# The Relationship Between Myocardial Blood Flow and Glucose Uptake in Ischemic Canine Myocardium Determined with Fluorine-18-Deoxyglucose

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The relationship between myocardial blood flow as a marker of severity of ischemia and exogenous glucose utilization was examined following occlusion of the left anterior descending coronary artery in 10 fasted, anesthetized, open-chest dogs. Fluorine-18-fluorodeoxyglucose (FDG) was injected 10 min after the onset of ischemia and serial blood samples were obtained to measure FDG in plasma. Tracer-labeled microspheres, used to measure myocardial blood flow (MBF), were injected 10 and 40 min postocclusion. After the last microsphere injection, the heart was arrested and removed rapidly. Tissue samples of the left ventricle were obtained, weighed and FDG counts were determined. Two days later, the same samples were assayed for radioactivity from the tracer-labeled microspheres and blood flow was calculated. Thus, FDG uptake and MBF measurements were made in the same tissue samples. When normalized for variations in blood flow, there were no significant differences in FDG uptake between the subendocardial and subepicardial halves of the tissue samples. FDG uptake was relatively high and uniform in normal myocardium, paralleling the pattern of MBF. In ischemic myocardium, however, FDG uptake and MBF did not vary in parallel. In tissue samples with MBF reduced by up to 80% from control levels, relative FDG uptake increased such that absolute FDG uptake remained at normal or near normal levels. In samples with more severe ischemia, FDG uptake decreased precipitously with additional decrements in MBF. We propose that sufficient glycolytic flux may be sustained to maintain cellular viability when perfusion is above the threshold value. Below the threshold, however, irreversible changes may be initiated.

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Recent clinical data have been accumulated to suggest that FDG imaging with PET can prove useful in patients with ischemic heart disease (*1–3*).

The glucose analog $^{18}$F-deoxyglucose (FDG) can accurately trace exogenous glucose uptake by the myocardium and positron emission tomographic imaging can be used to measure FDG uptake noninvasively (*3–5*). This approach has been employed to attempt to distinguish viable but ischemic dysfunctional myocardium from infarcted tissue in patients with advanced coronary artery disease (*2,6,7*). Relative FDG uptake may increase in reversibly injured or temporarily ischemic myocardium, whereas a sustained reduction in FDG uptake is observed in regions with irreversible injury.

There are few experimental data available, however, defining the relationship between regional myocardial blood flow as a marker of severity of ischemia and myocardial glucose uptake during coronary occlusion within and at the margins of an ischemic area. Based on experimental observations such as these that glucose uptake can increase in ischemic myocardium, we hypothesized that glucose uptake and retention may be sustained at relatively normal levels even with severe levels of blood flow reduction until a threshold level of residual perfusion is achieved. Below this level of perfusion, lactate may accumulate in tissue, inhibiting glycolysis, and exogenous glucose uptake will dramatically decrease. Therefore, the purpose of this study was to measure regional myocardial FDG uptake following occlusion of a coronary artery in anesthetized, open-chest dogs and to compare such measurements with regional myocardial blood flow measured with tracer-labeled microspheres. Accordingly, coronary occlusions were performed in open-chest, anesthetized dogs. Blood flow and FDG were measured in multiple tissue samples from both ischemic and nonischemic myocardium to enable correlation of FDG uptake with severity of ischemia.

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## METHODS

### Experimental Preparation

Eleven mongrel dogs (weighing 19 to 26 kg) were studied. The animals were fasted overnight prior to the procedure. Each animal was anesthetized with intravenously administered pentobarbital (30 mg/kg) and anesthesia was maintained with intermittent administration of pentobarbital as required. The animals were intubated and ventilated (Harvard respirator) with a mixture of room air and oxygen throughout the study. Catheters were placed in the carotid and femoral arteries to enable measurement of arterial blood pressure and heart rate and to collect arterial blood samples. A left thoracotomy was performed through the fifth intercostal space, the heart was suspended in a pericardial cradle and an occlusive snare was placed loosely around the left anterior descending coronary artery distal to the first major diagonal branch. A catheter for injection of microspheres was placed in the left atrium. Intravenous saline was infused (2 ml/min) continuously to maintain hemodynamic stability.

### Experimental Protocol

After completing instrumentation, baseline hemodynamic measurements were obtained. Then the left anterior descending coronary artery was occluded by tightening the snare around the vessel. After 10 min, tracer-labeled microspheres (15 $\mu$ diameter, labeled with either $^{113}$Sn, $^{51}$Cr or $^{141}$Ce, Dupont, N. Billerica, MA) were injected into the left atrium while obtaining a reference arterial sample at a rate of 7.9 ml/min in order to measure myocardial blood flow. Following the microsphere injection, 0.5–0.75 mCi of $^{18}$F-FDG were injected intravenously and serial 1–2-ml arterial samples for determination of an arterial FDG input function were collected at frequent intervals over the next 40 min. Forty minutes after onset of ischemia, a second microsphere injection and blood withdrawal was performed to verify whether or not blood flow levels had remained stable over the course of the coronary occlusion. The heart was then arrested by an intravenous injection of concentrated KCl and excised rapidly.

