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Temporal fluctuations in regional myocardial flows *

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Abstract

Considerable spatial heterogeneity has been observed in regional myocardial blood flow in isolated hearts and in both anesthetized and conscious animals. In order to study how local blood flow varies with time, the data obtained by King et al. (1985) from ten awake, healthy baboons were analyzed to estimate the role of temporal fluctuations. Four to six distributions of regional flows were estimated at intervals of 4 min to 27 h, using 15 μ diameter microspheres and dividing each heart into 204 locatable pieces (average piece mass = 0.17 g). The technique averages over the 40 s of the injection giving no measure of fluctuations over a few seconds. The temporal variation in regional blood flow, expressed as the relative dispersion (SD/mean) of the temporally separated measurements about the mean flow for each piece and corrected for methodological noise, was 12% for the whole heart (10828 observations). For the left ventricle, the temporal variation was 10% (8806 observations), for the right ventricle 14% (1455 observations), and for the atria 22% (567 observations). On a relative basis, temporal fluctuation was greatest in regions having low flows. Since the magnitude of the changes in flow distributions was the same after 4 min as it was in several hours, we conclude that much of the “twinkling” is a high frequency phenomenon occurring over seconds to a few minutes. Further, it is concluded that regional myocardial blood flow in conscious primates is relatively stable with time, temporal fluctuations causing only about one third of the variation between regions.

Keywords

Flow distribution; Spatial and temporal variation in flow; Microspheres; Primates; Myocardial metabolism

Introduction

The observation of considerable spatial heterogeneity in regional myocardial blood flows in both awake and anesthetized animals has aroused speculation as to its cause. It is not an artifact of the microsphere technique; Bassingthwaighe et al. (1987) showed that the technique has only an 8% reproducibility error and a small systematic bias toward overestimation in high flow regions.

The analysis of King et al. (1985) suggested that “twinkling” or temporal fluctuation in local flows contributed about 10% to the observed relative dispersions RD_{obs} of regional flows in awake baboons. They considered the spatial, temporal and methodologic contributions to the variation to be independent, so that RD_{obs} the coefficient of variation, or SD/mean, was explicable in terms of the component RD 's

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$$RD_{obs}^2 = RD_{spatial}^2 + RD_{temporal}^2 + RD_{method}^2 \quad (1)$$

The observed relative dispersions, RD_{obs} from 53 injections in 13 baboons averaged 28.3% (King et al. 1985), and the composite distribution for all 13 animals had an RD_{obs} of 32% (Bassingthwaighte 1985) indicating that the 53 distributions were quite similarly shaped, i.e. 32% is little more than 28.3%.

However, there are several questions as to the components of the variation:

1. Because their microsphere methodology provided measures of reproducibility at a given time and did not measure accuracy, could the true variation, RD_{method} , actually be larger than they estimated? Apparently not, for Bassingthwaighte et al. (1987) showed microsphere error in rabbit hearts, compared to a “molecular microsphere” IDMI, to be about 8–10%.
2. $RD_{temporal}$ was defined only for the heart as a whole from the averages in all the regions. What is the temporal variation in individual regions? Is it more or less in high flow than low flow regions?

We present here the data on flow fluctuations in regions of different time-averaged flows. Answers to the question “Can temporal fluctuations explain all the non-methodologic variation?” are the foci of this presentation. Rephrasing this, “Would temporal fluctuations in a region tend to bring its mean value over long times to be the same as the mean for the whole heart?” We cannot obtain data on very short intervals, less than several seconds. When tracers are injected into the left atrial cavity and flow downstream to enter the coronary arteries, the concentration-time curve for the entering tracer is spread over several seconds. When tracers are injected into the left atrial cavity and flow downstream to enter the coronary arteries, the concentration-time curve for the entering tracer is spread over several seconds, because of dispersion due to the force of injection and the mixing that occurs in the atrium and ventricle. Using 0.5 s left atrial injections, Knopp et al. (1976) observed that dye dilution curves obtained in the root of the aorta had a spread of 4 – 10 s depending on the flow. Even with left ventricular injections and high speed sampling, Bassingthwaighte and Ackerman (1967) observed similar spreads. There is further spread during traversal of the coronary arterial and capillary beds. Thus, it may be safely concluded that the minimum “shutter opening” for a “snapshot” of regional flow distributions is of the order of 10 s. This is almost as long as are the periodicities of fluctuations in velocities and diameters in small arterioles in the heart by Tillmans et al. (1981); so, apart from small effects due to locally changing values of the product of flow times inflow concentration as the bolus enters, such high frequency fluctuations cannot influence the data on microsphere depositions.

