Heterogeneity of Myocardial Perfusion Provides the Physiological Basis of Perfusable Tissue Index

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Assessment of viable from nonviable myocardium is critical for the care of patients being considered for revascularization procedures. Recently, the perfusable tissue index (PTI) has been proposed as an index of myocardial viability. **Methods:** Computer simulations were performed for homogeneously and heterogeneously perfused tissue over a wide range of flows (0.04–6.4 ml/g/min) using both bolus and infusion inputs. **Results:** PTI estimated from simulated homogeneously perfused tissue did reflect the amount of tissue being perfused independent of absolute level of flow, type of input or model configuration, whereas PTI obtained from simulated heterogeneously perfused tissue was consistently lower than the simulated "true" PTI and varied with flow, type of input function and model configuration. Flow estimated with ^{15}O-water was not significantly different from that measured with radio labeled microspheres. **Conclusion:** Oxygen-15-water can diffuse into both acutely and chronically ischemic myocardium irrespective of its functional status. The results suggest that PTI is most likely an index of the heterogeneity of myocardial flow rather than an index of the amount of tissue being perfused. Its utility for delineating myocardial viability is thus related to the amount of tissue perfused that has low absolute levels of perfusion or high degrees of flow heterogeneity.

Key Words: positron emission tomography; ^{15}O-water; myocardial blood flow; myocardial ischemia

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Diagnostic procedures help to define the functional outcome of jeopardized myocardium in patients being considered for coronary revascularization procedures is paramount for optimal patient care. A number of nuclear medicine approaches have been proposed for this purpose including delineation of membrane integrity with ^{201}Tl scintigraphy, imaging with some of the newer ^{99m}Tc cardiac agents and PET. PET has been shown to be both sensitive and specific. Approaches include the identification of enhanced glycolytic flux using ^{18}F-fluorodeoxyglucose (FDG) (*1–3*) or delineation using ^{11}C-acetate of regions of preserved oxidative metabolism (*4–7*). Although PET has been shown to have high predictive accuracy, metabolic imaging is technically involved and requires lengthy imaging procedures.

Recently, a number of studies have shown that ^{15}O-water acts as a freely diffusible tracer used for assessment of myocardial perfusion and can be used to identify viable myocardium. Identification of tissue viability with ^{15}O-water is based on the concept developed by Iida et al. (*8*) of the perfusable tissue index (PTI). The PTI is thought to reflect the admixture within a region of interest (ROI) of viable tissue (i.e., capable of recovering mechanical function after revascularization) can rapidly exchange radiolabeled water; and myocardial tissue that is nonviable (i.e., not capable of recovering systolic function after revascularization) which is felt to be incapable of exchanging water. Iida et al. (*8*) demonstrated that PTI decreased significantly in infarcted regions compared to values obtained in remote, normal regions. Yamamoto et al. (*9*) showed that PTI was decreased in reversibly injured myocardium compared with remote normal myocardium and decreased even further in irreversibly injured myocardium. Furthermore, PTI was a useful prognostic indicator of the recovery of contractile function after successful thrombolysis. De Silva et al. (*10*) studied 12 patients with chronic coronary artery disease and found that contractile function recovered after coronary bypass surgery only in segments where PTI was greater than 0.7. In addition, there was unanimity between estimates of viability made with PTI and those made with ^{18}F-FDG. If PTI can be used to accurately predict myocardial viability, it would greatly simplify tomographic procedures since measurements can be obtained within 5–10 min after attenuation measurements are made. In addition, ^{15}O-water can be conveniently prepared by automated procedures including those using "baby cyclotrons" or ion beam accelerators (i.e., not dependent on full cyclotron facilities).

Our group has been using ^{15}O-water as a perfusion tracer for a number of years and has shown that it can readily

diffuse into severely ischemic regions (11–14). The results of studies using direct assessments in acutely ischemic myocardium and with noninvasive measurements in studies of more prolonged periods of ischemia and infarction, indicated that ^{15}O-water did diffuse into ischemic, as well as infarcted regions. Thus, we felt that the explanation for the basis of PTI, i.e., that irreversibly injured myocardium is characterized by its inability to exchange vascular water, may be incorrect. Accordingly, the aim of the present study was to test an alternative hypothesis: that PTI represents heterogeneity of myocardial flow. Computer simulations were performed to evaluate the relationship between flow heterogeneity and PTI, and animal studies were performed to measure perfusion with ^{15}O-water in normal, acutely ischemic and chronically infarcted myocardium.

