Annals of Nuclear Medicine Vol. 10, No. 1, 93–98, 1996

Paradoxical uptake of F-18 fluorodeoxyglucose by successfully reperfused myocardium during the sub-acute phase in patients with acute myocardial infarction

Katsuji HASHIMOTO,* Toshiisa UEHARA,* Yoshio ISHIDA,** Hiroshi NONOGI,*** Hideo KUSUOKA* and Tsunehiko NISHIMURA*

*Division of Tracer Kinetics, Biomedical Research Center, Osaka University Medical School
Departments of **Radiology and ***Cardiology, National Cardiovascular Center

The myocardial uptake of F-18 fluorodeoxyglucose (FDG) has been shown to indicate ischemia. To elucidate whether this is applicable to reperfused myocardium in patients with acute myocardial infarction (AMI), Tl-201 SPECT and F-18 FDG PET were performed in 10 patients with successfully recanalized AMI (male : female = 8 : 2; mean age = 62 ± 9 years old). Regional myocardial perfusion of the infarct-related area was classified, on the basis of Tl-201 images, into 2 groups (normal and defect) during the sub-acute phase, and into 3 grades (normal, redistribution (RD), and persistent defect) during the chronic phase (1 and 3 months after onset). Regional FDG uptake was calculated as FDG uptake in the region of interest normalized relative to that in a normal area. During the chronic phase, FDG accumulated only in the region of RD, indicating ischemia, but during the sub-acute phase, FDG accumulated mainly in the peri-infarct area. To elucidate whether the reperfused myocardium itself shows signs of accelerated glucose uptake, an experimental study was performed in rats. Glucose uptake in the isolated heart was measured by deoxyglucose and ^{31}P-NMR spectroscopy, and was significantly increased after reperfusion compared with the pre-ischemic level. In conclusion, the enhancement of FDG uptake during the sub-acute phase was observed in successfully reperfused myocardium of patients with acute myocardial infarction. Such augmentation disappeared during the chronic phase. An experimental study in rats indicated that ischemia and reperfusion themselves augment glucose uptake. This mechanism may be responsible for the increase in FDG uptake of reperfused myocardium observed clinically.

Key words: F-18 FDG PET, acute myocardial infarction, Tl-201 SPECT, P-31 NMR spectroscopy

INTRODUCTION

THALLIUM-201 REDISTRIBUTION and persistent FDG uptake, i.e. enhanced glucose uptake relative to blood flow, is an ischemic but viable sign for myocardium.[1–3] Due to the technical progress in reperfusion therapy for acute myocardial infarction, FDG accumulation has been shown to occur in reperfused areas during the sub-acute phase of myocardial infarction.[4–6] This is paradoxical because reperfused myocardium should no longer be ischemic. Residual ischemia in reperfused myocardium and glucose uptake by infiltrating inflammatory cells[7] are considered as possible mechanisms of enhanced FDG accumulation in reperfused areas, but it is not clear whether ischemia is necessary to enhanced glucose uptake in reperfused myocardium, because FDG uptake during the sub-acute phase is especially noticeable in the peri-infarct area between the infarcted and normal myocardium. This study was performed to experimentally elucidate the time course of FDG uptake and tissue perfusion in infarct-related myocardium, and the mechanism of enhanced glucose uptake in reperfused myocardium.

Received October 12, 1995, revision accepted November 13, 1995.

For reprint contact: Tsunehiko Nishimura, M.D., Ph.D., Division of Tracer Kinetics, Biomedical Research Center, Osaka University Medical School, 2–2 Yamada Oka, Suita, Osaka 565, JAPAN.

MATERIALS AND METHODS

Clinical study

Ten patients (8 men and 2 women, mean age 62 ± 9 years) who were successfully recanalized during the acute phase of myocardial infarction participated in this study. Acute myocardial infarction was diagnosed by typical ischemic chest pain, acute ST-T wave changes in ECG, and serum creatine kinase MB isozyme levels. All patients received emergent coronary arteriography (CAG) followed by reperfusion therapy; six patients received intracoronary thrombolysis and three underwent coronary balloon angioplasty. The remaining patient showed spontaneous recanalization on catheterization.