To determine the distribution of regional myocardial blood flow and FDG uptake, a 1.5 to 2.0 cm wide full thickness strip of left ventricular muscle was cut away from the left ventricle in such a manner to include 3–4 cm of normally perfused muscle beyond the anterior margin of the ischemic region as depicted in Figure 1. The anterior margin of the ischemic zone was readily identified as the edge of the cyanotic area on the epicardial surface. The slice of left ventricle was divided into 15–18 sequential segments each of which were divided into subendocardial and subepicardial halves (Fig. 1). Each tissue sample was weighed and placed in a scintillation vial. To measure $^{18}$F activity, the tissue and blood samples were counted immediately in a gamma scintillation counter (Tracor Model 1185) using the appropriate energy window settings for $^{18}$F (450-530 keV). The $^{18}$F activity (cpm) was corrected for the weight of the sample, counting time and decay of $^{18}$F and expressed as cpm/g tissue.

To measure myocardial blood flow in the same samples, we waited 48 hr to allow for the $^{18}$F activity to decay (half-life 109 min). The tissue and arterial reference samples were counted in the same gamma scintillation counter with the window settings adjusted appropriately for the isotopes used. After correcting the sample counts for time, regional blood flow in each myocardial section at 10 and 40 min postocclusion was calculated with the equation for the reference withdrawal method (*8*). Blood flow in each sample was normalized to ml/min/g by dividing sample flow by sample weight.

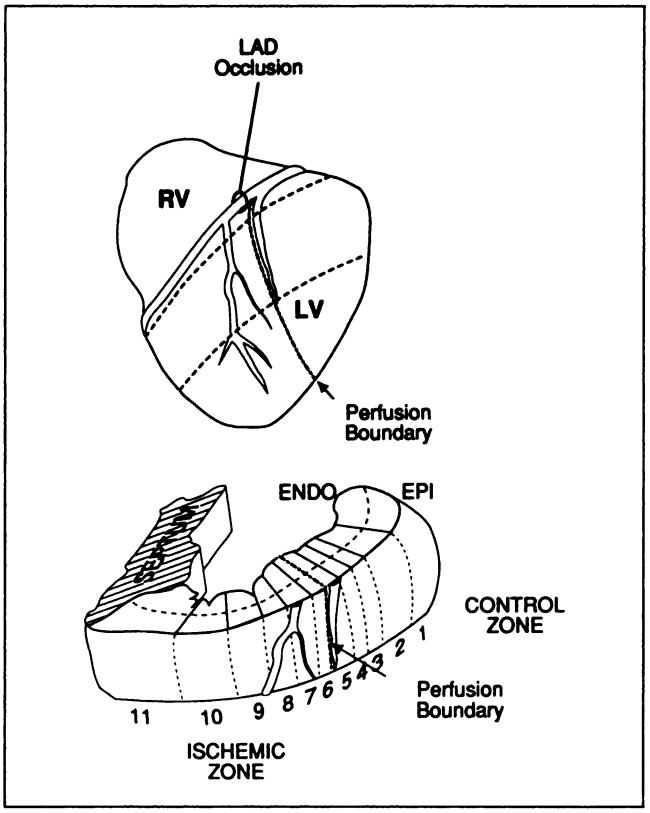


**FIGURE 1.** Diagrammatic representation of the myocardial sectioning procedure. Note that the sequential slices of myocardium were also divided into corresponding subendocardial (Endo) and subepicardial (Epi) halves for subsequent assessment of transmural FDG and myocardial flow gradients.

### Data Analysis

Regional blood flow in subendocardial and subepicardial samples was determined and related to regional $^{18}$F activity in the same tissue samples. To correct for variations of absolute flow and FDG uptake among animals, flow and FDG uptake were normalized by expressing them as percentages of average values in the nonischemic myocardium (two to three tissue samples) from the remote normal myocardium.

The ischemic zone data were defined as the mean of the values found in three myocardial samples from the center of the ischemic zone. The lateral border zones were defined as the two to three nonischemic sections immediately adjacent to the ischemic region based on the blood flow distribution data. The samples designated as constituting the lateral border zone were consistently characterized by increased epicardial blood flow. The narrow zone, identified as the lateral border zone in the present study, corresponds roughly to the functional border zone (nonischemic tissue adjacent to an ischemic area that displays reduced systolic function) demonstrated in previous studies in which sonomicrometers or two-dimensional echocardiography were used to define the distribution of functional impairment across the perfusion boundary produced by acute coronary occlusion (*9–14*). Nonischemic samples were those located beyond the lateral border zone.

