Measurement of Myocardial Glucose Uptake in Patients with Ischemic Cardiomyopathy: Application of a New Quantitative Method Using Regional Tracer Kinetic Information

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Quantification of myocardial glucose uptake (MGU) by ^{18}F-fluoro-2-deoxyglucose (FDG) using PET may be inaccurate, because the correction factor that relates myocardial FDG uptake to MGU, the lumped constant (LC), is not a true constant. Recent studies have shown that analysis of FDG time-activity curves allows determination of individual LCs and that variable LCs yield accurate determination of MGU. We compared the magnitude of the LC in different regions of the heart in patients with ischemic cardiomyopathy. **Methods:** Twenty patients with ischemic cardiomyopathy and an average ejection fraction of 33% underwent dynamic ^{13}N-ammonia and FDG PET. We determined myocardial perfusion and MGU in 177 regions classified as control (71 regions), mismatch (50 regions) and match (56 regions), according to findings on PET and echocardiography. Regional MGU was calculated with both regional LCs and a fixed LC of 0.67. **Results:** All results were expressed as mean ± SD. Myocardial perfusion was highest in control regions (0.52 ± 0.18 mL/g/min), reduced in mismatch regions (0.43 ± 0.19 mL/g/min; $P < 0.05$ versus control) and severely reduced in match regions (0.28 ± 0.17 mL/g/min; $P < 0.001$ versus control and mismatch). Regional LCs ranged from 0.45 to 1.30 and differed between patients ($P < 0.001$). Regional LCs were similar in regions diagnosed as control (0.78 ± 0.23), mismatch (0.80 ± 0.24) and match (0.72 ± 0.21). MGU (μmol/g/min) calculated by regional LCs was similar in control (0.52 ± 0.16) and mismatch (0.49 ± 0.19) regions and decreased in match regions (0.31 ± 0.12, $P < 0.001$). The agreement between MGU calculated with variable and fixed LCs was poor. **Conclusion:** The LC used in the calculation of MGU was not affected by regional differences in the metabolic state of the myocardium. However, the LC varied substantially between patients in control, mismatch and match regions. These findings indicate that quantitative measurements of MGU using a fixed LC must be interpreted with caution.

Key Words: fluorodeoxyglucose; PET; lumped constant; heart; metabolism

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PET can detect viable tissue in patients with left ventricular dysfunction by combining tomographic images obtained with a perfusion tracer and the glucose analog 2-deoxy-[^{18}F]fluoro-D-glucose (FDG). Reversible and irreversible ischemic dysfunction can be distinguished on a qualitative basis. Viable hypoperfused myocardium with preserved metabolism is characterized as "mismatch" regions and nonviable hypoperfused regions with reduced metabolism are characterized as "match" regions (*1*). This analysis provides no quantitative information about glucose metabolism in the heart. Tracer kinetic models developed for the brain (*2–4*) allow quantitative assessment of glucose uptake in the heart with FDG (*5*). However, myocardial uptake rates of FDG and glucose differ, and quantification of myocardial glucose uptake (MGU) therefore requires a correction factor called the lumped constant (LC), which is defined as the ratio between net FDG uptake and net glucose uptake. Currently a fixed estimate of the LC of 0.67, derived from experimental findings in the canine heart, is used to calculate MGU (*6*). The ability of FDG to yield accurate quantitative information about MGU has been questioned, because the LC may vary with changes in circulating insulin, glucose and competing substrates (*5,7–9*). We have demonstrated previously that the magnitude of the LC can be determined from the time course of the myocardial FDG uptake data (*5,10*). Determination of the LC in regions of interest (ROIs) allows quantitative measurements that form the basis for any investigation of glucose metabolism in the heart.

It remains unknown whether changes in regions of metabolically deranged heart muscle affect LC and assessment of MGU. Our aim was to study differences of the LC among different individuals and among control, mismatch and match regions in patients with ischemic cardiomyopathy. In addition, we studied the effect of regional LCs on MGU estimates.

METHODS

Patients

We studied 20 nondiabetic patients undergoing PET to assess myocardial viability (Table 1). All patients were men with a mean

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TABLE 1
Clinical and Angiographic Data