Coronary arteriography was performed in all patients one month after the onset of acute myocardial infarction. Cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and ^{201}Tl myocardial imaging (Tl-201-SPECT) were also performed once during the sub-acute phase (within 4 to 12 days from the onset) and twice during the chronic phase (one and three months after the onset of acute myocardial infarction).

Tl-201 SPECT

Tl-201 myocardial scintigraphy at rest was performed during the sub-acute phase. After intravenous injection of Tl-201 (111 MBq), myocardial SPECT images were obtained with a rotating gamma camera (GCA-901A/HG, Toshiba, Tokyo) equipped with a general purpose collimator. Thirty-two projections were acquired over 180°, from right anterior oblique to left posterior oblique (30 sec per step). The reconstructed tomographic data were displayed in four planes (trans-axial, horizontal long axis, vertical long axis and short axis). One and three months after onset, symptom-limited exercise testing was performed on a bicycle ergometer in all patients. During the last minute of exercise, 111 MBq ^{201}Tl was injected intravenously. Myocardial SPECT imaging was obtained within 10 minutes after the completion of exercise (early images) and again 3 hours after initial tracer injection (redistribution images).

^{201}Tl images were categorized visually in the trans-axial plane, which was also used for analysis of FDG-PET images. Infarct-related regions in the images obtained during the sub-acute phase were subdivided into two areas: the infarct area and peri-infarct area. The infarct area was determined as the central region in the defect, and the peri-infarct area was assigned to segments on the border of the defect. Information concerning infarct-related vessels from the coronary arteriographic data was also used to determine these two areas. Infarct areas were divided into two classes based on the degree of Tl uptake: Tl (−) showing complete defect in Tl images, and Tl (+) showing low but not a lack of Tl uptake. The segments related to infarct and peri-infarct areas in the Tl-SPECT obtained during the chronic phase (1 or 3 months after onset) were classified into three groups based on the results of stress tests: persistent defect (D), redistribution (RD) and normal (N).

F-18 FDG PET

^{18}F-FDG positron emission tomography was also performed on the same day as Tl-201 scintigraphy with a PET scanner (Headtome IV, Shimadzu, Kyoto). All patients were studied after more than 6 hours fasting. The imaging studies were performed under resting conditions. After transmission scan for attenuation correction, 185–222 MBq ^{18}F-FDG was injected intravenously. PET static images were obtained at 40 minutes after the injection over 15 minutes. PET data were reconstructed into transaxial cardiac planes. Regions of interest (ROI) in PET images were assigned to the infarct area, peri-infarct area and remote area (normal myocardium) by referring to the ^{201}Tl myocardial perfusion images. Remote areas were identified as those with normal perfusion which were obviously unaffected by infarction. Regional myocardial ^{18}F-FDG uptake in infarct-related areas was normalized by that in remote areas ("%FDG uptake") as follows:

$$\%\text{FDG uptake } (\%) = (\text{FDG uptake in the concerned area}/\text{FDG uptake in the remote area}) \times 100$$

Experimental study

To elucidate whether ischemia and reperfusion themselves cause increased glucose uptake in myocardium, an experimental study was performed in isolated, perfused rat hearts.