The influences of short term fluctuations were, in this study, minimal because microspheres were injected over 40 s periods. This assured that the observations of spatial heterogeneity would not be exaggerated by the presence of rapid “twinkling” and that only slower fluctuations and spatial variations would influence the apparent flow distribution data. Previous analysis (King et al. 1985) emphasized the spatial variation. In this analysis, we will show that when the influences of the rapid fluctuations in flow are rendered negligible, the presence of long term fluctuations in regional flows are clearly evident beyond methodologic error. The interesting conclusion is that these long term fluctuations are not sufficient to render the myocardial perfusion effectively homogeneous. Indeed, they are not even sufficient to bring the regions of lowest flow up to the mean, even for a short period, nor sufficient to bring the high flow regions down to the mean. An interesting phenomenon

is that there is smaller absolute variation, but much greater relative variation in low flow regions.

Materials and methods

The animals used for this analysis are the same awake baboons studied by King et al. (1985). The experimental methods are described there in detail and will therefore only be summarized here.

Animals

Ten male adolescent baboons (*Papio anubis*) weighing 8.2 – 15.5 kg were studied. The animals were adapted over a period of several weeks to living in primate chairs and to spending up to 10 h at anyone time seated quietly in an acoustically isolated booth. Three or more days before experimental observation, catheters and other probes were inserted under general anesthesia (halothane in oxygen) while observing sterile procedure. A polyethylene catheter was passed via the left common carotid artery to the apex of the left ventricle (LV) for the injection of microspheres. Three hours or more before commencing experimental measurements, the animal was placed in the acoustic booth, so that it was in a quiet state beginning well before the study.

In three control animals, two or six sets of microspheres labeled with different radionuclides were injected simultaneously to give a measure of the methodologic errors in the regional flow estimates following LV injection. In two animals, four sets were injected simultaneously, two in LV apex and two in left atrium but the latter two sets were not used in this analysis so that all data came from LV injections.

Our microsphere technique has been more fully described by Hales (1974), Hales et al. (1979), Yipintsoi et al. (1973), Heyman et al. (1977), and King et al. (1985) and is summarized here. Radioactive microspheres, nominally of 15 μm in diameter, were obtained from the 3M Company (St. Paul, MN, USA) with 6 different labels:

^{141}Ce , ^{51}Cr , ^{113}Sn , ^{85}Sr , ^{95}Nb , and ^{46}Sc . Microsphere doses were injected over approximately a 40 s period into the apex of the left ventricular cavity so that many cardiac cycles were encompassed. Each dose contained approximately 0.5×10^6 microspheres per kg body weight. The dose is small compared to the 48×10^6 microspheres injected by Baer et al. (1984) into dogs weighing 20 – 30 kg without evidence of significant peripheral obstruction. In our baboons there was no observable influence on heart rate or arterial blood pressure. Injections were made over 6 to 27 h of study; the average interval between injections was about 1 h, with a minimum of 4 min and a maximum of 16 h.

The animal was sacrificed by an overdose of barbiturate. The heart was sectioned into 204 locatable pieces of left ventricle (LV), right ventricle (RV) and atria as described by King et al. (1985). The pieces weighed 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.