To determine if there were differences in subendocardial and subepicardial blood flow or FDG uptake in the normal, ischemic and lateral border zones, the absolute values of blood flow and normalized FDG uptakes were compared with paired t-tests.

To examine the relationship of glucose utilization and blood flow over a wide range of values, all the normalized blood flow and normalized FDG uptake values from each dog were pooled and categorized based on levels of blood flow (percentage of nonischemic area blood flow). Since this analysis does not account for potential differences in the metabolic state of each dog, a modification of the method employed by Sochor et al. (*15*) was used. The FDG uptake values for each individual dog were divided by the integral of the arterial FDG input function in order to normalize FDG uptake to the injected dose (corrected FDG = FDG (counts × 1000/g/min)/integral of blood FDG in counts/g of blood/min). The corrected measurements of FDG uptake were obtained in seven of the ten dogs included in the study because the arterial input function was available only in these animals.

Mean values are reported with standard deviations. Group data were evaluated with analysis of variance. Appropriate corrections (Bonferroni) were made for repeated testing of data (*16*). Probability values listed in the text are converted so that p (corrected) $< 0.05$ is considered significant.

## RESULTS

Eleven dogs completed the full protocol without complications. One dog had an episode of ventricular fibrillation immediately after injection of the FDG. Although this dog was successfully resuscitated, the data were excluded from further analysis. In another animal, there was unsatisfactory delineation of the lateral border zone due to native collaterization and these data were not used. A last dog was characterized by an FDG uptake pattern that differed dramatically from the remaining eight dogs and data from this animal are presented separately but are excluded from the group analysis.

### Hemodynamic Data

Heart rate averaged 161 ± 42 bpm and 149 ± 19 bpm before and after coronary occlusion, respectively. Systolic and diastolic arterial blood pressures were 139 ± 59/95 ± 36 mmHg and 136 ± 26/97 ± 24 mmHg before and after coronary occlusion, respectively. Because there were no significant differences between blood flow measurements made 10 and 40 min after coronary occlusion, the data from the two time periods were averaged. Blood flow in the central ischemic area averaged 0.1 ± 0.2 ml/min/g and 0.3 ± 0.2 ml/min/g in the subendocardium and subepicardium, respectively; blood flow in the nonischemic samples averaged 1.3 ± 0.4 ml/min/g and 1.2 ± 0.3 ml/min/g in the subendocardium and subepicardium, respectively.

### Relationship Between Regional Myocardial Blood Flow and FDG Uptake

Figure 2 shows normalized blood flow and FDG uptake data from one of the experiments. Myocardial blood flow in the ischemic area (samples 6–12) was markedly reduced in both subendocardial and subepicardial layers and relatively sharp lateral borders separated ischemic and nonischemic myocardium. Subendocardial FDG uptake paralleled the flow pattern closely with near elimination of FDG uptake in the ischemic territory. The lateral borders were less sharply defined in terms of FDG uptake than blood flow, however, and the ischemic subepicardial samples had higher residual FDG uptake than did the subendocardial samples.

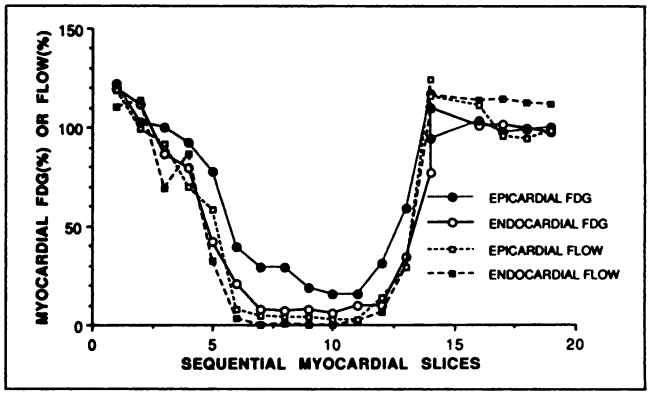


**FIGURE 2.** Example of myocardial FDG uptake and blood flow (Dog 6) depicted in an unrolled cross-section. Both regional FDG and myocardial blood flow have been normalized as outlined in the text. Note that the lateral border zone, i.e., the transition zone from normal to ischemic myocardium, is narrow for myocardial blood flow in both endo and epicardial slices. Note also the disparity of FDG uptakes in the ischemic zone.