Patient	Age (y)	Sex	Previous AMI	Risk factors	NYHA-class	CCS-class	Medication	Diseased vessels	Ejection fraction	Comments
1	49	M	Yes	HC, S	2	1	ACE, Diu, Nit	3	27%	
2	60	M	Yes	H, S	2	2	ACA, CA	3	40%	
3	67	M	Yes	HC	3	3	ACE, Diu	2	24%	
4	61	M	Yes		3	0	ACE, BB, CA, Diu	3	25%	Previous CABG
5	50	M	Yes		3	3	CA, Nit	3	45%	Previous CABG
6	50	M	Yes	HC, H	2	2	ACE, Diu	1	25%	Previous PTCA
7	59	M	Yes	HC, F	2	0	ACE, Diu	3	15%	
8	54	M	Yes	S	3	1	ACE, Diu	3	27%	
9	63	M	No	S	2	0	ACE, BB, Diu	2	43%	
10	47	M	Yes	F, S	3	0	ACE, Diu, Nit	1	15%	
11	64	M	Yes	S	2	1	ACE, CA, Diu	3	45%	
12	57	M	Yes	HC, F	3	3	ACE, BB, Nit	3	28%	
13	63	M	Yes	F, S	3	3	ACE, BB, CA, Diu, Nit	3	35%	Previous PTCA
14	52	M	Yes	HC, F	3	3	BB, CA	3	39%	
15	64	M	Yes	HC, F	2	3	ACE, Diu, Nit	3	45%	
16	58	M	Yes	F	3	2	Diu	3	39%	
17	53	M	Yes	H	2	2	ACE, CA	3	45%	
18	68	M	Yes		3	3	BB	3	44%	
19	48	M	Yes	F, S	3	0	ACE, Diu	3	14%	
20	80	M	Yes	H	3	3	ACE, BB, CA, Diu, Nit	3	38%	

AMI = acute myocardial infarction; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; HC = hypercholesterolemia; S = smoking; ACE = angiotensin-converting enzyme inhibitors; Diu = diuretics; Nit = nitrates; H = hypertension; CA = calcium antagonists; BB = beta blockers; CABG = coronary artery bypass angioplasty; PTCA = percutaneous transluminal coronary angioplasty; F = family history.

age of 58 y (range 47–80 y). Nineteen had previous Q-wave myocardial infarctions (≥4 mo before the study). Two patients had undergone coronary artery bypass surgery, and 2 had undergone balloon angioplasty. Eight patients suffered from severe angina pectoris (Canadian Cardiovascular Society class ≥ 3), and 12 from severe heart failure (New York Heart Association class ≥ 3). Medical treatment is detailed in Table 1. Two patients suffered from single-vessel disease, 2 from two-vessel disease and 16 from three-vessel disease. Mean ejection fraction was 33% (range 14%–45%).

Cardiac Catheterization

Significant stenosis was defined as >50% luminal diameter reduction in any major coronary branch. Ventriculography was not performed in 3 patients because of reduced renal function. Ejection fraction was determined by echocardiography in these patients.

Echocardiography

Echocardiographic examination was performed in all patients, and regional wall motion scoring was evaluated blindly by one observer with a 16-segment model, according to the guidelines of the American Society of Echocardiography (*11*). In each segment the wall motion scoring was graded as: 1 = normal, 2 = hypokinesia, 3 = akinesia and 4 = dyskinesia.

PET Scanning

A whole-body positron emission tomograph (EXACT HR 961; Siemens/CTI, Knoxville, TN) with a 15-cm field of view, acquiring 47 transaxial planes (plane separation 3.125 mm) was used in the studies. The transaxial planes were reconstructed with a Hanning filter with a cutoff frequency of 0.2 Nyquist, resulting in a resolution of 9.4 mm full width at half maximum (FWHM). Pixel size was 1.7 × 1.7 × 3.1 mm.

Myocardial Perfusion

A 20-min attenuation scanning was performed, followed by intravenous injection of 740 MBq ^{13}N-ammonia in 20 mL saline over 30 s with acquisition of a dynamic sequence of images (12 frames of 10 s). After the dynamic sequence, a 900-s static nongated frame was obtained for high-resolution images for assignment of ROIs. Patients remained on their usual medication during the studies (Table 1). Myocardial perfusion was calculated as previously described (*12,13*). Blood pressure and heart rate were registered during image acquisition, and both uncorrected and rate-pressure product corrected estimates of myocardial perfusion were calculated.

Myocardial Glucose Uptake

All patients were studied 30 min after intake of 50 g oral glucose administered as a 100 mL 50% glucose beverage. Patients were allowed to eat and drink before the study and were studied at different times of the day. After intravenous administration of 370 MBq FDG over 1 min, 19 frames were acquired over the next 69 min. The imaging sequence consisted of eight 15 s frames, six 30 s frames, four 1 min frames and six 10 min frames. Blood was sampled from the cubital vein before and at 39, 49 and 59 min after tracer injection for determination of blood glucose values (Beckman Autoanalyzer; Beckman Instruments, Palo Alto, CA).

For the analysis of PET data, all images were reoriented into 12 short-axis slices of the left ventricle. ROIs used for myocardial perfusion scoring were drawn in the appropriate regions on the last

frame of the reoriented FDG images. These ROIs were subsequently copied to the serially acquired dynamic image sequence to obtain myocardial tissue time-activity curves for FDG. The arterial input function was obtained by placing a small ROI in the center of the left ventricular blood pool of the static images and copying these regions to the serially acquired images. Spillover into the blood pool was minimized by drawing small ROIs approximately 4 mm FWHM away from the cardiac walls. We corrected the myocardial time-activity curves for the effect of partial volume, assuming a uniform left ventricular wall thickness of 10 mm (*14*). Blood-pool curves and myocardial time-activity curves were corrected for physical decay of FDG activity. The tissue time-activity curves were fitted using multilinear regression analysis (*15*).