The radioactivity in each sample was measured using a NaI crystal well detector. The γ -ray spectra were analyzed using a matrix inversion technique similar to that of Baer et al. (1984)

and described by King and Bassingthwaighte (1979). The flow per gram in each piece, F'_j , was calculated from the tracer activity in each piece for each microsphere label and the weight and normalized to the average flow for the whole heart: the relative regional flow f_j , the regional flow divided by the average myocardial blood flow, is:

$$f_j = \frac{c_j/m_j}{\sum c_j/\sum m_j} \quad (2)$$

where C_j is the activity of that radionuclide in the piece, m_j the piece weight, $\sum C_j$ the total activity of that radionuclide in the heart, and $\sum m_j$ the total heart mass. There were six estimates of f_j for six microsphere injections; the average of these six in a given piece, j , is $\bar{f}_j$, while the average for all the pieces is a relative flow of 1.0.

Calculation of the temporal variation in local flow

The flow in each piece at a given moment was defined relative to the mean flow in the heart and compared to itself over time. To see the temporal variability the probability density functions of $f_j/\bar{f}_j$ were then constructed for each piece, where $\bar{f}_j$ is the mean of the 4 – 6 estimates in that piece. The relative dispersion (RD = SD/mean) of the density function was used as an overall assessment of variation amongst the observations. We define two types of local relative dispersion of flows, RD_{piece} and RD_{local} . In each piece the coefficient of variation over four or six observations has two components

$$RD_{\text{piece}}^2 = RD_{\text{temporal}}^2 + RD_{\text{method}}^2 \quad (3)$$

assuming that these are independent sources of variation. We then lump together many pieces within a narrow range of $\bar{f}_j$'s, that is, all those in a heart or a group of hearts which fall into a group having $\bar{f}_j$ within $\pm 10\%$ of a chosen value. The aggregate distribution then is composed of a set of pieces whose mean flows are the same (nearly) but wherein temporal and methodologic variations are combined.

$$RD_{\text{local}}^2 = RD_{\text{temporal}}^2 + RD_{\text{method}}^2, \quad (4)$$

In this we recognize that RD_{method} includes the additional variation due to the grouping. We further recognize that RD_{method} varies with $\bar{f}_j$, being greater at low $\bar{f}_j$ due to microsphere variation (Buckberg et al. 1971; Bassingthwaighte et al. 1988). Thus RD_{local} is a measure of variability in a group of pieces, from one or several hearts, all of which have similar mean local flows $\bar{f}_j$.

In order to examine how the dispersion varied as a function of the magnitude of local flow, the heart pieces were grouped according to their $\bar{f}_j$'s. For this purpose, each piece was classified into one of 13 groups, each having a width of $0.2\bar{f}_j$. The eighth group was centered at $\bar{f}_j=1.0$ and the centers for the other groups were calculated such that the groups did not overlap. The few pieces (less than 1% of the total) with $\bar{f}_j$'s less than 0.22 or greater than 3.0 were not used. For each of the 13 groups, the probability density functions of f_j and $f_j/\bar{f}_j$ were constructed at the 68%, 95%, and 99% confidence limits determined directly from the distributions themselves rather than from a calculated standard deviation. The density function for each group contained pieces from the hearts of all the animals.

The effect of the time between measurements on the observed dispersions was examined in a similar manner. In addition to $\bar{f}_j$, the measurements were further grouped by the time

separating each pair of measurements, Δt . In an animal with six microsphere measurements, there are 15 pairs of observations each with an associated Δt . The RD of all the observations with a specified Δt and falling into any given flow range, based on $\bar{f}_j$, could then be calculated.

Results

The animals were awake with normal hemodynamic status. The data on pressures, rates, and flows are provided in King et al. (1985). Cardiac output in these primates was normally high, $0.22 \text{ l min}^{-1} \text{ kg}^{-1}$ body weight, as were the coronary flows, $2.1 \text{ ml min}^{-1} \text{ g}^{-1}$. There were no systematic relationships between the levels of coronary flow or cardiac output or the presence of thermal stress or undertaking of exercise and the various measures of temporal or spatial heterogeneity of regional myocardial blood flow, either in relative dispersions or the shapes of the distributions. Thus, the data are presented for all the experimental states examined, resting, mild exercise, and heat stressed.