Presented in Figure 3 are data from the animal that differed from the pattern shown in Figure 2 in terms of its regional FDG uptake. In contrast to the other dogs, this dog was characterized by relatively low FDG uptake in normal myocardium, but dramatically higher FDG uptake in the ischemic samples (nos. 6–13). Given the widely disparate pattern of FDG uptake values observed in this

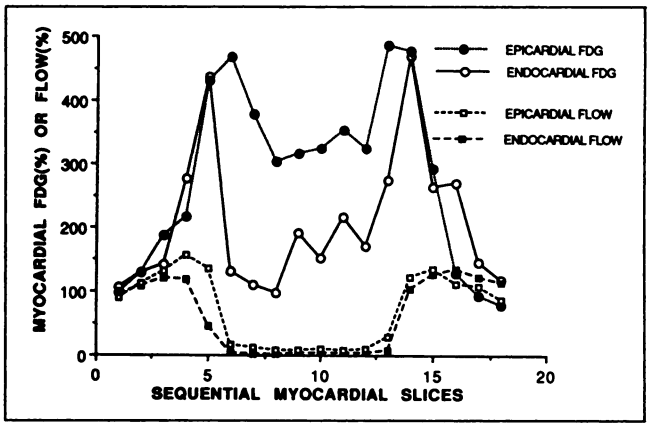


**FIGURE 3.** Myocardial FDG uptake and blood flow of Dog 4. The format is the same as in Figure 2. Note the different FDG uptake pattern in the endocardial and epicardial regions of the ischemic zone. As explained in the text and Figures 5A–B, this relative FDG uptake in the ischemic segments is increased because of markedly lower FDG uptake in normal myocardium.

**TABLE 1**
Subepicardial and Subendocardial Blood Flow and FDG Uptake in Control Area and Lateral Border Zone Samples

| | Control area samples | | | | Lateral border zone samples | | | |
|---|---|---|---|---|---|---|---|---|
| | SUBEPI | | SUBENDO | | SUBEPI | | SUBENDO | |
| Experiment | MBF | FDG | MBF | FDG | MBF | FDG | MBF | FDG |
| 1. | 0.55 | 71.0 | 0.69 | 84.0 | 0.69 | 77.6 | 0.74 | 80.4 |
| 2. | 0.48 | 10.7 | 0.51 | 10.0 | 0.53 | 12.6 | 0.51 | 11.3 |
| 3. | 1.28 | 33.8 | 1.39 | 37.6 | 1.46 | 41.2 | 1.52 | 46.6 |
| 6. | 1.82 | 23.4 | 2.04 | 22.7 | 2.13 | 24.9 | 2.09 | 24.4 |
| 7a. | 2.14 | 34.5 | 2.10 | 42.2 | 2.67 | 33.5 | 2.0 | 36.7 |
| 7b. | 2.36 | 29.2 | 2.26 | 41.5 | 2.49 | 35.9 | 2.41 | 42.7 |
| 8a. | 1.06 | 34.2 | 1.17 | 39.1 | 1.02 | 30.6 | 1.24 | 40.7 |
| 8b. | 1.07 | 30.0 | 1.23 | 33.5 | 1.16 | 33.2 | 1.25 | 33.5 |
| 9. | 0.80 | 49.0 | 0.96 | 62.2 | 1.06 | 65.0 | 1.23 | 84.0 |
| 10a. | 1.12 | 54.5 | 1.37 | 66.2 | 1.15 | 57.2 | 1.65 | 70.8 |
| 10b. | 1.02 | 47.0 | 1.50 | 63.2 | 1.20 | 50.6 | 1.56 | 68.2 |
| Mean ± s.d. | 1.25[1] ± 0.61 | 38 ± 17 | 1.38* ± 0.57 | 46** ± 21 | 1.42## ± 0.71 | 42# ± 19 | 1.47# ± 0.57 | 49** ± 24 |

SUBEPI = subepicardial; SUBENDO = subendocardial; control area samples represent the tissue samples from nonischemic myocardium the greatest distance from the perfusion boundary; lateral border zone samples represent average values in two to three apparently nonischemic samples immediately adjacent to the perfusion boundary separating ischemic and nonischemic territories. In five of the experiments, there was sufficient tissue to provide data at both lateral boundaries of the ischemic territory. MBF = myocardial blood flow expressed in ml/min/g. FDG = FDG uptake expressed as decay-corrected cpm/g/1000. Paried t-test comparisons between subendocardial and subepicardial data (* $p < 0.05$, ** $p < 0.01$) and between control and lateral border zone categories (# $p < 0.05$, ## $p < 0.01$). Letters a and b indicate data from different lateral boundaries obtained in the same animal.

experiment, the data from this dog were excluded from the overall analysis.

Blood flow and glucose uptake data in the nonischemic myocardium adjacent to the perfusion boundary (designated "lateral border zone") and at a greater distance from the ischemic area (designated "control myocardium") are summarized in Table 1. To compare the transmural pattern of blood flow and FDG uptake, 11 pairs of subendocardial and subepicardial tissue samples were available. In three of the dogs, enough nonischemic tissue samples were available at and beyond both lateral boundaries to provide two sets of lateral border zone and control area data from each experiment. Data from these experiments are indicated in Table 1 with a and b accompanying the experiment number. Five of the possible 16 pairs could not be used, however, because insufficient tissue samples were available and/or the septal perfusion boundary was not clearly delineated.