Regions of Interest

We studied 10 ROIs in each of the 20 patients. From myocardial segments with adequate echocardiographic images, we selected ROIs classified as control, mismatch and match regions within the same patient. The ^{13}N-ammonia and FDG images were scored by two independent observers as: 0 = normal, 1 = slightly reduced, 2 = reduced, 3 = severely reduced and 4 = absent. Disagreements (20 regions) were resolved by consensus.

The PET diagnosis was compared with findings on echocardiography and ventriculography to classify ROIs. In control regions, the wall motion score was 1, and the perfusion score ≤ 1. In mismatch regions, the wall motion score was ≥ 2, the perfusion score was ≥ 2, and the FDG score was ≤ 1. In match regions, the wall motion score was ≥ 2, the perfusion score was ≥ 2, and the FDG score was ≥ 2. Segments with discordant findings on PET, echocardiography and ventriculography were excluded from the analysis.

Determination of the Regional Lumped Constant

Derivation of Lumped Constant in the Heart. Myocardial uptake of hexoses includes transport across the myocyte membrane and subsequent phosphorylation by hexokinase. Using the conventional three-compartment mathematical tracer model (*2*), myocardial uptake of hexoses can be described by means of Michaelis-Menten kinetics (*5*). The kinetics assume that the magnitude of the rate constant of dephosphorylation, k^*_4, is low (i.e., low enzyme activity of the phosphatase that hydrolyses FDG-6-PO_4 (*16*). Three fundamental ratios between the rates of uptake of glucose and FDG in the myocardium can be derived from the Michaelis-Menten equation. The ratios relate each of the components of the three-compartment model to: (a) transport across the myocyte membrane, (b) transfer from myocyte to blood and (c) phosphorylation by hexokinase.

(a) When the glucose analog FDG is introduced in tracer quantities, the Michaelis-Menten equation yields an approximately constant transport ratio (R_t) between the rates of unidirectional FDG and glucose transfer across the membrane:

$$R_t = K_t T^*_{max}/K^*_t T_{max} \approx K^*_1/K_1, \quad \text{Eq. 1}$$

where K_1 is the unidirectional transfer coefficient, K_t the Michaelis-Menten half-saturation glucose concentration and T_{max} the maximal transport rate. Asterisks refer to the tracer. Symbols without asterisks apply to glucose, the native substrate. The approximation refers to the relationship between the apparent permeability-surface area product of hexose transport across cell membranes of which the unidirectional clearances are excellent (albeit not exact) estimates, when heart glucose clearance is low relative to blood flow.

(b) Assuming symmetrical transport between blood and heart, the value of the partition volume (V_e) is the same for glucose and its analogs (*17*), as well as a function of the myocardial glucose content (C_i):

$$V_e = K_1/k_2 = K^*_1/k^*_2 = V_d\,(K_t + C_i)/(K_t + C_a), \quad \text{Eq. 2}$$

where k_2 is the fractional clearance from heart to blood, V_d, the water volume of tissue in which hexoses are dissolved and C_a the arterial plasma glucose concentration. This means that the k_2/k_2^* ratio also equals R_t.

(c) FDG and glucose are competitive substrates of hexokinase. In the Michaelis-Menten formulation, the phosphorylation ratio (R_p) between FDG and glucose is:

$$R_p = K_m\,V^*_{max}/K^*_m\,V_{max} = k^*_3/k_3, \quad \text{Eq. 3}$$

where k_3 is the rate constant of phosphorylation, K_m the Michaelis-Menten half-saturation glucose concentration and V_{max} the maximal velocity of phosphorylation by hexokinase.

The LC is a ratio derived from the principles of competitive substrate kinetics that reflects differences in transport and phosphorylation between FDG and glucose. This rate contributes to the conversion of measured values of FDG uptake to the corresponding uptake rates for glucose. The LC was shown by Sokoloff et al. (*2*) to be a function of six constants:

$$LC = \lambda V^*_{max}\,K_m/\Phi\,V_{max}\,K^*_m, \quad \text{Eq. 4}$$

where λ is the ratio of distribution volumes (i.e., the steady-state tissue-to-plasma concentration ratios), V_{max} the maximum reaction velocity, Φ the fraction of phosphorylated glucose that is further metabolized and K_m the Michaelis-Menten half-saturation concentration.