Temporal fluctuations in individual samples

These are illustrated in Fig. 1 for a few samples from one animal's heart. Samples were selected in three different ranges of mean relative flows, $\bar{f}_j$, around 0.5, 1.0, and 1.5. The data are displayed as the estimated flow, $\bar{f}_j$, divided by the mean of all estimates in that piece, $\bar{f}_j$. This normalization (i.e. $\bar{f}_i/\bar{f}_j$), was used so that all pieces could be compared with each other to give a measure of the overall variability of regional blood flow over the whole heart or over any specific area. The scatter, a combination of temporal fluctuation and error in the microsphere technique, is substantial, but in no case did any member of a set exceed double the mean or diminish to less than one half the mean. There is a suggestion that the scatter is less at high than at low flows.

Temporal fluctuations in groups with similar relative flows

These temporal fluctuations are portrayed for statistical large groups in Fig. 2. In order to use larger numbers to construct a probability distribution, all the $\bar{f}_j$'s within three fairly narrow ranges were used from all ten animals. The ranges were 10% around mean $\bar{f}_j$'s of 0.5, 1.0, and 1.5 and the numbers of tissue pieces in each group were 235, 2445, and 1803. Using such a range naturally broadens each of the distributions artifactually to some extent, but it provided a large enough number of estimates to obtain moderately smooth distributions. Note that the curves in Fig. 2 are probability density functions. Thus, $\bar{f}_j$ and $\bar{f}_j$ is the probability that the mean flow of a region will fall between f_1 and f_2 . Although the range used is proportional to the mean at the three levels, the relative dispersion (coefficient of variation) decreases with increasing $\bar{f}_j$.

Satistical evaluation of temporal fluctuations with respect to mean local flow

In Fig. 3 (left) is shown the plot of f_j versus $\bar{f}_j$ with the 68%, 95%, and 99% confidence limits. The number of observations contained in each distribution is given above each point. As can be seen, the 68% confidence limits widen as the local flow increases. In relative terms, however, the variation decreases with increasing flow. Figure 3 (right) shows the confidence limits on a relative basis; that is, normalized with respect to $\bar{f}_j$. As suggested by the data in Figs. 1 and 2, the relative dispersion decreases with increasing mean local flow.

Figure 4 shows the distributions of the ratios from all the pieces of all the hearts of both the experimental (temporally separated injections) and control (simultaneous injections) animals. The class width for each of the probability density functions were 0.01. Separate distributions were constructed using only the pieces of the LV, RV, and atria. The dispersions of these distributions, RD_{obs} , for each of the regions of the heart over the 4 – 5 observations made in each tissue piece are summarized in Table 1. The observed average relative dispersion RD_{obs} is 13.6% in the whole heart and somewhat less in the LV, 12.2%. These observed dispersions include both variation due to the microsphere method and due to true fluctuations in local flow:

$$RD_{local}^2 = RD_{temporal}^2 + RD_{method}^2$$

The distributions in the control animals represent only methodological variation since the differently-labelled microspheres were injected simultaneously. Thus the dispersions due to local flow variation can be calculated. For the LV, substituting into the above expression and rearranging to calculate the temporal component, this variation is:

$$\begin{aligned} RD_{temporal}^2 &= [RD_{local}^2 - RD_{method}^2]^{1/2} \\ &= [0.122^2 - 0.062^2]^{1/2} \\ &= 0.105 \end{aligned}$$

For the whole heart $RD_{temporal}$ is 0.119, for the RV 0.140, and for atria 0.220.