FDG uptake in the control myocardium was significantly higher ($p < 0.004$) in the subendocardial (46 ± 21 cpm/g) than the subepicardial (38 ± 17 cpm/g) samples, paralleling a similar transmural difference ($p < 0.004$) in blood flow between the subendocardial (1.42 ± 0.71 ml/g/min) and subepicardial (1.25 ± 0.61 ml/g/min) halves.

In the central ischemic myocardium, blood flow and FDG uptake data were quite variable from dog to dog. Subendocardial blood flow, however, was invariably less ($p < 0.001$) than that in the corresponding subepicardial sample (averaging 0.1 ± 0.2 versus 0.3 ± 0.2 ml/min/g in the inner and outer halves, respectively). A significant difference ($p < 0.005$) was also found between the subendocardial and subepicardial FDG uptake (6 ± 6 versus 17 ± 13 cpm/g) in the ischemic area.

Since the ratios of subepicardial to subendocardial blood flow and FDG uptake in the ischemic region were similar (approximately 3) on average, it seemed plausible to hypothesize that perfusion was a major determinant of FDG uptake. Unfortunately, there were few samples in the ischemic regions in which the blood flow in a subendocardial sample was comparable (within 10%) to that in the overlying subepicardial sample. By pooling the data from samples in which subendocardial and subepicardial blood flows were not more than 10% different from one another, 16 pairs of subendocardial and subepicardial blood flow and FDG uptake were available and could be analyzed. In relative terms, there was no significant difference between subendocardial (35% ± 36%) and subepicardial (36% ± 38%) blood flow (normalized as a percentage of blood flow in the nonischemic control myocardium) or between subendocardial (61% ± 40%) and subepicardial (67% ± 41%) FDG uptake (normalized as a percentage of FDG uptake in nonischemic control myocardium). These findings support the hypothesis that FDG uptake and blood flow follow distribution of myocardial energy demand.

### The Relationship Between Severity of Ischemia and FDG Uptake

All the subendocardial and subepicardial blood flow and FDG uptake data from the eight dogs were pooled to examine the relationship of flow and FDG uptake over a

wide range of blood flow. The individual flow data were grouped based on increasing blood flow values and are presented in Table 2 and Figure 4. At control (100%) or higher levels of myocardial blood flow, normalized FDG uptake and perfusion paralleled one another. However, in segments with mild flow reduction (between 50% and 100% of nonischemic perfusion) FDG uptake was maintained at normal control levels, i.e., its retention fraction increased in proportion to the reduction in myocardial blood flow. More severe flow reduction (between 50% and 25% of nonischemic blood flow) was associated with significantly decreased FDG uptake, but the degree of metabolic impairment was still less than the flow reduction. Samples with flow 15%–24% of the nonischemic average displayed only a 22% reduction of FDG uptake compared to nonischemic myocardium. When ischemia was profound (blood flow reduced to less than 5%), FDG uptake then decreased markedly to only 18% of control. Thus, a nonlinear relation between blood flow and myocardial FDG uptake was observed with a transition or threshold point at approximately 20% of perfusion. Above the threshold, FDG uptake was normal or nearly normal whereas below the threshold, FDG uptake declined rapidly.

The effect produced by using different methods of FDG data analysis are depicted in Figure 5. Data from the dog with the very unusual FDG uptake pattern (shown earlier in Fig. 3) are superimposed on the mean data from the other animals. When this experiment's FDG values were normalized to remote myocardium (Fig. 5, top), they deviated dramatically from the other data and would have markedly skewed the results in the ischemic zone, blurring the threshold where FDG uptake begins to decline rapidly. When the data were analyzed using the integral method, however, the data from the ischemic area are distributed in line with the data from the other animals (Fig. 5, bottom). In samples with normal (100%) or higher levels of blood flow, the data are distributed substantially out of line with the mean data from the other experiments. Thus, the nonlinear relationship between blood flow and FDG uptake is most easily appreciated when data from the unusual experiment were excluded from the overall analysis using either method, but it is our view that the integral analysis is the method of choice if the main focus is glucose metabolism in the ischemic zone.

## DISCUSSION

The objective of this study was to evaluate the relationship between FDG uptake and alterations in myocardial blood flow during acute ischemia. Although blood flow reduction of 50% results in dramatically altered contractile function (*17–20*), this degree of blood flow restriction did not change relative glucose utilization in the present study. More substantial flow reductions (to approximately 20%–40% of control values) were associated with relatively minor impairment of FDG uptake. Reduction of blood flow to less than 20% of control, however, resulted in marked impairment of FDG uptake.

