates of perfusion (Hales, 1974). This relatively large number of microspheres has not been observed to have any ill effects on gross cardiorespiratory functions in sheep (Hales, 1974) or on microcirculation in the rabbit's ear (Hales and Cliff, 1977). Yipintsoi (personal communication) has found that very large doses, up to 10^4 spheres/g myocardium, given over a few seconds, have a negligible effect (less than 2%) on coronary vascular resistance when they are well disaggregated. In the baboon, there was no observable influence on heart rate or arterial blood pressure, but in one baboon the renal blood flow, monitored by electromagnetic flowmeter, showed a transient decrease.

A reference or "artificial organ" sample was drawn at a flow, F_{ref} , of approximately 6 ml/min from either an axillary or femoral artery. This sampling rate is about one-third that commonly used and was arrived at experimentally, following concern over the proportion of the blood volume which would have to be taken if the usual 20 ml/min sampling rate was used. As far as obtaining adequate numbers of microspheres is concerned, less than 1 ml/min would be adequate with the dosage levels used. Multiple comparisons (from six tracers injected at once) were also made in one baboon (no. 13) in the control state, showing a 12% standard deviation in estimates of cardiac output and 11% in cardiac flow.

Sectioning of the Heart—At the end of the experiment, the animal was killed with an overdose of barbiturate. The heart was removed and cut perpendicularly to the axis into four rings about 1 cm thick, as illustrated in Figure 1. The papillary muscles were contained in ring 2 or 3. Large epicardial vessels were trimmed off. The atria and the right ventricular free wall were removed from the left ventricle. The rings of left ventricle were placed on a sheet of dry ice to harden the muscle to prevent distortion and to facilitate subsequent sectioning. When just frozen, each ring, except the apical one, was then cut radially into eight sectors in an ordered fashion; the septum was always denoted as sectors 6 and 7 and the LV free wall as sectors 2 and 3. The apical ring, being smaller, was cut into only four sectors. Each sector was sliced manually into six slices, using cuts parallel to the epicardial surface. Each slice, with dimensions averaging roughly $15 \times 10 \times 1$ mm was weighed immediately upon slicing; their weights ranged from 0.032 to 0.737 g with a mean of about 0.17 g. There were 168 samples per left ventricle, 27 per right ventricle, and 9 from the atria, for a total of 204 pieces per heart.

Sample Counting—The radioactivity in each sample was measured with a $3'' \times 3''$ NaI well crystal (Harshaw Chemical) equipped with an automatic sample changer (Baird Atomic model 708). Each piece of tissue was placed in the same geometric position in the bottom of a test tube. The γ -ray spectra from the samples were acquired with a 1024-channel

multichannel analyzer (Tracor Northern Econ 700), stored on digital magnetic tape, and analyzed on a Perkin-Elmer 8/32 computer by the matrix inversion technique. This technique, rather than spectrum stripping, was used, because the matrix technique avoids the propagation of error inherent to any method of successive subtractions. In addition, it has the advantage of accounting for spillover by any nuclide into energy windows both above and below its own, which spectrum stripping does not permit. With the nuclides and windows used here, for example, when equal amounts of ^{95}Nb and ^{46}Sc were used, the value for ^{46}Sc would have been overestimated by 15% using spectrum stripping, and this error would have been propagated through the calculations for all the other nuclides.

Estimation of Blood Flow

Cardiac Output—The cardiac output (CO) (ml/min), was calculated from the reference sample flow, F_{ref} , activity in the reference sample, q_{ref} , and the total activity injected, q_o

$$\text{CO} = F_{\text{ref}} \frac{q_o}{q_{\text{ref}}}$$

Myocardial Blood Flow—The calculation of total myocardial blood flow, F_T (ml/min), which is independent of the dose administered, is based on F_{ref} , q_{ref} , and the total activity in the heart, q_T

$$F_T = F_{\text{ref}} \frac{q_T}{q_{\text{ref}}}$$

The average flow per gram of myocardium, F_H' is F_T/W , where W is the total heart mass in grams. (In this study, the prime on F' denotes flow per gram.)

The fundamental assumption in all microsphere studies is that the relative regional flows, f_i , are equal to the relative deposition densities, d_i , that is, that microspheres are delivered to each small region in proportion to flow. (This assumption cannot be tested until a non-microsphere technique for obtaining regional flow estimates is developed.) Local deposition densities are calculated either absolutely or relative to the mean density. The relative deposition density, d_i , is activity in counts per minute per gram in a piece, divided by the mean activity for the whole heart. The step-by-step procedure is archived (Bassingthwaite, 1982). For each large anatomical region, LV, RV, and atria (A), the flow per gram, F'_{LV} , F'_{RV} , and F'_A were calculated from $\bar{f}_i \cdot F'_H$, where $\bar{f}_i$ is the mean relative flow in the region.