The LC is defined as the ratio between the net extraction fractions of FDG and glucose:

$$LC = K^*/K, \quad \text{Eq. 5}$$

where $K = \Phi K_1 k_3/(k_2 + k_3)$. It follows from the definitions of R_t and R_p that $K_1 = K_1^*/R_t$, $k_2 = k_2^*/R_t$ and $k_3 = k_3^*/R_p$. Since the vast majority of glucose-6-phosphate is further metabolized in the heart, Sokoloff et al. (*2*) assumed Φ to be unity in all subsequent calculations. When the unmarked symbols are replaced by their respective counterparts, marked by asterisks, the following rearrangement is obtained:

$$LC = [k_2^*/(k_2^* + k_3^*)]R_p + [k_3^*/(k_2^* + k_3^*)]R_t, \quad \text{Eq. 6}$$

Because:

$$k_3^*/(k_2^* + k_3^*) = K^*/K_1^* \text{ and } k_2^*/(k_2^* + K_3^*) = 1 - (K^*/K_1^*), \quad \text{Eq. 7}$$

then

$$LC = R_p + (R_t - R_p)K^*/K_1^*. \quad \text{Eq. 8}$$

Equation 8 is more useful than Equations 4 and 5 because it defines the LC in terms of the measurable parameters K^* and K_1^* when R_t and R_p are known. The K^*/K_1^* ratio quantitatively describes the relative influence of the transport and phosphorylation processes on the overall rate of hexose uptake (*18,19*). It has a theoretical range between 0 and 1. When the rate of phosphorylation approaches that of transport, net uptake is determined by the transport rate and the

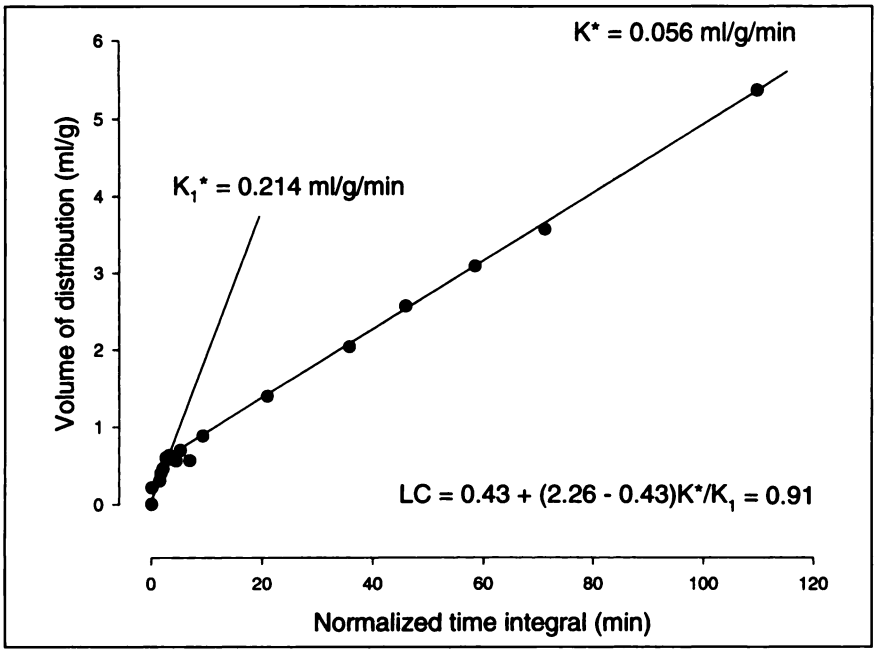

FIGURE 1. Graphical analysis of time course of FDG uptake in myocardial region (Patlak plot). K_1^* and K^* are identical to slopes of initial and steady state fitting lines. Regional lumped constant (LC) was calculated as described, using values for R_p and R_t of 0.43 and 2.26 and the equation $LC = R_p + (R_t - R_p)K^*/K_1^*$.

K^*/K_1^* ratio approaches its maximum value of 1. As phosphorylation declines (for a given transport rate), the net uptake rate and the K^*/K_1^* ratio decrease, approaching 0 when phosphorylation is rate limiting. An intermediate value of the transport limitation ratio corresponds to the situation in which both transport and phosphorylation determine the overall rate of uptake.

Determination of Unidirectional (K_1^*) and Steady-State Clearances (K^*). Both K^* and K_1^* can be determined from the myocardial FDG retention curve after the uptake data have been subjected to conventional graphical analysis as described by Gjedde (*3*) and Patlak et al. (*4*). The graphical analysis of the time course of FDG uptake involves the normalized time integral of the tracer radioactivity in blood plasma:

$$\theta t = \int_0^T [C_a(t)dt/C_a(T)]. \qquad \text{Eq. 9}$$

The term θ has the unit of minutes and accounts for the variations of the tracer concentration in the blood plasma, because FDG is introduced as a bolus. Measured pairs of regional volume of distribution of tracer in the myocardium $V(T)$ and $\theta(T)$ can be regressed by the equation describing the monoexponential approach of a function towards an asymptote at the rate of γ to describe the curve (*20*):

$$V(T) = \alpha\theta(T) + \beta(1 - e^{-\alpha\theta(T)}), \qquad \text{Eq. 10}$$