Hearts excised from rats (Sprague-Dawley, body weight; 350–400 g) were perfused by the Langendorff technique with a modified Tyrode's buffer of the following composition (in mM) bubbled with 100% O_2 at 37°C: NaCl 108, KCl 5, $MgCl_2$ 1, $CaCl_2$ 1.5, HEPES 5, glucose 10, and Na acetate 20 (standard perfusate, pH 7.4). The heart rate was maintained at 273 beats/min by right ventricular pacing. A latex balloon tied to the end of a polyethylene tube was passed into the left ventricle through the mitral valve. The balloon was filled with 25 mM magnesium trimetaphosphate solution as a standard for ^{31}P-NMR spectroscopy.[8] Left ventricular end-diastolic pressure (EDP) was set at 3–6 mmHg by adjusting the balloon volume, and the balloon was kept isovolumic throughout the experiment. Aortic pressure was monitored at the cannulation point of the aorta. Left ventricular pressure and aortic pressure were recorded with a direct-writing recorder. Aortic pressure was adjusted to 70–80 mmHg.

The preparations were put into a tube 20 mm in diameter and placed into the superconducting magnet. P-31 nuclear magnetic resonance (P-NMR) spectra were obtained on an NMR spectrometer (AMX 400wb, Bruker, CO), the resonance frequency for ^{31}P of which was 161.98 MHz. The free induction decays from the heart obtained

with 90° pulses delivered at 2-second intervals were accumulated and processed. Each spectrum was obtained with 144 pulses, resulting in a total acquisition time of 5 minutes for each spectrum.

The method used to quantify metabolites has been reported previously.[8] Briefly, the amounts of sugar phosphates (SP), inorganic phosphates (P_i), phosphocreatine (PCr), and adenosine triphosphate (ATP) in the myocardium were obtained by planimetry of the areas under individual peaks with a digitizer (see Fig. 4). The SP, P_i, PCr and ATP in tissue were normalized by the peak for the magnesium trimetaphosphate standard in the left ventricular balloon.

Myocardial glucose uptake was detected by accumulation of SP when glucose in the perfusate was replaced by 2-deoxyglucose (DG, 10 mM). When DG is taken up into myocytes, DG is phosphorylated to DG-6-phosphate (DG-6-P) by hexokinase, accumulated in the myocardium[9] and appears at ~6 ppm in the spectrum.

NMR spectra and mechanical function were measured for 10 minutes to determine initial basal values. After this phase, glucose in the perfusate was replaced by DG (DG perfusate, pH 7.4) and the hearts were perfused for 10 minutes to evaluate the change in [SP] during the non-ischemic control phase. The hearts were then perfused again with the standard perfusate for 20 minutes, and subjected to 15 minutes of global ischemia at 37°C. After the period of global ischemia, the hearts were reperfused with the perfusate containing DG for ten minutes to assess the change in [SP] just after reperfusion.

Statistical Analysis

Data are expressed as means ± SEM. For statistical analysis, Student's paired t-test was used. Probability values less than 0.05 were considered as statistically significant.

RESULTS

FDG uptake in reperfused myocardium

Figure 1 shows the changes in Tl-201-SPECT and FDG-PET in the patient who was successfully reperfused after anterior wall myocardial infarction. During the sub-acute phase (3 days after the onset), FDG uptake was most prominent in the peri-infarct area identified by the ^{201}Tl images performed on the same day. In the chronic phase, a persistent increase in FDG uptake was observed in the area of infarction where the myocardium showed signs of redistribution on exercise ^{201}Tl SPECT.

Figure 2 summarizes the relationship between %FDG uptake and Tl uptake during the sub-acute phase. In the center of the infarct area where the myocardium showed a defect on Tl imaging, %FDG (118 ± 20%, n = 5) was not the same in all cases, and did not show any significant change compared with the normal area (p = 0.42) indicating reduced FDG uptake. In contrast, %FDG (128 ± 11, n = 4) in successfully reperfused myocardium showing Tl