Distribution of Myocardial Blood Flow—Two methods were used to display the distribution of flows within the myocardium. First, the *spatial distribution* of f_i in the left ventricle was displayed graphically by using a computer-driven raster-graphics device and assigning gray shades, which became increasingly darker with increasing f_i . The patterns gave us a general view of each nuclide of the distribution of deposition for the parts of the heart studied. Second, the *density functions* of relative regional flows were calculated by determining the fraction of the total heart mass, w_i , which fell into each of 25 intervals, with width, Δf_i equal to 10% of the mean flow. This procedure produces a standard probability density function of flow per gram of tissue relative to the mean flow for the heart, $w(f)$. The area, $\sum w_i \Delta f_i$ is unity; the mean $\sum w_i f_i \Delta f_i$ is also unity as detailed by Bassingthwaite (1982).

The degree of heterogeneity was expressed by the relative dispersion ($RD = s_d/\text{mean}$) of the values of f_i . Spatia heterogeneity was estimated from the RD of the values in the 204 heart pieces for each measurement. Temporal heterogeneity was estimated from the RD of the four to six values measured in each piece. Thus, an animal in which six measurements were made and whose heart was sectioned into 204 pieces gave six estimates of spatial heterogeneity (204 values in each) and 204 estimates of temporal heterogeneity (six values in each). Statistics are reported as mean $\pm 1 s_d$ (n = number of observations). (The standard error of the mean is not reported or used.)

Assessment of the Microsphere Method

Several experiments were undertaken to assess the systematic noise of the microsphere method as we used it. These experiments and their results are detailed by King and Bassingthwaite (1984) in an archive available publicly. In one control awake animal, six differently labeled spheres were injected simultaneously. With our techniques, making sure that the microspheres did not aggregate prior to injection, etc., the correlation coefficients between pairs of distributions of differently labeled spheres injected simultaneously averaged 0.97 ± 0.01 ($n = 15$), showing that methodological scatter was small. In the same heart, the relative dispersion of the six observations of deposition density in each of 204 individual pieces in the whole heart averaged 6.5 ± 1.0 , $n = 720$, and for the 168 pieces of the LV averaged 6.7 ± 1.0 , $n = 504$. Thus, this 6–7% noise, RD_{method} , defines the variation attributable to the microsphere methodology. It is small compared to the heterogeneity of regional flows of 30% or more.

Two control studies were done to assess two sources of variability: (1) microsphere size, 9 μm vs. 15 μm , and (2) the injection site, left atrium (LA) vs. the apex of LV. We anesthetized these two baboons in order to place the LA injection catheter by the transseptal technique. Four differently labeled microspheres were injected: 15- μm and 9- μm spheres into LA, and 15- μm and 9- μm spheres into LV. The results were: (1) the differences in relative dispersions for the whole heart between the two sphere sizes were 0.027, 0.001, -0.003 , and 0.016, averaging 4% out of 0.34 (± 0.024 , $n = 8$), which is statistically insignificant; (2) for the 15- μm spheres, the relative dispersions after LA injection in the two animals for the whole heart were 0.35 and 0.31, whereas those for the simultaneous LV injection were 0.34 and 0.38. For the 9- μm spheres, the results were 0.32 and 0.31 from LA, and 0.33 and 0.36 from LV. The plots of the density functions showed similar shapes for the two injection sites. The first conclusion is that 9- and 15- μm spheres are similar, even with the small piece sizes that we used. Second, in these baboon studies in which catheter placement at the tip of the LV apex was carefully confirmed in all 14 animals, the siting of the injection catheter into LV apex vs. LA makes no difference to the shapes of the deposition density functions or the relative dispersions of the distributions.

Results

Mean Flow in Ventricles and Atria

Control State—In Table 1 are shown data on mean flows in the control state. The heart weight was $35 \pm 4\%$ (mean $\pm s_d$, $n = 11$) of body weight. Of the total heart weight, the left ventricle was $70.0 \pm 2.0\%$ ($n = 13$), the right ventricle $20.2 \pm 2.1\%$, and the atria $9.8 \pm 1.6\%$. On a body weight basis, the cardiac outputs averaged 223 ± 69 ml/min per kg ($n = 11$), and the total coronary blood flows averaged 2.13 ± 0.80 ml/g per min ($n = 11$). Flow to the LV was higher than the average coronary flow, 2.41 ± 0.90 ml/g per min ($n = 11$), and $80 \pm 3\%$ ($n = 13$) of the coronary flow goes to the LV. F_{LV} is one-third greater than F_{RV} and almost three times atrial flow. The regional flows in LV, RV, and atria were rather consistent relative to the mean flow. The flow per gram to LV divided by the flow per gram to the total