In all the results presented thus far, all observations have been pooled without regard for the time which had elapsed between the observations. Figure 5 is a plot of the observed dispersion between observations, RO_{local} versus the time separating the injections, Δt . In order that there would be sufficient data to give a reasonable estimate of the dispersion at each time point, measurements were grouped according to Δt . Since, as shown in Fig. 3, the dispersion is dependent on local flow, each group was further divided into subgroups based on $\bar{f}_j$. So that there would not be too great a spread in the elapsed times within a group, only selected groups were analyzed; thus not all the observations in all the hearts are represented in this figure. The points at $\Delta t = 10$ min represent seven sets of paired observations in four different animals. (Each set included all the pieces of the heart which fell into the given flow range.) In order of increasing Δt , the remaining points represent 4 sets in 4 animals, 6 sets in 4 animals, 4 sets in 3 animals, 4 sets in 4 animals, 4 sets in 2 animals, 4 sets in 2 animals, and finally 3 sets all in the same animal. The decrease in dispersion with increasing local flow is apparent, but no significant effect of Δt is seen. The conclusion is that the degree of measureable temporal fluctuation is not obviously greater over intervals of many hours than over 4 – 30 min, and this temporal fluctuation, though small, is distinctly greater than can be accounted for by methodologic variation. In general, the temporal variation is 2 – 3 times the variability in the microsphere technique.

Discussion

The variations that occur in the myocardium in metabolic rate (Griggs et al. 1972, Dunn and Griggs 1975), oxygenation (Gamble et al. 1974; Schubert et al. 1978; Weiss and Sinha 1978), and myocardial fiber shortening (LeWinter et al. 1975) have become generally recognized. Similarly, the spatial heterogeneity of regional myocardial blood flow has been clearly demonstrated with indicator dilution methods (Bassingthwaite et al. 1972; Rose

and Goresky 1976; Roselli and Harris 1979) and with the microsphere technique (Yipintsoi et al. 1973; Falsetti et al. 1975; Marcus et al. 1977; Sestier et al. 1978).

The studies of Bassingthwaighe et al. (1987) indicate that microsphere error is not the main source of the heterogeneity, but flow variation is real. They made comparisons of flow estimates measured with microspheres with those measured simultaneously in the same animal with the newly developed “molecular microsphere” iodinated desmethylinipramine (IDMI). They found small but consistent biases in microsphere depositions, which means that the methodologic variation is slightly larger than estimated from microsphere reproducibility. For seven comparisons, the slope of the regression for estimates of flow with microspheres against estimates with IDMI was 1.087 ± 0.003 (average correlation coefficient, $r = 0.914$). The probability distributions constructed from the IDMI data were therefore a little narrower than those of the microspheres, but now require consideration in assessing sources of variation.

Reeves and Rakusan (1988) provided data showing that micro spheres do not block capillaries. They used colored microspheres to show the direction of flow in myocardial capillaries. They found hundreds of instances of capillaries contained two or more differently colored spheres when the injections of the differently colored spheres were separated by a few minutes from the previous one. This is irrefutable evidence that spheres stop in capillaries without blocking them. They used this method to show the relationship between propinquity of capillaries and degree of concurrency of flow.

One explanation for this observed heterogeneity of flow is arteriolar “twinkling” in which arteriolar dilation and flow increase in one region are associated with constriction and flow reduction in a nearby region. If regional blood flow oscillated about the mean myocardial flow, a “snapshot” of regional blood flow, as provided by the microsphere technique, would demonstrate spatial heterogeneity while a method which measured the average flow over a time interval nearly equal to or greater than the period of the oscillation would not. While Yipintsoi et al. (1973) considered the contribution of twinkling to be small, others have argued that it is the major source of the spatial variation. Falsetti et al. (1975) and Marcus et al. (1977) reported that, in both anesthetized and conscious dogs temporal variation of local flow was of the same order of magnitude as spatial variation; and Sestier et al. (1978) in their studies of anesthetized dogs, concluded that twinkling is required for adequate perfusion of all the myocardium and that regional myocardial flow oscillated about mean myocardial flow with a period of 30 – 90 s.

Other studies can be interpreted to indicate that spatial heterogeneity is not simply a product of regional twinkling. The iodoantipyrine washout curves which Yipintsoi and Bassingthwaighe (1970) obtained at several different mean blood flows in blood-perfused isolated dog hearts could be well superimposed on each other by scaling with respect to their mean transit times, indicating that the overall dispersion of transit times (and presumably of the regional relative flows) remained constant. This “similarity” phenomenon was also observed in a more precise study by Knopp et al. (1976) which showed the similarity of intravascular transcortical transport functions in intact dogs. There was some variation among the approximately 20 transport functions obtained in each heart over about a 3-fold range of flows, but no random or systematic changes of shape suggested either major temporal fluctuations or systematic redistribution of flow. Nevertheless, twinkling amongst regions of the size of a few percent of the heart mass might well be unresolvable by these studies. Therefore, the suggestions coming from the microsphere studies cited above merit continuing examination.