METHODS

Mathematical Basis of PTI

Quantification of regional myocardial blood flow with ^{15}O-water and PET using a one-compartment kinetic model has been validated extensively in a number of studies (11,14–17). The approach currently used estimates of myocardial blood flow from PET tissue and blood-activity curves along with tissue count recovery and blood-to-tissue spillover fractions. Accurate measurements of tracer concentration within the myocardium with PET is not possible due mainly to the limited spatial resolution of available tomographic systems (8–12 mm FWHM) in relation to the dimensions of the myocardial wall imaged. Tracer activity obtained in objects smaller than twice the resolution of the tomograph results in partial volume effects (underestimation of true tracer concentration) and spillover (contamination of activity in one region with that from adjacent regions). These effects contaminate the measurement of myocardial activity obtained noninvasively with PET. The operational equation used to estimate flow, tissue count recovery and blood-to-tissue spillover fraction is thus:

$$C_T(t) = F_{MM}\left(\frac{F}{V}\, Ca(t) * \exp\left(\frac{-Ft}{V\lambda}\right)\right) + F_{BM}Ca(t), \quad Eq.\ 1$$

where $C_T(t)$ is the tissue tracer concentration at time t (cpm/g); F_{MM} is the tissue recovery coefficient; F/V is the flow per unit of tissue volume (ml/g/min); Ca(t) is the arterial tracer concentration at time t (cpm/ml); λ is the tissue/blood partition coefficient (ml/g); and F_{BM} is the blood-to-tissue spillover fraction and * represents convolution. Iida et al. (8) defined F_{MM} in Equation 1 as the ratio of the mass of perfusable tissue within an ROI to the total volume of that region. Consequently, F_{MM} is not only a function of the myocardial dimensions and the resolution of the tomograph used, but also a function of the amount of tissue that is perfused. In totally perfused tissue, F_{MM} will measure the tissue recovery coefficient, but in partially perfused tissue F_{MM} will measure both count recovery and fraction of tissue perfused. Thus, if true tissue count recovery can be measured independently then, the estimated F_{MM} (F_{MM_c}) can be corrected to obtain the PTI.

Iida et al. also (8,18) validated a simple method to correct for the partial volume effect using the transmission scan and a scan obtained after administration of ^{15}O-carbon monoxide (C^{15}O) which labels erythrocytes. This method assumes that the trans-

mission image measures total tissue density (which encompasses both vascular and extravascular tissue density) and that extravascular tissue density can be obtained by subtracting the vascular component from the transmission scan after normalizing the C^{15}O image to the density of blood (1.06 g/ml):

$$F_{MM_{TR}} = 1.06((TR_{TIS}/TR_{BLD}) - V_B), \quad Eq.\ 2$$

where $F_{MM_{TR}}$ is the tissue recovery coefficient obtained from transmission scan; TR_{TIS} is the counts in a tissue ROI from transmission scan; TR_{BLD} is the counts in a blood ROI from transmission scan; and V_B is the blood volume.

In a given ROI this method measures the mass of extravascular tissue to the total volume of that ROI and therefore is representative of the amount of underestimation of true tissue activity in that region provided that both emission and transmission have the same resolution. PTI is defined as the mass of ^{15}O-water perfusable extravascular tissue divided by the mass of total extravascular tissue:

$$PTI = \frac{F_{MM_c}}{F_{MM_{TR}}}, \quad Eq.\ 3$$

where F_{MM_c} is obtained from Equation 1 and $F_{MM_{TR}}$ is obtained from Equation 2.

Computer Simulations

Computer simulations were used to evaluate the relationship between PTI and the heterogeneity of tissue perfusion. Since two types of input functions are currently used in ^{15}O-water studies, we performed all simulations using both types of input: bolus and infusion. The bolus input curve was modeled using a gamma-variate function of the form:

$$Ca(t) = At\, \exp\,(-t/tp), \quad Eq.\ 4$$

where Ca(t) is the amount of radioactivity in arterial blood, A was fixed to 2000, and tp to 10 sec. Data points were generated every second for 120 sec.

The infusion-input curve was modeled by splicing two biexponential curves, the first curve representing the uptake of tracer and the second representing the clearance of tracer from blood. Data points were generated every second for 400 sec. For each type of input, tissue curves were generated using Equation 1 after fixing F_{MM}, F_{BM} and λ values of 1.0, 0.0 and 0.92 ml/g, respectively, for a wide range of flows (0.04–6.4 ml/g/min).