where α is the slope of the steady-state asymptote, which equals K^*. β is the kinetic distribution volume for unmetabolized FDG. Two distinct asymptotes can be derived from Equation 10, as illustrated in Figure 1. In addition to the steady-state asymptote, a tangent through the origin has the slope of K_1^*. Because the value of K_1^* must equal or exceed K^*, K_1^* can always be represented by an expression of the form $\alpha + \beta/p$, where p has the unit of time. Because the approach of $V(T)$ toward the steady-state asymptote is monoexponential, it can be represented by Equation 10, where γ equals p exactly (*20*). The approximation to a monoexponential function is analogous to the representation of plasma concentration by a sum of exponentials (*21*). Although the graphical presentation of the fitting results in Figure 1 implies that K_1^* is determined as the initial slope of the uptake data, its evaluation by Equation 10 actually depends on the fitting of the entire uptake curve, which provides a considerable advantage in statistical reliability.

The LC lumps several components to correct for all of the kinetic differences between FDG and glucose in the metabolic pathways of transport and phosphorylation. We have used a specific combination of kinetic rate constants for transport and phosphorylation and the measurable parameters net (K^*) and unidirectional (K_1^*) transport of FDG to predict a variable LC (*5,10*). This combination allows determination of the LC from the individual FDG time-activity curve in specific ROIs as specified in Equation 8. Specific values for R_t and R_p are not available for the human heart. The values therefore were adapted from studies in animals. We used values for $R_t = 2.26$ and $R_P = 0.43$, because we have previously found that calculation of MGU with these values agrees perfectly with global myocardial glucose consumption determined by the Fick principle (*5*), when calculated as:

$$MGU = K^*[glucose]_p/LC. \qquad \text{Eq. 11}$$

The parameters required for the estimation of the LC from FDG retention were generated by graphical analysis (*3,4,22*). Corresponding tissue time-activity curves and plasma time-activity curves were combined to produce curves representing changes of the apparent volume of distribution (V) as a function of the normalized time integral of plasma radioactivity (θ), normalized against that radioactivity, as described by Equation 10. The coefficients α, β and γ were determined by nonlinear regression. Unidirectional (K_1^*) and net (K^*) clearances of FDG were calculated as:

$$K_1^* = \alpha + \beta\gamma, \qquad \text{Eq. 12}$$

and

$$K^* = \alpha, \qquad \text{Eq. 13}$$

expressed in mL/g/min.

Statistics

Data are given as mean ± SD. We compared LC, myocardial perfusion and MGU between patients and type of region (control, match and mismatch) by unbalanced general factorial analysis of variance (ANOVA), with a model including interaction between patient and segment type. For post hoc analysis Tukey's Honestly Significant Difference test was used. Influence of medication on the LC was tested by unbalanced general factorial analysis using patient, type of segment and medication as independent variables. Comparison between MGU calculated by different methods was done by paired *t* test and according to Bland and Altman (*23*), using raw and log-transformed data. The F test was used to compare variances of MGU. Least-square linear regression and correlation coefficient were used to test the relationship between perfusion and LC. We used the statistical software program SPSS 8.0 (SPSS, Inc., Chicago, IL) for statistical analyses.

RESULTS

Regions of Interest

Of the 200 regions studied, 23 were excluded from analysis as a result of discordance between PET and echocardiographic findings. The remaining 177 regions were classified as control (71 regions in 20 patients), mismatch (50 regions in 17 patients) or match (56 regions in 20 patients).

Regional Lumped Constants

On average, LC was similar in regions diagnosed as control, mismatch and match (Fig. 2 and Table 2). However, the LC showed great variability within each region: control (range 0.49–1.68), mismatch (range 0.49–1.64) and match (range 0.46–1.54). ANOVA shoved this variability to be caused by differences among patients ($P < 0.001$). This is illustrated in Figure 2, where average patient values of LC, derived from pooling of all regional LCs within each patient, is seen to differ considerably among subjects. No type of medication affected the estimates of the LC. We found a weak correlation between absolute values of perfusion and the regional LCs ($r^2 = 0.036$, $P < 0.05$).

Myocardial Glucose Uptake

MGU (μmol/g/min) calculated by a variable LC was similar in control and mismatch regions and reduced in match regions ($P < 0.001$ versus control and mismatch) (Table 2).