Thus, mild to moderate blood flow reduction (less than 80% from control) was associated with increasing retention of FDG such that relative FDG uptake remained at or near normal levels. These findings contrast with those obtained with other substrates (such as acetate or palmitate), the uptake of which tends to parallel changes in perfusion (*1,7*). Uptake and metabolism of fatty acids and acetate are closely related to myocardial oxidative metab-

**TABLE 2**
Normalized Myocardial Blood Flow Versus Normalized FDG Uptake

| Flow% | No. points | MBF% | FDG% | INT FDG |
|---|---|---|---|---|
| 0–5% | 35 | 2.5 ± 3* | 18 ± 19† | 22 ± 9† |
| 5–14% | 31 | 8.5 ± 3* | 31 ± 18† | 45 ± 14† |
| 15–24% | 19 | 19 ± 3** | 77 ± 32† | 79 ± 21† |
| 25–34% | 14 | 8 ± 2** | 77 ± 31† | 82 ± 21† |
| 35–54% | 18 | 45 ± 6** | 85 ± 27‡ | 107 ± 11‡ |
| 55–74% | 15 | 65 ± 7** | 94 ± 19 | 107 ± 19 |
| 75–94% | 34 | 87 ± 6** | 98 ± 17 | 123 ± 21 |
| 95–105% | 36 | 100 ± 3 | 105 ± 12 | 130 ± 38 |
| 106–125% | 58 | 115 ± 5 | 115 ± 25 | 131 ± 38 |
| >125% | 20 | 140 ± 15 | 149 ± 52# | 225 ± 50‡@11 |

Flow% = range of normalized myocardial blood flow values and their corresponding normalized FDG uptakes to be pooled; No. points = number of samples with blood flows within the specified range. MBF% = mean ± s.d. of the myocardial blood flow values within the specified range; FDG% = mean ± s.d. of normalized FDG uptakes in the tissue slices having blood flows within the specified range using data from all dogs excluding the values of Dog 4 (FDG%); INT FDG = mean values from FDG data corrected by the integral of FDG input function, and expressed as counts/g/min; and @ = mean of 11 points.

Paired t-test [all values corrected: (Bonferroni corrected: n = 0)].

* $p < 0.01$ vs. corresponding FDG%.

† $p < 0.001$ vs. corresponding control (95%–105%) FDG or FDG%.

‡ $p < 0.01$ vs. corresponding control (95%–105%) FDG or FDG%.

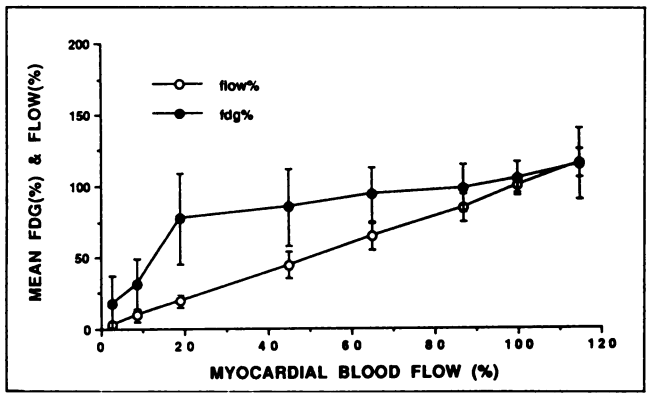


**FIGURE 4.** Relationship between individual and pooled normalized FDG uptakes and myocardial blood flow (both parameters are expressed as percentage of the normal remote epicardial values and individual dog data have been pooled so that endocardial and epicardial differences could be seen). Dog 4's data have been excluded in these plots to more clearly demonstrate the main features of the nonlinear relationship between blood flow and FDG uptake in the ischemic zone and the threshold below which, FDG uptake rapidly falls towards baseline. MBF = myocardial blood flow; MEAN FLOW (%) = mean ± s.d. of the normalized blood flow values within the specified range; MEAN FDG% = mean ± s.d. of normalized FDG uptake in tissue slices having blood flows within the above specified ranges.