Tissue curves representing heterogeneously perfused tissue were simulated by assuming that a given ROI was composed of a number of subregions with each subregion having a given homogeneous flow (Fig. 1). The tissue curve from this region was generated by averaging the tissue curves from each of the subregions. Tissue curves for a wide range of flows were generated for totally perfused tissue (i.e., PTI = 1.0) and also for tissue where only 50% of tissue was perfused (PTI = 0.5). Note that for a PTI of 0.5, the average transmural flow will be half of the average transmural flow obtained when PTI is 1.0 (Fig. 1). In order to maintain the same degree of heterogeneity for each tissue curve generated, the four homogeneous tissue curves used had a four-fold flow range. Table 1 summarizes the flows for which curves were generated. Figure 2 shows simulated bolus and infusion-input curves, and corresponding tissue curves from either homogeneously or heterogeneously perfused tissue for three representative values of flow for a PTI of 1.0 and a PTI of 0.5. Using the tissue curves, values of PTI were then estimated using bolus and
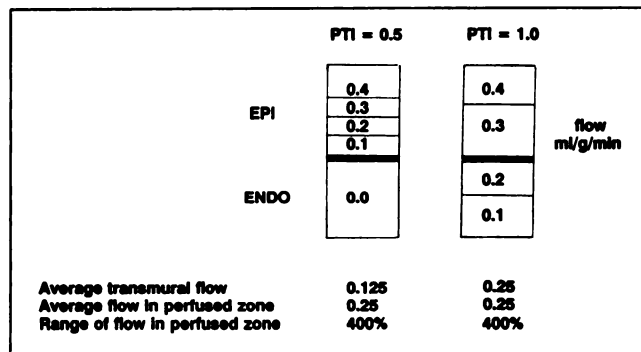
FIGURE 1. Schematic representation of the computer model used in the simulation studies. The diagram to the left represents the situation where only the epicardium (EPI) representing 50% of the myocardium is perfused (PTI = 0.5), while the diagram to the right represents myocardium that is totally perfused (PTI = 1.0). Flow heterogeneity in the perfused regions is modeled by different homogeneous flows in four subregions. Note that in the partially perfused myocardium, the heterogeneous transmural flow is half of that in the totally perfused myocardium (0.125 versus 0.25 ml/g/min) and that the flow range in the perfused zones is fourfold. Using these templates, tissue curves from homogeneously and heterogeneously perfused myocardium were generated for flows shown on Table 1 for bolus, as well as for infusion input curves.

infusion-input curves first using the three-parameter fit (where estimates of flow, F_{MM} and F_{BM} are obtained) and then using a two-parameter fit, after fixing F_{BM} to its modeled value of 0.0. Thus, for each value of flow, a total of eight different simulations were performed. Percent error in parameter estimates from "true" values were then computed for each set of tissue and input curves. In these simulations, PTI was the same as the estimated F_{MM} (F_{MM_e}) since the modeled tissue recovery (or $F_{MM_{TR}}$ in Equation 3) was 1.0.

Animal Studies

To directly confirm whether ^{15}O-water can rapidly exchange in acutely ischemic or chronically infarcted myocardium, we evaluated 12 dogs. All studies were performed under general anesthesia

TABLE 1
Flows Used in Computer Simulations to Generate Tissue Curves

Homogeneous transmural flows (ml/g/min)		Average transmural flows (for heterogeneous flow simulations ml/g/min)		Homogeneous flows used to obtain heterogeneous flows (ml/g/min)
PTI = 1.0	PTI = 0.5	PTI = 1.0	PTI = 0.5	
0.10	0.050	0.10	0.050	0.04, 0.08, 0.12, 0.16
0.25	0.125	0.25	0.125	0.1, 0.2, 0.3, 0.4
0.50	0.250	0.50	0.250	0.2, 0.4, 0.6, 0.8
1.00	0.500	1.00	0.500	0.4, 0.8, 1.2, 1.6
1.50	0.750	1.50	0.750	0.6, 1.2, 1.8, 2.4
2.00	1.000	2.00	1.000	0.8, 1.6, 2.4, 3.2
2.50	1.250	2.50	1.250	1.0, 2.0, 3.0, 4.0
3.00	1.500	3.50	1.500	1.2, 2.4, 3.6, 4.8
3.50	1.750	3.50	1.750	1.4, 2.8, 4.2, 5.6
4.00	2.000	4.00	2.000	1.6, 3.2, 4.8, 6.4

and conformed to the Position of the American Heart Association on Research Animal Use. Dogs were sedated with 1 mg/kg body weight of morphine subcutaneously after an overnight fast and anesthetized with 12.5 mg/kg of thiopental and 72 mg/kg of α-chloralose administered intravenously. The dogs were intubated and ventilated with room air. In all dogs, regional ischemia was induced in the left anterior descending coronary artery by placement of a thrombogenic copper coil intracoronarily, as described previously (19). Four were evaluated 2 hr after coronary occlusion and eight were evaluated 5–6 wk after coronary occlusion.