Comparison Between Myocardial Glucose Uptake Calculated with Regional and Fixed Lumped Constant

On average, MGU (μmol/g/min) calculated with a variable LC was decreased compared with MGU calculated with an LC of 0.67 in control and mismatch regions ($P < 0.001$, Table 2). In match regions the two methods yielded similar results. Variability of MGU was not altered when calculated by a regional LC. However, the differences in regional estimates of MGU with a fixed versus a variable LC correlated with the average MGU estimate (Fig. 3). This finding indicates that MGU is overestimated at high and underestimated at low values when a fixed LC is used. Analysis of log-transformed data showed that limits of agreement were wide. In 95% of cases MGU calculated with a variable LC differed from 35% below to 85% above the

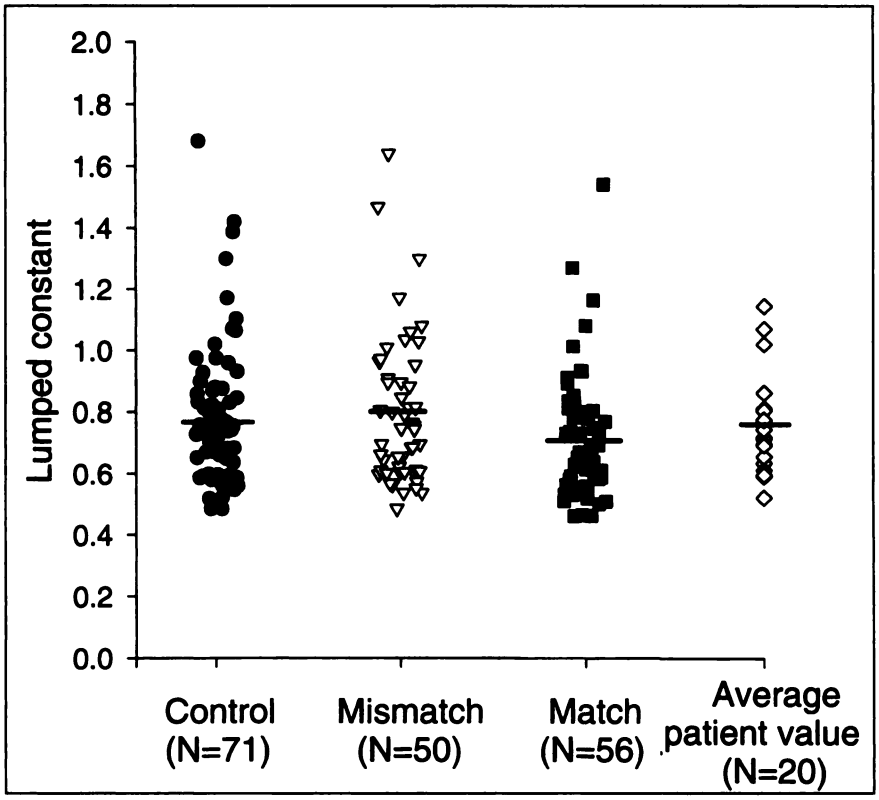

FIGURE 2. LCs calculated from FDG time-activity curves in 177 ROIs in 20 patients with left ventricular dysfunction. ROIs were diagnosed as control (n = 71), mismatch (n = 50) or match (n = 56). LCs did not differ among regions diagnosed as control, mismatch and match. Average patient values for LC, obtained by pooling all regional LCs within each patient, differed among patients ($P < 0.001$). Horizontal lines indicate mean values.

TABLE 2
Lumped Constant, Myocardial Glucose Uptake and Myocardial Blood Flow

Region of interest	LC (regional)	MGU (regional LC) (μmol/g/min)	MGU (LC = 0.67) (μmol/g/min)	Myocardial perfusion (mL/g/min)	Myocardial perfusion (RPP corrected) (mL/g/min)
Control (n = 71)	0.78 ± 0.23	0.52 ± 0.16*	0.59 ± 0.20	0.52 ± 0.18	0.70 ± 0.24
Mismatch (n = 50)	0.80 ± 0.24	0.49 ± 0.19*	0.57 ± 0.24	0.43 ± 0.19†	0.58 ± 0.30†
Match (n = 56)	0.72 ± 0.21	0.31 ± 0.12‡	0.32 ± 0.13‡	0.28 ± 0.17‡	0.37 ± 0.22‡

*$P < 0.001$ versus MGU (LC = 0.67).
†$P < 0.05$ versus control.
‡$P < 0.001$ versus control and mismatch.
LC = lumped constant; MGU = myocardial glucose uptake; RPP = rate-pressure product.
Values in mean ± SD.

estimate of MGU calculated with a fixed LC of 0.67. This indicates a considerable discrepancy between the two methods. No systematic bias was found between the two methods, because mean differences did not differ significantly from zero.

Myocardial Perfusion

Myocardial perfusion (mL/g/min) differed among the three types of regions (Table 2). It was highest in control, intermediate in mismatch and lowest in match regions. Correction for rate-pressure product did not affect differences between regions.

DISCUSSION

The results of this study demonstrate that the LC is not affected by regional differences in the state of the myocardium in patients with ischemic cardiomyopathy. However, we observed a significant difference in the magnitude of the LC among individuals. Consequently, the agreement between MGU calculated with a variable and a fixed LC was poor. We suggest that the use of a regional variable LC, determined in accordance with its physiological dependence on membrane transport rates and hexokinase activity, can improve quantitative assessment of MGU and provide further insight into the pathophysiology of reversible ischemic dysfunction.