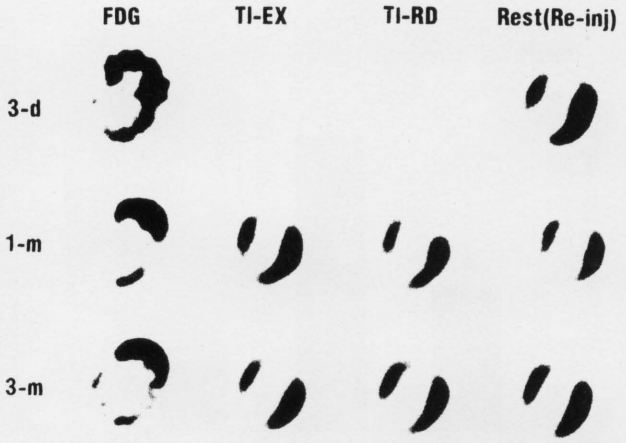

Fig. 1 The changes in Tl-201-SPECT and FDG-PET of successfully reperfused myocardium of the patient with the anterior wall infarction. The ^{18}F-FDG PET (FDG) and ^{201}Tl SPECT at rest (Rest) were performed on 3 days after the onset (3-d). At 1 month (1-m) and 3 months (3-m) after the onset, FDG-PET, exercise ^{201}Tl SPECT, and re-injection of ^{201}Tl (Re-inj) were performed. Tl-EX and Tl-RD indicate early images, and delayed images of exercise ^{201}Tl myocardial SPECT, respectively.

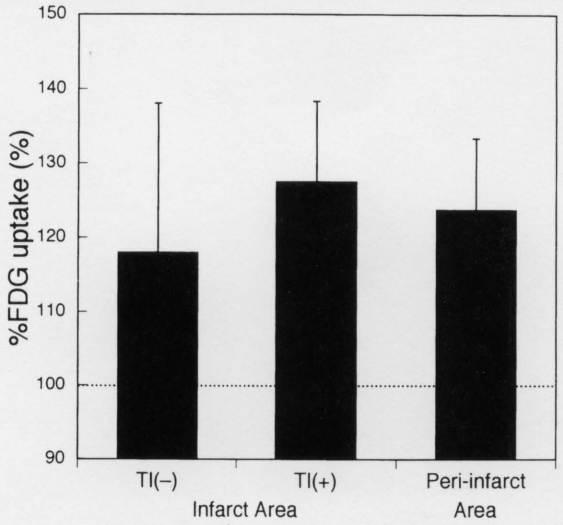

Fig. 2 Normalized %FDG uptake of myocardium during the sub-acute phase in patients with successful revascularization for acute myocardial infarction. Tl (+): area showing Tl-uptake in infarct area; Tl (−): area showing defects in Tl images in infarct area.

uptake was increased, but did not reach the level of significance (p = 0.09). Peri-infarct areas showed significant increases in %FDG (124 ± 10, n = 9, p < 0.05). These results indicate that glucose utilization is augmented in non-ischemic myocardium during the sub-acute phase of myocardial infarction.

At 1 month (129 ± 19%, n = 6, p = 0.19) and at 3 months (100 ± 8, n = 6, p = 0.95) after onset, necrotic areas showing poor Tl uptake (D) showed little FDG uptake, as observed in normal cases. In contrast, the myocardium with hypoperfusion (RD) showed significant increases in FDG uptake in the chronic stage (169 ± 13