The analyses by King et al. (1985) suggested that in awake baboons spatial heterogeneity is relatively stable and is the dominant phenomenon. In this study we examined the extent and nature of the temporal variation of regional myocardial blood flow in these baboons. This analysis supports the hypothesis that the spatial variation is a stable phenomenon. As shown in Fig. 3 (left), even at the 99% confidence limit, the flow distribution in those pieces with the lowest blood flow does not overlap the distribution of those pieces whose average flow is equal to the mean flow for the whole heart. Only when the average flow is at least one half the mean flow (i.e. $\bar{f}_j > 0.5$) do the distributions for the low flow regions overlap those in which $\bar{f}_j = 1.0$ at the 95% level. Considering the regions with higher than average local flow, at the confidence 95% limit the distributions do not overlap those with $\bar{f}_j = 1.0$ unless $\bar{f}_j < 1.7$.

Figure 3 (right) indicates that local flow is most variable in those pieces with low mean local flow. Consider the 68% confidence limit, whose value is by far the best determined due to the large number of observations which fall within it and which demarcates a change of one standard deviation from the mean flow in the piece. The upper 68% limit demarcates the border between the 34% of observations with values closest to but above the mean and those with higher values; the lower 68% limit separates the 34% with values below but closest to the mean; for a Gaussian distribution these positions fall at ± 1 SD from the mean; for a leptokurtic distribution these positions are narrower than ± 1 SD and for a platykurtic distribution, broader. These limit lines in the right panel are flat for flows $\bar{f}_j > 0.8$, which suggests that the capacity for variation in the medium and higher flow regions of the heart is less than in low flow regions. It is unfortunate that the stresses imposed on these animals were not sufficient to significantly increase coronary blood flow and thus test this hypothesis. Further experiments will be needed in which cardiac demand will be significantly increased.

Further observations are needed using methods designed to obtain the highest reasonable temporal and spatial resolution. Much finer piecemealing cannot be achieved with microspheres due to their particulate nature, but the problem may be addressed using a soluble flow tracer such as IDMI if sufficiently high specific activity can be obtained for five or more radioactive labels.

We have no information on local metabolism. Local uptake of substrates like glucose, whose uptake is barrierlimited, may be quite independent of flow since their transcapillary extraction is small. But for highly extracted solutes like oxygen, and perhaps for fatty acids, uptake is inevitably most closely limited by flow. Local limitations to flow may therefore result in an imbalance between flow and metabolism. One hint of this is to be found in the results of Eng et al. (1984) who found that, when vasopressin infusion was used to superimpose a vasoconstrictor influence on adenosine-induced vasodilation, an apparently normal autoregulatory flow-pressure relationship was observed in dog hearts; but at the same time there was net lactate production in the heart, which suggested that there were some ischemic regions. How closely metabolic need governs local flow is yet to be worked out.

The main result of this study is the demonstration that the heterogeneity of flows which has been observed in the heart using microspheres is due to a relatively stable spatial variation and is not an artifact of the method. In 0.2 g pieces, the local myocardial blood flow in the baboon fluctuates about some local mean; this variation is proportionally more in low flow regions but is about 11% of the mean local for flows of 80% of the heart mean or higher.

The magnitude of this temporal fluctuation in small regions of the LV is about one third the spatial variation observed across the whole ventricle at any instant in time.

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Fig. 1.