The Lumped Constant

The LC changes under conditions that affect hexose transport and phosphorylation, because the magnitude of the LC depends on the relative control strengths of the membrane transport and hexokinase activity for FDG and glucose uptake (*5,24*). These changes are reflected in the time-activity curves of FDG retention and provide a basis for

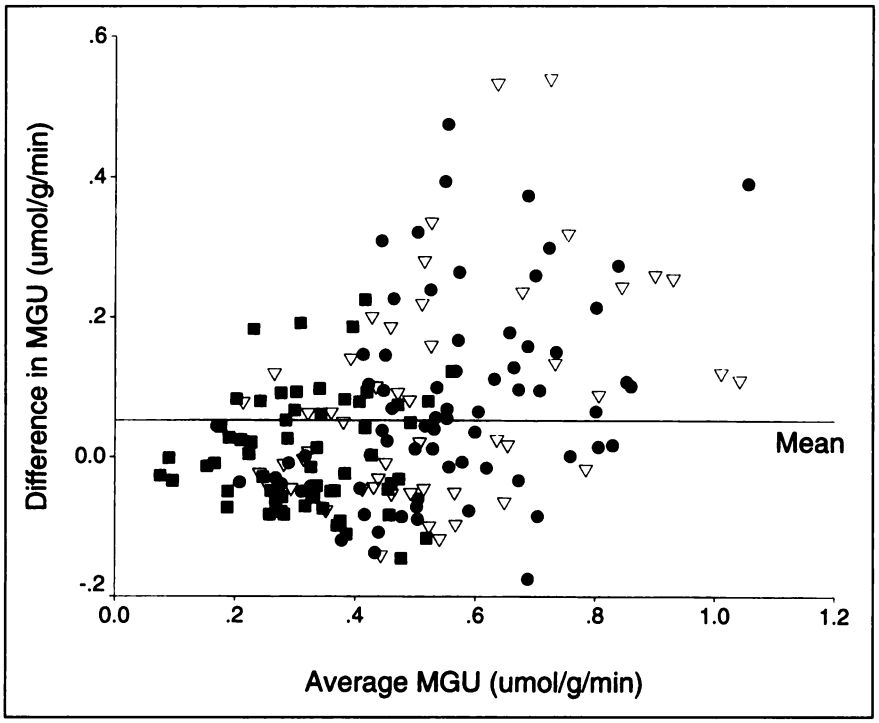

FIGURE 3. Comparison of MGU determined by fixed and variable LC using Bland-Altman plot of average MGU versus difference in MGU. Horizontal line represents mean difference. ● = control (n = 71), ▽ = mismatch (n = 50) and ■ = match (n = 56). Differences in regional estimates of MGU with fixed versus variable LC correlated with average MGU estimate. Finding indicates that MGU is overestimated at high and underestimated at low values when fixed LC is used. Analysis of log-transformed data showed that limits of agreement were wide.

individual determination of the LC (*5*). Theoretically, the constants R_t and R_p represent the upper and lower limits of the LC. The LC approaches its maximum value when membrane transport is rate limiting for FDG and glucose uptake and reaches its minimum value when phosphorylation is rate limiting (*18*).

The similarity of the LC in mismatch and control regions indicates that the relative control strength between membrane transport and phosphorylation for FDG and glucose uptake is similar in these two conditions. Our data show that the magnitude of the LC is only slightly correlated with myocardial perfusion. In isolated perfused rabbit myocardium, the LC is unchanged during short-term ischemia induced by increased demand or low flow (*25,26*). In contrast, the LC is decreased in the reperfusion period after short-term, low-flow ischemia (*26*), indicating that reperfusion shifts the relative control strength from transport to phosphorylation. The underlying mechanism may be translocation of the glucose transporters GLUT4 and GLUT1 to the cell membrane during acute ischemia (*27*), which increases membrane transport more than hexokinase activity. This causes a shift in the limitation of hexose uptake towards phosphorylation. The result of this shift is a decrease in the LC. In contrast, the similar magnitudes of the LC in mismatch and control regions suggest that adaptation of metabolism in areas of chronic hypoperfusion does not involve a shift in control strength compared with control regions.

The LC varies with circulating levels of insulin, lactate and free fatty acids, because these substances exert their influence on MGU by different actions on membrane transport and hexokinase activity (*5,7,9*). The variability of LC among patients, but not among different regions within the individual patient, shows that the magnitude of the LC depends on the metabolic state of the patient at the time of the examination, rather than on regional metabolic differences within the myocardium of that patient. We standardized the dietary state of the patients at the time of PET by an oral glucose load before the investigation. Theoretically, a hyperinsulinemic euglycemic clamp may optimize metabolic standardization during metabolic PET studies, but the influence of this approach on the considerable variation we observed among subjects is controversial (*28–30*).