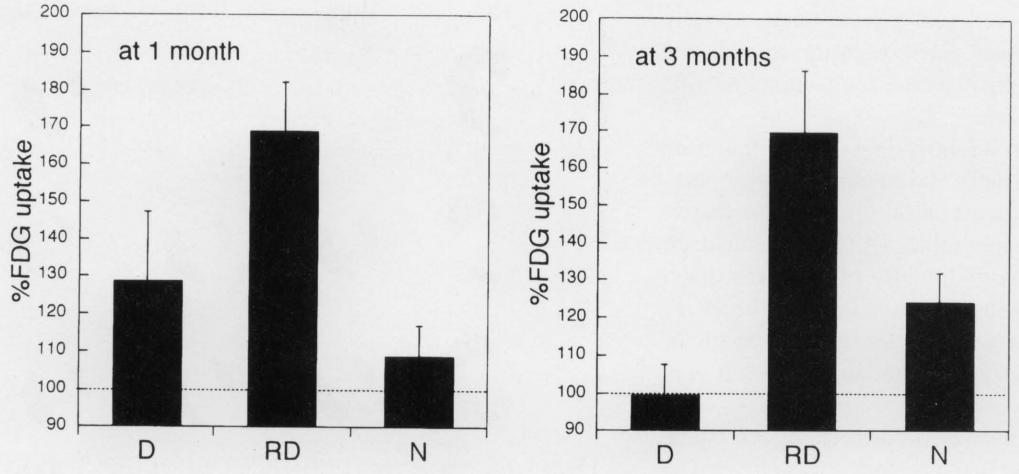

Fig. 3 Normalized %FDG uptake during chronic phase in infarct-related area. D: area showing persistent perfusion defects in Tl images, RD: area showing redistribution in Tl images, N: area showing normal pattern in stress ^{201}Tl study.

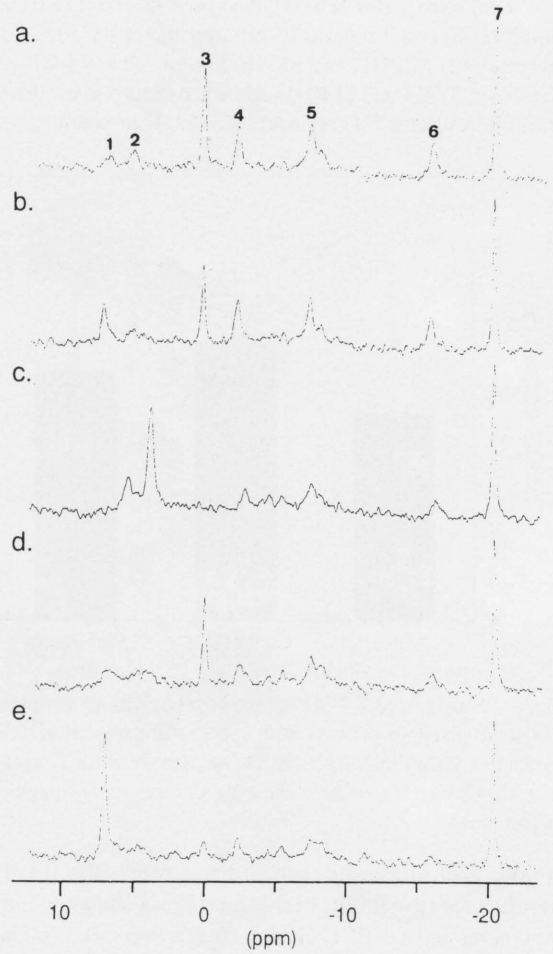

Fig. 4 Typical changes in ^{31}P-NMR spectra before and after application of DG. a: before application of DG during the pre-ischemic phase, b: 10 min after application of DG during the pre-ischemic phase, c: at the end of 15-min ischemic period, d: just after reperfusion, e: 10 min after application of DG in reperfused myocardium. The numbered peaks are as follows; 1: sugar phosphates (SP), 2: inorganic phosphate (P_i), 3: phosphocreatine (PCr), 4, 5, 6: the three phosphates of ATP (γ, α, and β, respectively), 7: magnesium trimetaphosphate standard.

at 1 month ($n = 8$, $p < 0.01$), and 170 ± 17 at 3 months ($n = 6$, $p < 0.01$)) (Fig. 3). These findings during the chronic phase were identical to those reported previously in FDG studies on ischemic myocardium.[1,3,10]

Experimental study

To determine the mechanism responsible for augmented glucose uptake in reperfused myocardium, we evaluated glucose uptake in isolated perfused hearts by using the P-NMR technique.