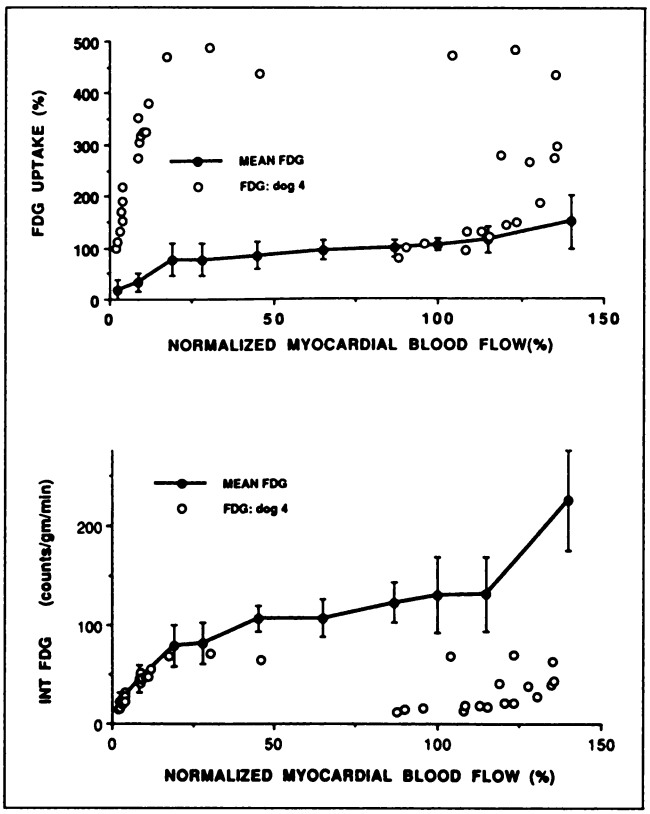


**FIGURE 5.** (Top) The effect of using the two outlined methods of normalization on Dog 4's results are highlighted in the following two figures. Note the limitations of the normalization procedure using relative change (top). In the ischemic and lateral border zones, Dog 4's results are different when compared to the mean ± s.d. of the pooled data from the remaining nine dogs (Table 4). When using the integration approach (bottom), available in seven dogs, it becomes obvious that Dog 4's response in the ischemic zone is the same as that of other animals in this study, but that FDG uptake is lower in normal myocardium. INT FDG refers to the values of FDG uptake obtained by normalizing dog FDG data using the integral of the blood FDG input function (expressed as counts/g/min).

olism and, hence, follow myocardial oxygen consumption as myocardial blood flow does. They also contrast with the observation that mechanical function is closely coupled to perfusion such that small reductions in perfusion are associated with significant regional contractile impairment (*17–20*).

Relative glucose uptake did not parallel perfusion until ischemia was severe and a threshold value of residual blood flow was achieved. At this point, glycolysis may no longer have been sustainable and glucose uptake decreased dramatically, potentially signifying the onset of cellular demise. Support for this possibility is provided by experimental studies which showed that absolute glucose utilization is increased in hypoxic and in ischemic myocardium (*1,21,22*). A crucial factor in maintaining glucose utilization during low flow ischemia is removal of lactate from ischemic myocardium which may, in turn, depend on maintaining perfusion above a critical level. Increased tissue lactate levels and decreased pH inhibit glycolysis, thereby reducing nonoxidative glucose utilization. Thus, glycolytic flux in ischemic myocardium appears to depend critically on residual perfusion of ischemic tissue. Based on these data, one could speculate that the lower perfusion limit for hibernating myocardium (*6*) may be defined by the blood flow threshold for maintenance of glucose uptake and utilization, below which viability can not be sustained. Additional investigation will be required to evaluate these issues further.

Other investigators have shown that a comparable threshold of perfusion is associated with development of histochemical, pathological and biochemical patterns of irreversible cell injury (*25–27*). In conscious dogs (*23*) and open-chest, anesthetized dogs (*1,15*), the effect of transient blood flow reduction on glucose utilization was examined. The ratio of ischemic-to-normal FDG uptake remained at unity until blood flow was less than 20%–30% of normal, which is consistent with the findings of the present study. Although Russell et al. (*23*) and Sochor et al. (*15*) observed that FDG uptake was significantly augmented in moderately ischemic segments of the left ventricle compared to the control zone, the disparity from our findings may be explained by differences in hormonal environment and dietary state among the various experimental models. In the normal regions, myocardial glucose utilization is affected by dietary state, whereas this may not occur in the ischemic zone (*24*).

It should be acknowledged that data from open-chest, anesthetized dogs may differ significantly from the situation of patients with ischemic heart disease.

Ischemic heart disease is a chronic process reflecting progression of vascular changes of varying degree and possibly adaptation of myocardium to repetitive ischemia. In contrast, the used animal model employed acute occlusion of a normal artery supplying normal myocardium. However, the open-chest dog model was chosen because it represents an established model for the investigation of regional myocardial ischemia. Occlusion of the left anterior descending artery leads to a considerable amount of ischemic tissue, which is well suited for the correlation of metabolic and blood flow measurements. In addition, the degree of collateral blood flow to the ischemic segments can vary considerably in dogs. We took advantage of the wide range of flows to facilitate comparison of FDG uptake and blood flow at different levels of perfusion.

The in-vivo analysis of $^{18}F$ and regional microsphere activity allowed direct comparison of blood flow and an index of metabolic activity within a given tissue sample and, hence, the quantitative evaluation of regional tracer distribution. This approach clearly is superior to PET imaging, because it is not limited by the spatial resolution of the currently available imaging instrumentation (about 6–8 mm). This results in an underestimation of time tissue tracer concentration by PET imagery (partial volume effect). Sectioning of the heart into small samples with subsequent division into subendocardial and subepicardial segments enabled examination of transmural gradients of both myocardial blood flow and FDG uptake.