heart, F_{LV}'/F_H' , averaged 1.14 ± 0.047 ($n = 13$), whereas, for RV, the relative flow per gram was 0.81 ± 0.13 and for the atria 0.41 ± 0.13 . There is much less variation in these relative flows than in the absolute flows per gram of tissue, an observation which is consistent with the stability of relative regional flows. In the control state, the mean arterial pressure was 108 ± 14 torr ($n = 10$). The heart rate was 141 ± 24 beats/min ($n = 9$), and the stroke volume was 20.3 ± 4.7 ml ($n = 9$).

Test States—There were no statistically significant increases in cardiac output or in coronary blood flow during heat stress. Although the inter-animal variation was high in the three exercising animals, there was a significant increase in cardiac output from 205–319 ml/min per kg ($P < 0.01$ by paired t-test), but not in coronary blood flow. This was due to an increase in both heart rate (109–142 beats/min, $P < 0.005$) and stroke volume (26.0–30.3 ml, $P < 0.05$). The fractional flows to LV, RV, and atria were unchanged during all test states.

Distribution of Regional Myocardial Blood Flows

Mapping of Left Ventricular Flows—In Figure 2 are shown the relative flows in regions of the LV for one animal during control and at three levels of heat stress. Each column contains data from one injection of microspheres. Each circular array represents one ring of the left ventricle, the basal ring at the top and the apical ring at the bottom. Darker shades represent higher flows. The sectors are numbered as in Figure 1 so that the lateral free wall is on the right and the septum is on the left.

At the top of each column is the density function of regional flows for the left ventricle; the abscissa is F_i'/F_{LV}' (rather than F_i'/F_H'), and the area is unity. In this case, the flow distribution for the control state is perhaps a little more sharply peaked than those during heating, but the difference is slight compared to the variation in the details of the shapes of these functions. The body core temperatures are given above the plots; body temperature had no significant influence on the regional distribution of microspheres in the heart.

Similar maps were made for all other animals; all showed generally consistent patterns of deposition over the four to six separate observations in each.

Density Functions of Regional Flows—In addition to the polygons of regional flows shown in the top row of Figure 2, the distributions of LV flows for the six states in two additional animals are shown in Figure 3. Since the distributions are for LV samples only, the mean for the distribution is F_{LV}'/F_H' , i.e., about 1.14, and the area under each is the fraction of the total heart weight comprised by the LV myocardium, i.e., about 70%. In the 13 animals, the distribution themselves were skewed very little, but they did tend to be leptokurtic, that is, high-peaked, relative to a Gaussian distribution.

In Figure 4 is shown the probability density function of the relative flows for the accumulated data from all 13 hearts, a total of 13,114 estimates of f_i in 2,708 pieces of myocardium. The curve for the whole heart and its LV, RV, and atrial components are depicted. The shaded patch outlines 1 SD of the f_i in each of the 25 classes or relative flows for the whole heart; each class width here is 10% of the mean flow. The standard error of the mean within each flow class is much smaller, since n is large for each category—for example, at $f_i = 0.5$ (i.e., from 0.45–0.55), 1.0, and 1.5, the n are 885, 3556, and 1716.

Assessment of the Heterogeneity of Flow

Observed Total Heterogeneity—The relative dispersion of the distribution of relative flows in the pieces of myocardium at each measurement was used as the measure of heterogeneity. These are summarized in Table 2. The control states have been averaged for

each animal; the test states are averaged separately in the middle column. In the control group, microspheres were simultaneously injected in a control state, awake in animal 13 (six tracers), and lightly anesthetized in animals 11 and 12 (four tracers in each: two in LV apex, two in LA).

The regional relative dispersions were fairly consistent in the several groups and states. The broader dispersions in RV and atrial myocardium are evident in Figure 4. These greater RD, combined with the distinctly lower mean flows in these regions, as shown in Table 1, mean that the whole heart density functions have considerably more spread than do the LV flows. As with the LV flows, the density functions of RV and atrial flows are rather consistent, both in shape and in their mean flows relative to the whole heart mean. From the accumulated data ("All States" in Table 2), the average values of relative dispersions were: 0.36 ± 0.06 in the whole heart, 0.28 ± 0.07 in the LV, 0.36 ± 0.10 in the RV, and 0.33 ± 0.12 in the atria.