In all dogs, 3 to 4 × 10^6 15 μm of labeled microspheres (New England Nuclear, Boston, MA) were injected into the left atrium while blood was collected from the femoral artery at a rate of 10 ml/min using a constant withdrawal pump. Immediately after the withdrawal of blood was completed, approximately 95 mCi of ^{15}O-water was infused intravenously at a constant rate of 7 ml/min. The arterial blood concentration as a function of time was obtained by collecting samples every 2 sec from a free-flowing catheter positioned in the midthoracic aorta. At 60 sec of ^{15}O-water infusion, KCl was administered intra-atrially and the heart was excised when electrical activity ceased (usually 10–20 sec later). Six to 15 endo- and epicardial samples from ischemic or infarcted sectors and from normal regions weighing approximately 0.9 g each were placed in preweighed vials. Oxygen-15 radioactivity in tissue and blood samples was assayed in a gamma well counter within 10 min after excision of the heart. After sufficient time had elapsed for the ^{15}O to decay to background levels, samples were recounted to assess radioactivity due to microspheres. Myocardial blood flow was determined by the standard microsphere reference technique (20). Oxygen-15-water flows were estimated using the following equation (11):

$$C_T(T) = \frac{F}{V} Ca(T) * exp\left(\frac{-F}{V\lambda}T\right), \qquad Eq. 5$$

where $C_T(T)$ is the tissue activity at time T (excisional time); $Ca(T)$ is the arterial blood activity at time T; F/V is the flow per unit volume (ml/g/min); and λ is the tissue/blood partition coefficient (ml/g).

In dogs studied early after ischemia, regions in the anterior myocardium subtended by the left anterior descending coronary artery were selected by inspection of the vascular distribution of the artery distal to the coronary artery coil. In dogs studied more than 1 mo after intracoronary coil placement, regions were selected based on the typical findings of infarcted myocardium (i.e., clear white scar formation) since we were most interested in evaluating the diffusibility of radiolabeled water into scarred tissue. Regions from the posterolateral myocardium supplied by the left circumflex coronary artery were obtained for samples from normal tissue. Infarcted tissue delineated by gross inspection was fixed in formalin and subjected subsequently to histological analysis using hematoxylin and eosin and Masson's trichrome stains for verification of infarction.

Statistical Analysis

Flows obtained with ^{15}O-water were compared with flows obtained using radiolabeled microspheres by regression analysis and by a three-way analysis of variance for repeated measurements using a Duncan's test for comparing differences. All values are expressed as mean ± standard deviation.
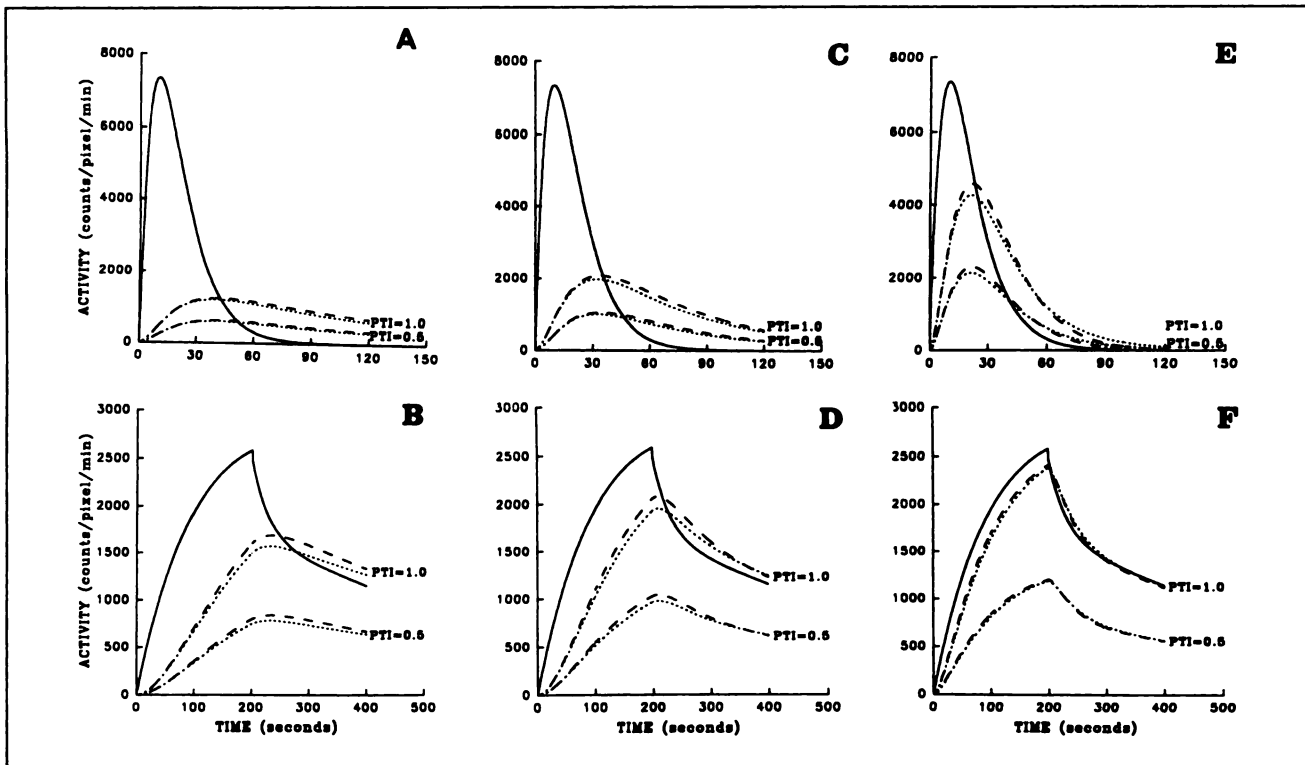
FIGURE 2. Simulated homogeneous (dashed lines) and heterogeneous (dotted lines) tissue curves for totally (PTI = 1.0) and partially (PTI = 0.5) perfused myocardium obtained from Equation 1 using a bolus or an infusion input (solid lines) for low (0.50 ml/g/min; A and B), normal (1.0 ml/g/min; C and D), and hyperemic (4.0 ml/g/min; E and F) flows. Note that tissue curves from heterogeneously perfused tissue (dotted lines) have a consistently lower amplitude and different shape from corresponding tissue curves from homogeneously perfused tissue (dashed lines). Curves from tissue that is only half perfused (PTI = 0.5) have the same shape and half the amplitude of tissue curves from totally perfused tissue (PTI = 1.0).