Myocardial Glucose Uptake Calculated with Regional and Fixed Lumped Constant

MGU was decreased in control and mismatch regions when calculated by a variable LC compared with the conventional LC of 0.67. The extrapolation of values for R_t and R_p from animal studies may introduce an error in the exact values for MGU. This error would be systematic and on the same order of magnitude for mismatch and control regions. The results of the quantitative comparison of the two different states of the myocardium in this study are therefore reliable. Although the exact values may be slightly different in humans and in animals, our previous comparison between MGU using values for $R_t = 0.43$ and $R_P = 2.26$ and MGU obtained with coronary sinus catheterization revealed an excellent agreement (*5*). More important, the individual agreement between MGU calculated with a variable and a fixed LC was poor.

Quantitative analysis of MGU has not yet proven superior to qualitative analysis of MGU in detecting functional outcome after revascularization (*28,31*). Changes in the LC may be responsible for the demonstrated inferiority of quantitative analysis of FDG uptake for the assessment of viability compared with qualitative analysis (*31*). However, calculation of MGU by a regional LC does not reduce the variation in MGU, because the variation is likely to be caused not only by individual differences in the metabolic state but also by individual responses to the actual metabolic state. We cannot at this point be certain whether the use of regional LCs in calculating MGU can improve the prediction of functional outcome after revascularization compared with qualitative analysis. The individual disagreement between values for MGU obtained with a variable and a fixed LC emphasizes the importance of individual determination of the LC in accordance with its physiological dependence on membrane transport and phosphorylation.

Myocardial Glucose Uptake in Chronically Ischemic Myocardium

It remains uncertain whether MGU is maintained or increased in regions of reversible ischemic dysfunction compared with control regions. Marinho et al. (*32*) used a fixed LC of 1 to show that MGU during hyperinsulinemic clamp was decreased to a similar extent in ischemic and control regions of patients with coronary artery disease compared with healthy control subjects. This finding was explained by myocardial insulin resistance in patients with coronary artery disease. In accordance with that study, we found similar rates of glucose uptake in mismatch and control regions. In contrast, we found that MGU in mismatch and control regions was increased compared with our previous findings in young healthy males, in whom MGU is 0.20–0.30 μmol/g/min at physiological circulating insulin levels between 10 and 70 pmol/L (*5*). The discrepancy in the results may be explained by differences in the magnitude of the LC in mismatch and remote control areas on one hand and truly normal myocardium on the other. Studies using coronary sinus catheterization have demonstrated that myocardium supplied by normal coronary arteries in patients with coronary artery disease exhibits metabolic abnormalities characterized by increased MGU (*33*). These findings are in accordance with the results of a study from our institution demonstrating altered global myocardial metabolism in patients with angina pectoris caused by coronary artery disease (*34*). MGU in remote areas with preserved contractility is consequently not truly normal and may not be different from MGU in mismatch areas. This could be caused by increased work loads in the remote regions to compensate for depressed contractile function in the ischemic zones (*35*).

Myocardial Perfusion in Viable Regions

It is unsettled whether myocardial perfusion is reduced or preserved in regions of reversible dysfunctional myocardium (*36,37*). Our finding of reduced perfusion in mismatch regions is implicit, since we deliberately studied regions with reduced perfusion scores on the tomographic images.

Study Limitations

The noninvasive approach used in this study does not allow an independent validation of the LC determined by direct measurement of regional rates of MGU. Exact measurements cannot be obtained in vivo in man, because the coronary sinus catheterization method allows only a global assessment of MGU, which does not take into account regional differences caused by the ischemic cardiomyopathy (*38*). However, the principles underlying the calculations have been validated in the isolated rabbit interventricular septum and the isolated working rat heart (*10,39*). We have also tested the consequences of the approach in healthy human males and found that the LC varies with the metabolic condition as predicted from studies in the animal heart under experimental conditions (*5*).

We did not document reversible dysfunction in the study patients, because they were not examined after revascularization. The regions fulfilled all PET and echocardiographic criteria of normally contracting and reversibly and irreversibly dysfunctional myocardium. Furthermore, the study was not intended to provide information about the predictive value of quantitative analysis of perfusion and metabolism for the results of revascularization.

Partial-volume correction assumes a uniform wall thickness of 10 mm. This may not be correct, because wall thickness may differ among normal, mismatch and match regions. However, this inaccuracy is inherent in PET examinations and should not affect the comparison between the use of a fixed and a variable LC for calculation of MGU. Comparison between control and mismatch regions is unlikely to be affected by such differences, because accurate imaging techniques such as MRI have shown that wall thickness is preserved in viable regions (*40*).

CONCLUSION

The LC was not affected by regional differences of the state of the myocardium in patients with ischemic cardiomyopathy, but the LC showed considerable variation among individual patients in control, mismatch and match regions. These findings indicate that measurements of MGU using a fixed LC must be interpreted with caution.

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