Temporal Heterogeneity—The temporal change in the distribution of blood flow within each piece of the myocardium was assessed by computing the mean of the relative dispersions of the four to six flow values in each of the 204 pieces of myocardium of the 10 exercised or heated animals. The results are summarized in Table 3 for data from all the pieces of each heart. The overall mean of RD_{temporal} is $12.7 \pm 2.4\%$ ($n = 2040$ sets of four to six microspheres) in the whole heart, and insignificantly less for LV alone, $11.4 \pm 2.7\%$ ($n = 1680$ pieces). Temporal heterogeneity is greatest in the atria and least in the LV. The controls, where all microspheres were injected simultaneously, presumably contain only methodological variation and are excluded. Temporal heterogeneity includes both methodological variation and true flow fluctuations or twinkling:

$$RD_{\text{temporal}}^2 = RD_{\text{method}}^2 + RD_{\text{twinkling}}^2.$$

Variation due to the twinkling in LV, RD_{twinkle} , is:

$$\begin{aligned} RD_{\text{twinkle}}^2 &= \left[RD_{\text{temporal}}^2 - RD_{\text{method}}^2 \right]^{1/2} \\ &= \left[0.114^2 - 0.067^2 \right]^{1/2} \\ &= 0.092 \end{aligned}$$

which is most of the temporal variation observed, and indicates that regional flows do fluctuate. For the whole heart, $RD_{\text{twinkle}} = [0.127^2 - 0.065^2]^{1/2} = 0.109$. This variation due to twinkling or local flow fluctuations is about 10%.

The similarity between states can be assessed by considering the 204 pieces of the heart as a linear array, thus permitting the calculation of correlation coefficients between pairs of the four to six states. For any given animal in which M measurements were made, the number of unique comparisons, excluding self-comparisons, which can be made is $M(M-1)/2$. The mean correlation coefficients for these comparisons were grouped into comparisons of control state vs. other control states, control vs. test states, and test vs. test states. The mean coefficients for these three categories are 0.86 ± 0.07 ($n = 21$), 0.83 ± 0.10 ($n = 65$), and 0.86 ± 0.09 ($n = 33$); each of these n is based on the $M(M-1)/2$ comparisons in each animal. The correlation between control and test states was not significantly lower than the correlation within either of the two states.

Spatial Heterogeneity—At any given moment, the flow heterogeneity is a combination of a stable spatial flow distribution with some temporal fluctuation superimposed. The idea of a stable spatial profile would be deemed invalid if temporal fluctuations dominated so strongly that the flows in all small regions over a long period had averages indistinguishable from the mean for the whole heart. Statistically, an equivalent statement would be that if the observed dispersion, RD_{obs} , could be accounted for by the combined variation due to temporal fluctuations, $RD_{temporal}$ and methodological noise, RD_{method} then stable spatial differences would be inconsequential. That is, is $RD_{spatial}$ distinguishable from zero?

The equation in the Introduction, dividing the SD^2 by the square of the mean, may be restated as:

$$RD_{obs}^2 = RD_{spatial}^2 + RD_{twinkling}^2 + RD_{method}^2$$

allowing direct calculation of $RD_{spatial}$, e.g., for the LV:

$$\begin{aligned} RD_{spatial}^2 &= \left[RD_{obs}^2 - RD_{temporal}^2 \right]^{1/2} \\ &= \left[0.283^2 - 0.114^2 \right]^{1/2} \\ &= 0.26 \end{aligned}$$

For the whole heart, the equivalent calculation is $RD_{spatial} [0.57^2 - 0.127^2]^{1/2} = 0.333$.

The ratios of $RD_{spatial}/RD_{twinkle}$ are 2.8 for the LV alone and 3.0 for the whole heart, leading us to conclude that the spatial variation clearly dominates.

Discussion

For the 11 baboons in which cardiac output was measured, the average resting value was 223 ml/min per kg. Although the figure appears quite high, about twice the resting value in humans, it is similar to previously reported values for the baboon (Levitsky et al., 1982; Casey et al., 1983) and for the rhesus monkey (Forsyth et al., 1968) at rest. It was hoped that by subjecting the animals to heat and exercise stresses, the distribution of myocardial blood flow could be studied over a wide range to total myocardial flows, but this did not prove to be the case. Although heat stress caused a marked redistribution of cardiac output (Hales et al., 1979) and exercise caused a small but significant increase in cardiac output, neither stress caused a significant change in total myocardial flow. In contrast to man (Rowell et al., 1970), the baboon did not increase its cardiac output with hyperthermia but, rather, redistributed an already high resting cardiac output. Similarly, the high level of myocardial blood flow at rest, about 2 ml/g per min, seems adequate to allow the baboon to cope with mild stresses without an increase.