RESULTS

Computer Simulations

Figure 3A shows the estimated PTI as a function of flow for regions with homogeneous and heterogeneous perfusion in totally (PTI = 1.0) and partially (PTI = 0.5) perfused tissue obtained using a bolus input. Figure 3B shows the equivalent results obtained using an infusion input. In these simulations, F_{MM} was estimated along with F_{BM} and flow. For regions with homogeneous perfusion, PTI reflected the perfusable tissue fraction since, for completely perfused tissue, the expected PTI was 1.0, and for the case where only 50% of the tissue was perfused, PTI was 0.5. For regions with homogeneous flow, PTI was independent of the type of input used. The results were quite different for regions with heterogeneous perfusion. The estimated PTI values were consistently lower compared with regions with homogeneous flow. In contrast, when a bolus input was used, PTI decreased as flow decreased (Fig. 3A). When an infusion input was used, PTI increased with reductions in flow to approximately 0.5 ml/g/min but then decreased with further reductions in flow (Fig. 3B).

Figure 3C shows the percent error between estimated and true simulated PTI, flow and F_{BM} as a function of flow obtained from regions with heterogeneous flow and bolus

input. Figure 3D shows the corresponding results obtained when an infusion input was used. When a bolus input was used, PTI was consistently underestimated and decreased as flow decreased. In regions with heterogeneous perfusion, flow was overestimated for flows lower than 1.0 ml/g/min and underestimated for flows greater than 1.0 ml/g/min. Blood-to-tissue spillover fraction estimates increased slightly as flow increased. When an infusion input was used (Fig. 3B), F_{BM} estimates increased greatly as flow increased. PTI was consistently underestimated, and flow was overestimated for flows under 0.5 ml/g/min and underestimated for flows greater than 0.5 ml/g/min.

Figures 4A and B show the same plots as Figures 3A and B displaying the results obtained when the spillover fraction was fixed to the "true" simulated value of 0.0, and only flow and PTI were estimated. When a bolus input was used, PTI estimates obtained from heterogeneously perfused tissue and a three-parameter fit (Fig. 3A) are very similar to those estimates obtained when only PTI and flow were estimated (Fig. 4A). Also, PTI estimates obtained from homogeneously perfused tissue were exactly the same as those estimated using the three-parameter fit (Figs. 3A and 4A). In contrast, when an infusion input was used, estimates of PTI obtained from heterogeneously perfused