In contrast to the blood flow measurements by microspheres, the absolute quantification of FDG uptake is more complicated and depends on several factors. Myocardial glucose utilization is critically influenced by the overall metabolic state of the animal at the time of the study. In order to standardize the metabolic state, all animals were fasted overnight. This dietary approach was chosen to enhance relative FDG uptake in ischemic myocardium and differs from the commonly employed glucose loading in patients undergoing tissue viability studies. Despite this dietary standardization, the uptake of FDG, especially in the normal myocardium, varied widely from dog to dog (Table 1). Therefore, normalization of regional FDG uptake to control area segments was performed to reduce variability in the measurements of glucose uptake. Previous studies have shown that regional myocardial glucose utilization can be quantified by FDG using a three-compartment model (*5*). However, the tissue FDG kinetics could not be accurately determined in this study since only one measurement of tissue tracer concentration at 40 min after tracer injection was available. In addition, little data are available demonstrating stability of the lumped constant during ischemia. In order to normalize the regional FDG uptake to the injected dose, we divided the tissue activity by the integral of the arterial input function for FDG and derived a quantitative index of regional FDG uptake.

Our results demonstrate that this approach reduces the inter-animal variation in the regional FDG retention as evidenced by the smaller standard deviation of the data in the ischemic myocardium (Fig. 3). There was one animal (Dog 4) who demonstrated a markedly enhanced relative FDG uptake in the ischemic segment. Myocardial FDG uptake in control segments was very low in this animal most likely reflecting preferential use of fatty acids. The increase of relative FDG uptake in ischemic myocardium is consistent with the known metabolic shift to increased nonoxidative glucose utilization in ischemic myocardium. However, if the data were normalized to the arterial input function, the absolute FDG uptake in this animal was similar in the ischemic bed to the results obtained in the remaining animals, indicating that this animal differed primarily by displaying low FDG uptake in normal myocardium. Such marked variation in glucose utilization among individuals clearly emphasizes the need of metabolic standardization and absolute measurements of FDG uptake in order to correct for changes in the dietary state. This is of utmost importance for clinical studies in which relative FDG uptake may be used as a marker of tissue viability.

In conclusion, the results of this study indicate that there is a dissociation between regional glucose utilization (assessed by FDG uptake) and myocardial blood flow in mild to moderately ischemic myocardium, whereas FDG retention markedly decreases in segments with severe ischemia (perfusion <20% control). A threshold blood flow level was evident for maintaining glycolytic flux in ischemic canine myocardium and we speculate that whether or not residual perfusion during coronary occlusion is above or below the threshold may determine the ultimate survival of ischemically compromised tissue.

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**EDITORIAL**

# Myocardial Blood Flow, Deoxyglucose Uptake, and Myocyte Viability in Ischemia

It has long been supposed that provision of glucose by glycolytic flux should be beneficial to the ischemic myocardium (*1*). The basic logic relies on the benefits of production of ATP independently of oxygen, during the glycolytic process. Even when glycolysis is maximally accelerated in anoxia with maintained coronary flow, glycolytically-produced ATP cannot meet the total energy requirements of the normally contracting heart. ATP produced by glycolysis may, however, play a different role by helping to protect the cell membrane (*2*). Thus, ATP generated by glycolysis preferentially interacts with potassium channels in isolated guinea-pig cardiac myocytes (*3*). Furthermore, it is ATP produced by glycolysis rather than the total ATP level that prevents ischemic contracture in the moderately underperfused myocardium (*4*).

These studies strongly suggest that it is not the overall level nor the concentration of ATP that is critical in the maintenance of ion gradients across the sarcolemma, but rather the rate of provision of ATP derived specifically from glycolysis.

## MYOCARDIAL BLOOD FLOW AND GLUCOSE UPTAKE

If glycolysis (both from exogenous glucose uptake and from glycogen) were always increased by ischemia, then the above protective scheme would be relatively straightforward. Rather, in severe ischemia, it is proposed that the accumulation of glycolytic products in the myocardium (e.g., lactate, protons produced from turnover of ATP and from other sources, and increased levels of reduced coenzymes) act to inhibit glycolytic flux at several points and thereby to decrease glucose uptake (*5*). There should accordingly be a "flip-flop" mechanism whereby glucose utilization, initially increased by relatively mild degrees of ischemia, is inhibited by severe degrees of ischemia. Therefore, as the coronary flow rate progressively falls, there will be a critical flow level at which increased uptake of exogenous glucose switches to decreased uptake. A recent hypothesis (*6*) proposes that an increased glucose uptake reflects continued cell viability, whereas a decreased uptake is associated with loss of viability of the ischemic cells which then pass from reversible to irreversible damage.

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