The outstanding feature of all the experiments is the consistent form of the spatial distribution of flow within the heart. Although there exists considerable heterogeneity of flow within the myocardium of the conscious baboon, and there was no consistent pattern of distribution between the hearts, the pattern of flow within each heart remained relatively constant with time. The temporal stability of the flow distribution was evident in the maps of LV flows, frequency functions of flows, and statistical analysis of the regional flows. Although this stability is not absolute, when maps of LV flows at different times (as in Fig. 2) are compared, regions of higher than average flow (shaded heavily) tend to remain, as do regions of lower than average flow (shaded lightly). Likewise, when the regional flow histograms are examined, the consistency of the shape and spread of the histograms over

extended periods of time and through a range of experimental conditions is apparent. The shape of the density function appears almost characteristic for each animal, e.g., being very high-peaked in animal 4 (left panel, Fig. 3), but relatively low-peaked and right-skewed in animal 5 (right panel, Fig. 3). When a density function was skewed, to the left or right, it retained about the same skewedness throughout all states.

Our results do not conflict with those of previous investigators who concluded that there is temporal heterogeneity of myocardial blood flow. The value for variability of flow (i.e., range of local flow/mean local flow) found by Falsetti et al. (1975) and Marcus et al. (1977) was about 30% for four measurements over a 20-minute period in anesthetized dogs; analysis of our data in the same manner (i.e., the mean over all pieces of all hearts of the highest flow in a piece minus its lowest divided by the mean flow in that piece) gives a value of 38%. A recent study by Castellana and Case (1982) indicates even less variability in dogs, 10–15%. Sestier et al. (1978) found a mean coefficient of variation in all pieces of 11.1% for measurements separated by 20 seconds; for our baboons, the value was 14.5% for measurements separated by up to several hours.

The difference between their conclusions and ours lies in the fact that their studies measured only the degree to which local flow varied, without considering the value about which these flows vary. The point to be made is not that regional flows do not vary with time, but that they vary about a local mean which is different from the mean flow for the whole heart. Furthermore, this temporal variability was small compared with the spatial variability within the heart. Any temporal fluctuations in flow, such as “twinkling” of capillary flows (Yipintsoi et al., 1973) or changes in local vasoregulation, had, at most, modest effects. These were never such that the lowest flow regions achieved a flow as high as the average for the heart, or that the highest flow regions fell as low as the average. The tests of exercise and hearing likewise failed to induce large changes in local flows, just as they had failed to make large changes in cardiac output and myocardial flow. The high average correlation of 0.86 observed between the flows in an individual piece for the various states, including all the pieces from ventricles and atria, indicates a strong stability in the regional flows. This stability is definite, clear, and, since the range of flows is so great, is all the more remarkable.

The question can be asked as to whether the heterogeneity observed is an artifact of the microsphere technique and, if not, whether the technique used here over- or underestimates the true heterogeneity. The findings of Yipintsoi et al. (1973) using iodoantipyrine and potassium and of Little et al. (unpublished results) using desmethylinipramine, a plasma-soluble flow marker, showed similarly heterogeneous flows in the dog heart, thus indicating that heterogeneity is not an artifact of the microsphere method. Regarding the second question, the functional microvascular unit in the heart is about a millimeter cubed: the distances between arterioles or inflow points are about 1 mm (Bassingthwaight et al., 1974), and this unitary dimension is also suggested by the photographs of NADH fluorescence in the heart by Barlow and Chance (1976) and Steenbergen et al. (1977) during hypoxia. If the flow through each such unit were uniform, then the true relative dispersion could not be measured until the heart was divided into individual units of that size. Any coarser division, or any division that splits individual units, must give an underestimate of relative dispersion, i.e., artifactually greater *uniformity*. When there is no measurement noise, any division that is finer than the fundamental homogeneous unit will give exactly the same density function of flows as that for the units themselves. When there is measurement noise that increases with the fineness of division, the apparent RD can spread with increasing fineness of the divisions.

In these experiments, the pieces of tissue were 100–300 times the estimated size of the microvascular unit, so that if there were no measurement error, we would know that the true heterogeneity was still *underestimated*. Presumably measurement error might also increase if the hearts were cut into much smaller pieces. Suffice it to say that we know that the observed relative dispersions of 35.7% in whole heart and 28% in LV in Table 2 (or 35.1% and 27.5% when corrected for measurement variation) may be somewhat small, but *not* erroneously large. Another factor making the RD erroneously smaller might be the duration of the microsphere injections, which took as long as 40 seconds. Rapid temporal fluctuations would be averaged out; on this basis, it is more likely that RD_{twinkle} is underestimated, than RD_{spatial} . Nevertheless, since the anticipated unit size, 1 mm^3 , is two orders of magnitude smaller than our pieces, there is certainly the possibility of greater spread. From observations (our own and others') of unquannfied autoradiographs and from the photographs of NADH fluorescence (Barlow and Chance, 1976), we surmise that the spread is not much greater than in our observed density functions. Even so, this question should be subjected to further study.