FIGURE 3. Estimated PTI as a function of myocardial flow for simulated true PTI of 1.0 and 0.5 obtained from homogeneously (solid circles) and heterogeneously (open circles) perfused tissue obtained from bolus (A) or infusion (B) input curves using a three-parameter fit (flow, F_{MM}, and F_{BM} were estimated). PTI estimated from homogeneously perfused tissue reflected the amount of tissue being perfused (solid circles) while PTI obtained from heterogeneously perfused tissue was consistently lower than the simulated "true" values and varied with flow and type of input (open circles). Percentage error in PTI, flow and F_{BM} estimates as a function of flow obtained from heterogeneously perfused tissue and a bolus input (C) or an infusion input (D). Note that the pattern of error in parameter estimates obtained using a bolus input (C) is very different from that obtained using an infusion input (D).
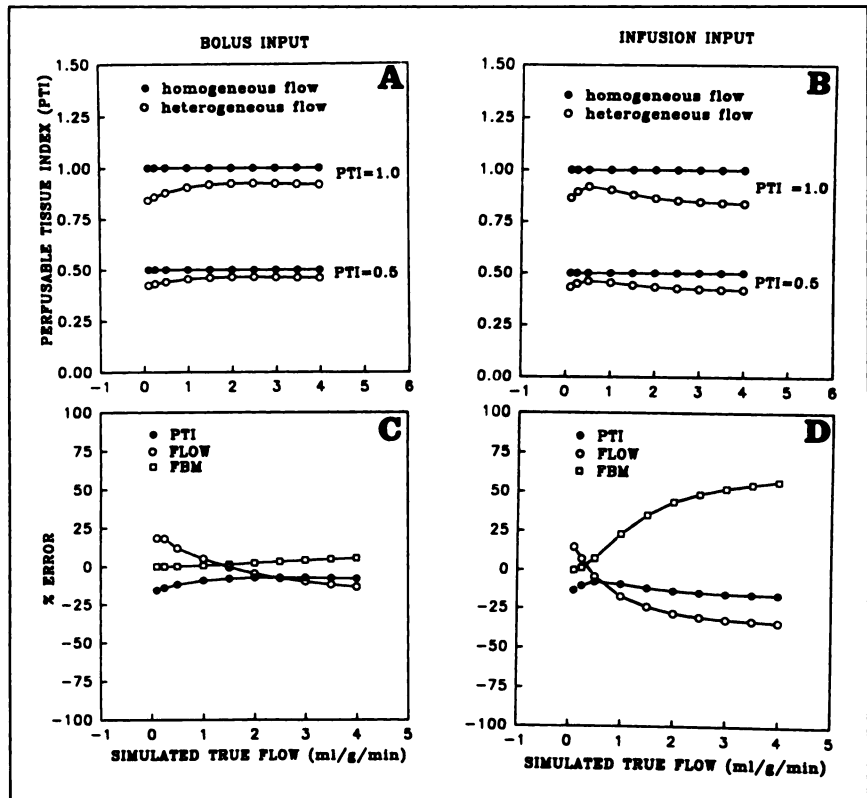
tissue when only two parameters were fitted (Fig. 4B) were markedly different from estimates obtained using a three-parameter fit (Fig. 3B). Figures 4C and D show the percent error in PTI and flow as a function of flow obtained from regions with heterogeneous flow and bolus or infusion input.

Animal Studies

Myocardial blood flow was estimated with ^{15}O-water and microspheres in 248 heart samples from the 12 dogs studied. Figure 5 shows the correlation between myocardial blood flow estimated with ^{15}O-water and the corresponding flows obtained with radiolabeled microspheres. Although there was a significant correlation between ^{15}O-water and microsphere flows ($y = 0.57x + 0.19$, $r = 0.65$, $p < 0.001$), flow estimated with ^{15}O-water underestimated high flows and overestimated low flows (compared with microspheres).

Figure 6 shows a histogram displaying endocardial and epicardial blood flow measured with microspheres and with ^{15}O-water in normal and ischemic or infarcted regions. Analysis of variance showed no significant differences between estimates in either normal, ischemic or infarcted tissue. Because of the modest number of samples in each group and the large variance, the power from the ANOVA analyses were 0.064 for acute data and 0.053 for the chronic data. These low values preclude us from concluding that differences between estimates do not exist (i.e., a beta error cannot be excluded). Nonetheless, the results dem-

onstrate that ^{15}O-water diffuses rapidly into acutely ischemic, as well as infarcted myocardium.

DISCUSSION

PTI has been shown to be a potential predictor of viability in several recent clinical studies (8–10). The use of PTI is based on the assumption that in regions of irreversible damage, water cannot exchange rapidly and that the ratio of this nonperfusable tissue-to-total tissue will predict functional recovery. We were interested in testing this hypothesis since our group has previously shown that water can exchange rapidly in normal as well as ischemic tissue (11–14).