Examples of the variation in local flow estimates from microsphere depositions. Local “instantaneous” flow relative to the local mean flow, $f_j/\bar{f}_j$, is plotted versus the local mean flow relative to the whole heart mean, $\bar{f}_j$. Twelve pieces are shown from the heart of a single animal (no. 8) in each of which six estimates were made over a period of 4 h: three pieces with local mean flows in the range 0.45–0.55 contribute 18 points, five in the range 0.90 – 1.10 give 30 points in the middle group, and four in the range 1.35 – 1.65 give 24 estimates. The symbol at a given abscissa value represents one tissue sample. (Note: Six measurements are shown for each sample, but some are so close to each other that their symbols overlap)

Fig. 2.

Distributions of flow estimates at three selected flow levels, 0.5, 1.0, and 1.5 times the mean flow in the whole heart. The probability density per unit mean heart flow, P , is plotted versus $\bar{f}_j$ the mean local flow relative to the whole heart mean. Each distribution includes those pieces from the 10 hearts whose $\bar{f}_j$'s fell within $\pm 10\%$ of the group mean; the dispersion is a combination of temporal and methodologic variation. The absolute variation in the group with $\bar{f}_j$ ranging between 0.45 and 0.55 is narrower but the relative dispersion (RD) is larger than in the higher flow groups

Fig. 3.

Variations in local flow as a function of local mean flow in the hearts of 10 awake baboons. The tissue sections from all hearts were sorted into 13 groups according to the average of the measurements in each section, $\bar{f}_j$. A probability distribution, similar to those shown in Fig. 2, was constructed for each group and the confidence limits were calculated for 1, 2, and 3 standard deviations, that is, enclosing 68%, 95%, and 99% of the observations. *Left panel:* The local “instantaneous” flow (estimated from one microsphere injection) relative to the whole heart mean, f_j , is plotted versus $\bar{f}_j$ the mean local flow relative to the whole heart mean. The confidence limits are indicated by the brackets, and the number of observations is shown for each group. *Right panel:* Same as the left panel except that the *ordinate* is the local “instantaneous” flow relative to the local mean flow, $f_j/\bar{f}_j$. Narrowing of the confidence limits at higher flows indicates diminished temporal fluctuation relative to that in low flow regions

Fig. 4.

Comparison of the variation in local flow estimates from microsphere depositions to the variation due to the microsphere technique. The probability density per unit mean heart flow, P , is plotted versus the local “instantaneous” flow relative to the local mean flow, $f_j / \bar{f}_j$. The density function labeled “Simultaneous Injection” is comprised of observations from three animals in which two to six sets of microspheres with different labels were injected simultaneously. This distribution contains variation due to all sources of error in the methodology (e.g. non-uniform labeling of the microspheres, microsphere size variation, counting error, error in γ -ray peak separation, etc.). The “Temporally Separated” density function ($\bullet$) is comprised of observations from 10 animals in which 4 – 6 injections were made; the separation between injections ranged from 4 min to 26 h. This distribution contains variation due to the methodologic sources discussed above plus temporal fluctuations, i.e. variation due to any change in the local flow during the interval between the measurements

Fig. 5.

Effect of temporal separation of regional blood flow measurements on the dispersion of the flow estimates. The myocardial sections of the ten hearts were sorted into groups based on mean local flow relative to the whole heart mean. The observed relative dispersion, $RD_{local} = SD/mean$, for each group is plotted versus the time between the injections, Δt . Four points are missing from the graph: for three of the groups at $\Delta t = 4$ min and one at $\Delta t = 1350$ min; the number of observations was too small to permit calculation of a meaningful dispersions

Table 1

Temporal variation of flow in individual regions of the myocardium

	Whole heart	LV	RV	Atria
	in percent			
Test animals, RD_{local}^a (Number of pieces)	13.6 (10828)	12.2 (8806)	16.3 (1455)	23.0 (567)
Control animals, RD_{method}^b (Number of pieces)	6.6 (2286)	6.2 (1783)	8.3 (408)	6.6 (140)
Temporal dispersion, $RD_{\text{temporal}} =$ $[RD_{\text{local}}^2 - RD_{\text{method}}^2]^{1/2}$	11.9	10.5	14.0	22.0

^a 4–6 observations in ten animals;^b six simultaneous tracers in one animal and two simultaneous tracers in two animals