A question raised by our study is why such a degree of heterogeneity might be so stable in a functioning heart. The implication is that metabolic needs and local geometric and physiological factors are different in different regions. This is quite consistent with the observations of Barlow and Chance (1976) and Steenbergen et al. (1977) in showing that, after the onset of hypoxia in rat hearts, the NADH fluorescence repeatedly showed first in certain small regions, of about 1 mm^2 epicardial surface area, in test after test on the same heart. The pattern was different in different hearts, but in each was quite reproducible. Thus, we suspect that in future studies we will find that local flows are related to metabolic needs, and that these are stable but different in different regions. One can only speculate on whether or not one region of LV myocardium might require more fuel than another, but it may be that there is a stable pattern of tension development which differs in each locale. Only very refined finite element analysis of mechanical deformations is likely to reveal this, a type of testing which is being approached by investigators using geometric imaging techniques (Pao et al., 1976; Heethaar et al., 1977).

The stability of the spatial heterogeneity of flow provides a qualitative and quantitative basis for the uniformity of shapes of washout curves and transcoronary dilution curves. Bassingthwaighe et al. (1970) showed the uniformity of shape of washout curves for xenon, and Yipintsoi and Bassingthwaighe (1970), for iodoantipyrine, over wide ranges of flows in isolated hearts. This is precisely what would be predicted from the present study, namely, whenever flow increases in each region in proportion to an increase in the mean flow, the shape of the washout curves relative to their mean transit time would not change at all. The same mechanism probably is responsible for the observations of Knopp et al. (1976), who determined the form of the transcoronary transport functions in intact dogs from indocyanine green concentration-time curves recorded simultaneously from the coronary artery inflow (the aortic root) and from the outflow (the coronary sinus) over a 3- to 4-fold range of flows. The intriguing result was that when the transcoronary transport functions—the probability density functions of transit times—were scaled relative to their individual mean transit times, they became fairly closely superimposed on one another. The probable explanation is that when mean flows change, both the distribution of flows and the regional volumes remain constant; in this circumstance, the transit times through each region change in inverse proportion to the local flow *and to the total flow*, thus maintaining the relative distribution of transit times.

Whereas the similarity of the transit time distributions and the stability of relative regional flows go hand in hand, their dominance would not deny the efficacy of local regulatory

processes such as autoregulation or an association between metabolic needs and the degree of vasodilation.

A wide variance of normal regional myocardial blood flows has at least two direct implications and applications. The first is that the variation in flow must be taken into account in obtaining estimates of capillary permeability and of cellular uptake rates. Rose and Goresky (1976) attempted an analysis of myocardial permeability with a heterogeneous flow model, but had no data on the actual regional flows. Levin et al. (1980) first used the microsphere depositions to provide estimates of flows for use in a multicapillary analysis. They showed that failure to account for flow heterogeneity gave large systematic errors in estimates of permeability (reviewed by Bassingthwaighe and Goresky, 1984). Likewise, Bassingthwaighe et al. (1985) found that, for glucose transport in the heart, the conductances were underestimated by 30–50% if heterogeneity of flows was not taken into account.

The second implication concerns a different aspect of blood-tissue exchange rates, namely, diffusional shunting of rapidly exchangeable substances, particularly gases, noticed for xenon by Bassingthwaighe et al. (1968). A difference in flows between adjacent regions tends to produce concentration gradients for native substances as well as for foreign indicators. Roth and Feigl (1981) demonstrated that intraarterially injected H₂ gas was detectable in the coronary sinus outflow before either erythrocytes or plasma protein markers. Bassingthwaighe et al. (1981, 1984) showed that, for thermal indicators, the shunting was very great, particularly at lower flows. Such shunting could occur between arterioles and venules serving a region when regional flows are completely homogeneous, but it may also occur between regions of differing flows. The possible mechanisms presented by Bassingthwaighe (1977) may be distinguishable by performing a series of experiments while making changes not only in the mean flows, but also, using vasoactive agents, in the degree of heterogeneity of flow. By carefully measuring sets of outflow dilution curves for substances of differing diffusibility in tissue, along with regional flow measurement, and incorporating the anatomical arrangements of the microvasculature as well as possible, one has a good chance of determining the relative importance of counter-current exchange diffusional shunting vs. shunting between neighboring regions having different tracer arrival times.