The computer simulation results show that when flow was homogeneous, PTI is exclusively an index of perfusable tissue, but when flow is heterogenous, PTI is not only an index of how much tissue is perfused but also an index of the heterogeneity of tissue flow. PTI is consistently lower for heterogeneously perfused regions and decreased further in regions with very low absolute flow. PTI is also influenced by the shape of the input function as well as by model configurations (Figs. 3 and 4). These observations can be explained by comparing tissue curves for a given flow value (Fig. 2). Tissue curves from a heterogeneously perfused region have a lower amplitude and a different shape than the corresponding curve from a homogeneously perfused zone. These discrepancies vary with altered flow, and consequently F_{MM}, F_{BM} and flow estimates from het-
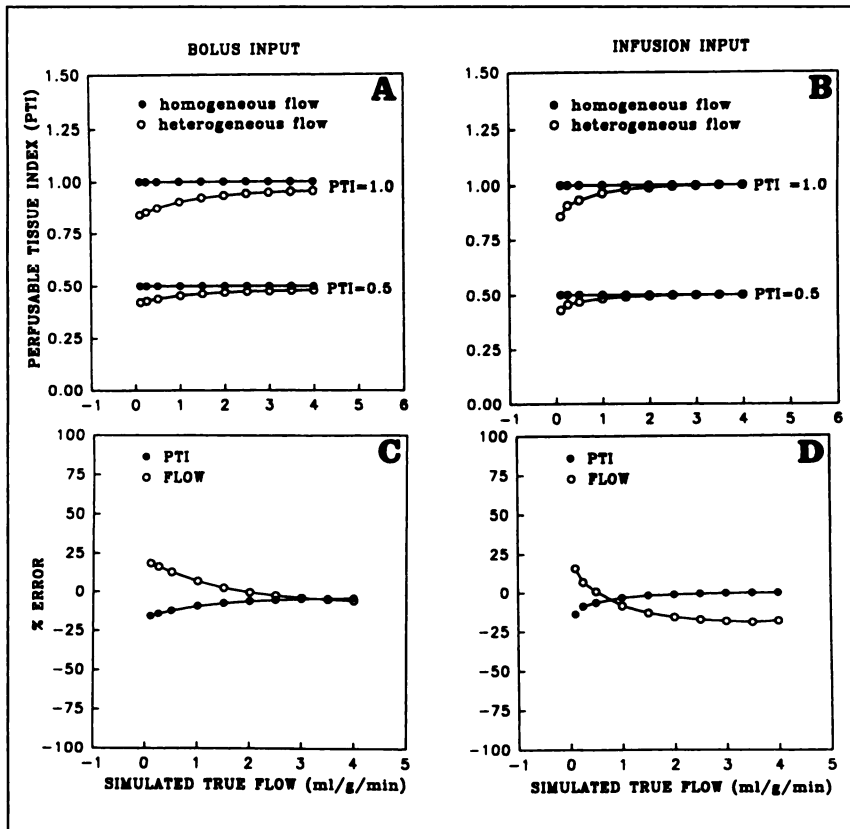
FIGURE 4. Estimated PTI as a function of myocardial blood flow for simulated "true" PTI values of 1.0 and 0.5 obtained from homogeneously (solid circles) and heterogeneously (open circles) perfused tissue obtained from bolus (A) or an infusion (B) input curves using a two-parameter fit (flow and F_{MM}) after fixing F_{BM} to its simulated value of 0.0. PTI estimates obtained from homogeneously perfused tissue flows reflected the amount of tissue being perfused (solid circles) while those obtained heterogeneously perfused tissue are consistently lower than the simulated "true" values when a bolus input is used (A) and decreased from their expected value for flows under 2 ml/g/min when an infusion input is used (B). Percentage error in PTI and flow estimates as a function of flow obtained from heterogeneously perfused tissue obtained from a bolus input (C) or an infusion input (D). Note that the pattern of error in parameter estimates varied with varying input (C and D) and with the number of parameters fitted (Figures 3C, 4C, 3D and 4D).

erogeneously perfused tissue are different from those obtained from homogeneously perfused tissue.

The type of input, as well as the number of parameters fitted (i.e., the model configuration), also effect how PTI changes as a function of flow. These findings indicate that

PTI is a model-related parameter. The compartmental model used assumes that the tracer enters the compartment, mixes instantaneously and thus assumes that the distribution of tracer within an ROI is homogeneous. The simulations performed in the present study clearly show that errors in parameter estimates are observed when this assumption is not met and that the magnitude of the errors
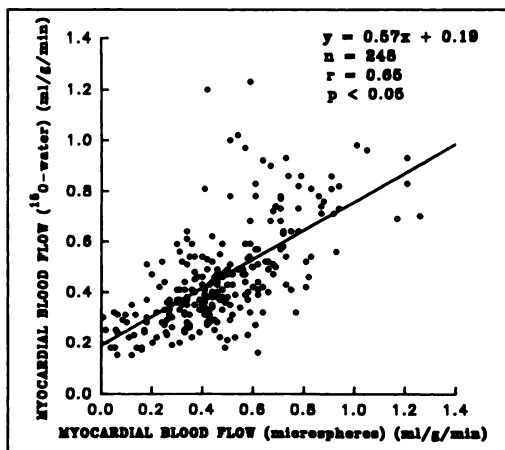

FIGURE 5. Correlation between myocardial blood flow estimated with 15O-water and flows obtained with radiolabeled microspheres for all myocardial samples obtained from 12 dogs. Although there is a significant correlation between 15O-water and microsphere flows, flows estimated with 15O-water underestimated high flows and overestimated low flows, probably due to the limitations of the static sampling approach used in the present study and to the continued perfusion of tissue even after electrical arrest with equilibration of tissue levels.
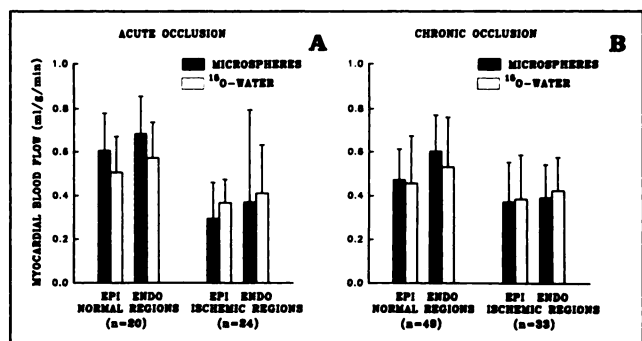