In summary, the main purpose of this study is to demonstrate that regional myocardial blood flows in normal awake animals is markedly heterogeneous. It is not significantly different from that found in open-chest situations and in isolated heart preparations. Much further study is required before the anatomical, hydrodynamic, metabolic, and functional bases and physiological implications of the observed heterogeneity can be understood. Particularly intriguing is the stability of the patterns of regional flows and the question of how these relate to local muscle tension development and metabolic needs.

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FIGURE 1.
Schema for dividing the heart into identifiable pieces allowing reconstruction.

FIGURE 2.

Regional myocardial blood flow in baboon #3 during heat stress. Each column portrays data from one injection of microspheres. The histogram at the top of each column is the normalized density function of relative flows f_i for the left ventricle alone, i.e., f_i/f_{LV} , at the time of deposition of the microspheres. The four rings from above to below give the f_i in rings 1–4, base to apex; darker shades arc higher flows, as indicated by the scale in the left lower corner. Injections were made in the control state and during increasing heat stress at the body core temperatures noted at 1, 2.5, and 5 hours after the control state.

FIGURE 3.

Probability density functions of relative regional flows in the left ventricular myocardium in two baboons each receiving six microsphere injections over a period of 6 hours. Animals were seated at rest in either warm or neutral chamber temperatures. The ordinate is w_i , the fraction of the mass (per unit average flow) having flow f_i , the abscissa is the relative microsphere deposition density or flow, f_i relative to the mean for the whole heart. Left panel: (animal no. 4) Injections were at 0, 3, and 5 hours on the first day and at 0, 2.5, and 4 hours on the following day. The relative dispersions were 0.314, 0.239, 0.259, 0.262, 0.250, and 0.213 for the six experiments. The average relative dispersion (RD) was 0.256 ± 0.033 ($n = 6$). Right panel: (animal no. 5) The injections, all made on the same day, were at 0, 2, 2:05, 2:34, 2:42, and 252 hours after the first. The relative dispersions of these curves were 0.397, 0.380, 0.347, 0.364, 0.374, and 0.389 for an average of 0.375 ± 0.018 ($n = 6$).

FIGURE 4.

The distribution of relative flows in the hearts of 13 awake baboons, from 13,114 estimates at four to six times in 2,706 tissue pieces. The solid line represents the distribution for the whole heart, while the dotted lines are its left ventricular (LV), right ventricular (RV), and atrial (Atr) components. The standard deviation ($_{SD}$) for the whole heart curve is shown by the shaded region. The area under each curve represents its fraction of the total heart weight, and the mean is its flow relative to the total heart flow. These are, by definition, unity for the total heart curve. For the regional curves the values are: LV 0.70 and 1.14, RV 0.20 and 0.81, and atria 0.10 and 0.41. the relative dispersion of each curve is a measure of the spatial heterogeneity of the flow. The values are: whole heart 0.38, LV 0.30, RV 0.31 and atria 0.17.