FIGURE 6. Endocardial (ENDO) and epicardial (EPI) blood flow measured with radiolabeled microspheres (solid bars) and with 15O-water (open bars) in normal and ischemic regions obtained from four dogs studied 2 hr after occlusion (A), and eight dogs studied 5-6 wk after coronary occlusion (B). There were no significant differences between flow estimated with microspheres and 15O-water in either normal (normal region in A and B), ischemic (ischemic regions in A), or infarcted (ischemic regions in B) regions. These results demonstrate that water diffuses rapidly into normal, ischemic as well as infarcted myocardium.

vary as a function of flow, with changing the input function, as well as with varying number of parameters fitted to the model.

Animal studies were performed to answer the physiological question of whether infarcted tissue can exchange water rapidly. Flows estimated with ^{15}O-water were underestimated at high flows and overestimated at low flows compared with estimates made with microspheres (Fig. 5). The deviation of the slope from unity and the scatter observed was likely due to the well known limitations of the static sampling approach (11,21), the inaccuracies in the timing of arterial and myocardial samples using the direct sampling approach, and to the continued perfusion of tissue with equilibration of tissue radioactivity levels even after electrical arrest. Nonetheless, it should be noted that at low flow, tissue does exchange water. The overestimation of flows with ^{15}O-water at very low flows when compared with those obtained with microspheres may also reflect underestimation of flows with microspheres at very low flows since, due to their relatively large size, 15-μm microspheres are shunted to high flow regions whereas ^{15}O-water diffuses readily into tissue (22,23). Another potential explanation for the relatively high levels of flows obtained with ^{15}O-water is flow heterogeneity. As shown by the simulations, flow heterogeneity leads to higher estimates of average flows at very low flows. These experimental observations are consistent with the hypothesis that myocardial tissue, even infarcted, can exchange water rapidly. When flows obtained with ^{15}O-water were compared with those obtained with microspheres in normal, ischemic and infarcted tissue, no significant differences between the two measurements were observed (Fig. 6) further suggesting that ^{15}O-water diffuses rapidly into normal, as well as damaged tissue.

Established infarction was verified in tissue samples by gross and histological analysis. All chronically instrumented dogs showed large necrotic areas in the anterior myocardium. These necrotic areas had significantly decreased perfusion when compared to normal areas, and levels not different from those obtained in myocardium from the acutely ischemic regions (0.38 ± 0.17 versus 0.33 ± 0.29). These results indicate that if ^{15}O-water can arrive in myocardial tissue, it will diffuse into tissue independent of whether the tissue is infarcted or viable.

There might be instances where myocardial blood flow is so low that, for all practical purposes, it can be considered zero. If flow is to be estimated in an ROI which includes areas with near-zero flow and areas with non-zero flow, PTI estimated from this region will reflect the heterogeneity within the non-zero flow areas, as well as the degree of near-zero flow and consequently the degree of perfusable tissue. To corroborate this, additional computer simulations were performed. A tissue curve was generated from a homogeneously perfused tissue representing 75% of anatomical tissue at normal flow (1.0 ml/g/min) and 25% of tissue receiving near-zero flow (0.01 ml/g/min). The tissue curve which represented a flow of 0.753 ml/g/min was then

used with a bolus input function and PTI, F_{BM} and flow were estimated. The estimated flow was 0.99 ml/g/min while the estimated PTI was 0.76. Thus, there may be instances where the estimated PTI can be representative of the percentage of non-zero flow regions and for all practical purposes, representative of the amount of tissue being perfused while the estimated flow is more representative of the flow in the well perfused area. Nonetheless, regions with near-zero flows are very rare.

CONCLUSIONS

The results of the present study demonstrate that PTI is most likely an index of myocardial flow heterogeneity rather than the percentage of myocardium that is rapidly exchanging water. In addition, PTI is sensitive to levels of absolute flow and to the shape of the input function. It should be stressed that these results do not invalidate the use of PTI as an index of tissue viability but suggest that tissue flow heterogeneity rather than the amount of non-perfusable tissue may be the physiological explanation for its use. Regions with a PTI < 1 reflect high degrees of tissue flow heterogeneity and/or low levels of absolute tissue perfusion, both of which may contribute to the incapability of myocardium to maintain viability. Further clinical studies will be necessary to delineate the utility of PTI as a marker of tissue viability. If the initial promising reports are corroborated, use of ^{15}O-water with PET will be an attractive and likely cost-effective imaging approach for delineation of viable from nonviable myocardium.

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