TABLE 1

Flows in the Control State

Animal no.	Body wt. (kg)	Heart wt. g (% body wt.)	Fraction of heart wt. (%)			Cardiac output liters ($\frac{\text{ml}}{\text{min}} \cdot \text{kg}$)	coronary flow (ml/min per g) F^*_{H}	Regional flows (ml/min per g)			Fraction of coronary flow (%)			Relative flow			Foot-notes
			LV	RV	A			F^*_{LV}	F^*_{RV}	F^*_{A}	LV	RV	A	$\frac{F^*_{\text{LV}}}{F^*_{\text{H}}}$	$\frac{F^*_{\text{RV}}}{F^*_{\text{H}}}$	$\frac{F^*_{\text{A}}}{F^*_{\text{H}}}$	
1	12.7	32.0 (0.25)	69	18	13	2.94 (232)	2.40	2.70	2.00	1.00	80	14	6	1.15	0.8	0.42	[†]
2	10.0	34.5 (0.35)	72	18	10	2.99 (298)	1.47	1.63	1.31	0.55	80	16.5	3.5	1.11	0.92	0.38	[†] §
3	9.6	39.6 (0.41)	73	17	10	2.31 (242)	2.59	2.86	2.48	0.94	80	16	4	1.10	0.96	0.36	[†]
4	10.6	36.7 (0.35)	69	22	9	2.01 (180)	2.33	2.45	2.42	1.11	73	23	4	1.05	1.04	0.48	[†]
5	10.2	29.8 (0.29)	20	23	7	2.26 (222)	3.39	3.84	1.99	1.06	82	15	3	1.19	0.63	0.32	[†] §
6	8.5	31.7 (0.37)	69	20	11	3.26 (384)	3.16	3.53	3.01	1.01	77	19	4	1.12	0.95	0.35	[†]
7	9.8	37.5 (0.38)	67	23	10	1.86 (190)	2.21	2.71	1.43	0.66	82	15	3	1.23	0.65	0.30	[†]
8	10.8	37.5 (0.35)	71	18	11	2.43 (225)	1.99	2.29	1.64	0.60	82	15	3	1.15	0.82	0.30	[†]
9	17.5	60.3 (0.34)	71	20	9	2.70 (154)	0.54	0.59	0.47	0.28	78	17	5	1.10	0.87	0.55	[†]
10	14.4	52.8 (0.37)	69	21	10	2.39 (166)	1.83	2.19	1.27	0.54	82	15	3	1.19	0.69	0.30	[†]
11	43.5		70	20	10						79	15	6	1.13	0.76	0.58	//
12	35.8		67	23	10						75.5	16.5	8	1.14	0.73	0.72	//
13	17.0	63.6 (0.37)	73	20	7	2.46 (145)	1.52	1.74	1.09	0.52	82.8	14.5	2.7	1.15	0.72	0.34	¶
<i>n</i>	11	13 (11)	13	13	13	11	11	11	11	11	13	13	13	13	13	13	13
Mean	11.9	41 (0.35)	70	20.2	9.8	2.51 (223)	2.13	2.41	1.74	0.75	79.5	16.3	4.2	1.14	0.81	0.41	
SD	3.1	11 (0.04)	2.0	2.1	1.6	0.43 (69)	0.20	0.90	0.73	0.28	3.0	2.4	1.6	0.05	0.13	0.13	

* F^* is used to denote total flow to an organ or region. Thus F^*_{H} , F^*_{LV} , F^*_{RV} , and F^*_{A} are the total flows (ml/min per g) to the whole heart, left ventricle (LV), right ventricle (RV), and atria (A), respectively.

[†] Heat stress experiments; animal numbers are from Hales, Rowell, and King (1979).

[‡] Exercise experiments.

[§] Data are the average of two control states.

// Data are the average of four simultaneously injected tracers; animals were anesthetized for transseptal catheterization for LA injection.

¶ Data are the average of six simultaneously injected tracers.

TABLE 2

Observed Heterogeneity of Regional Flows, RD_{obs}

Group	Control states					Test states					All states				
	n	Whole	LV	RV	Atria	n	Whole	LV	RV	Atria	n	Whole	LV	RV	Atria
Heated animals	11	0.371 (0.053)	0.304 (0.052)	0.330 (0.032)	0.315 (0.140)	24	0.364 (0.047)	0.271 (0.053)	0.376 (0.102)	0.307 (0.100)	35	0.366 (0.048)	0.281 (0.054)	0.363 (0.088)	0.309 (0.112)
Exercised animals	11	0.318 (0.052)	0.253 (0.067)	0.355 (0.051)	0.376 (0.125)	7	0.326 (0.088)	0.282 (0.114)	0.337 (0.043)	0.320 (0.158)	18	0.321 (0.060)	0.265 (0.086)	0.348 (0.048)	0.354 (0.137)
Control animals	14	0.379 (0.053)	0.313 (0.055)	0.370 (0.164)	0.332 (0.129)						14	0.379 (0.053)	0.313 (0.055)	0.370 (0.164)	0.332 (0.129)
All animals	36	0.358 (0.054)	0.292 (0.062)	0.353 (0.112)	0.340 (0.130)	31	0.355 (0.059)	0.273 (0.069)	0.369 (0.085)	0.309 (0.112)	67	0.357 (0.056)	0.283 (0.066)	0.361 (0.100)	0.326 (0.122)

Results are expressed as mean relative dispersions (plus or minus standard deviations, in parentheses).

TABLE 3

Temporal Heterogeneity of Flow, RD_{temporal}

Group	All states			
	n	Whole	LV	RV Atria
Heated animals	1428	0.115 (0.012)	0.103 (0.014)	0.140 (0.017) 0.223 (0.058)
Exercised animals	612	0.155 (0.021)	0.141 (0.033)	0.204 (0.055) 0.283 (0.060)
All test animals	2040	0.127 (0.024)	0.114 (0.027)	0.159 (0.043) 0.241 (0.059)

Results are expressed as mean relative dispersions (plus or minus standard deviations, in parentheses) of four to six observations per piece at different times.