Figure 4 summarizes the changes in P-NMR spectra. When the standard perfusate was switched to that containing DG, the peak of SP was increased (Fig. 4b) compared to that with control perfusate (Fig. 4a). The increase in SP indicated glucose uptake during 10 minutes with normoxic perfusion. The hearts were then subjected to ischemia, and the peaks of PCr and ATP decreased, but the peak of P_i increased (Fig. 4c). Note that the peaks of SP and P_i shift to the right side due to acidosis.[11] After reperfusion, all peaks except that of ATP recovered to the pre-ischemic level (Fig. 4d). A rapid increase in the peak of SP was observed in reperfused myocardium when the perfusate was switched to that containing DG (Fig. 4e).

During the non-ischemic control phase, the increase in myocardial [SP] was small; the accumulation of DG during the 10-minute control period (Δ[SP]) was 3.63 ± 0.37 μmol/g wt. On the other hand, Δ[SP] was significantly augmented after reperfusion (8.93 ± 0.74, $p < 0.05$) (Fig. 5). These results indicate that reperfusion after ischemic insult itself enhances myocardial glucose uptake.

DISCUSSION

It has been demonstrated experimentally that myocardium prefers fatty acids to glucose as energy substrates under normoxic conditions.[12–14] This was also confirmed clinically by FDG-PET studies in which FDG was shown not to accumulate in normal myocardium under fasting

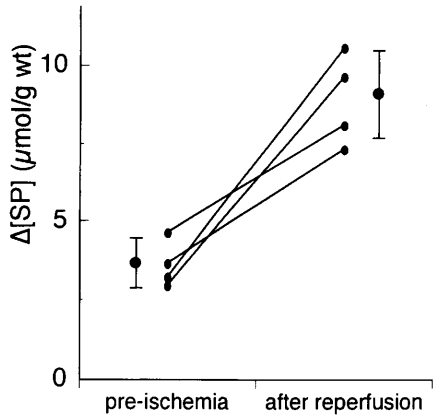

Fig. 5 SP accumulation during the pre-ischemic phase and after reperfusion. Δ[SP]: increase in [SP] during 10-min application of DG.

conditions. In contrast, ischemia enhances myocardial glucose uptake probably due to accelerated anaerobic glycolysis,[2,10,15] but, as shown in this study, myocardium successfully and sufficiently reperfused during the acute phase of myocardial infarction obviously accumulated FDG.

During the sub-acute phase of myocardial infarction, FDG accumulation was augmented in the peri-infarct area and in well-reperfused myocardium of the infarct area. Residual ischemia in reperfused myocardium and glucose metabolism of infiltrating inflammatory cells are considered as possible mechanisms of the enhanced FDG accumulation in reperfused areas,[7] but it was reported with regard to the glucose uptake of inflammatory cells that leukocyte metabolism is not related to FDG accumulation in infarct-related areas.[16] The results of our experimental study indicated that glucose uptake is accelerated in myocardium reperfused after ischemia. Thus, ischemia and reperfusion themselves are considered to enhance myocardial FDG uptake in the peri-infarct area or in reperfused myocardium in the infarct area. In areas showing defects on thallium imaging, the number of viable cells was assumed to decrease due to failure in salvaging. This may be responsible for the low FDG uptake in these areas even if glucose uptake is augmented in each viable myocyte. The large fluctuation in FDG uptake in the area may also reflect the inconsistency in the number of viable cells in each case.

Myocardium with defects in thallium images during the chronic stage showed decreases in FDG uptake. This implies that myocardial infarction was completed in these areas. The myocardium showing thallium redistribution (RD) could be considered to be ischemic but viable. It is therefore understandable that augmented glucose uptake was observed in the myocardium in this group.

In conclusion, the enhancement of FDG uptake during the sub-acute phase was observed in the successfully reperfused myocardium of patients with acute myocardial infarction. Such augmentation disappeared during the chronic phase. Our experimental study indicated that ischemia and reperfusion themselves augment glucose uptake. This mechanism may be responsible for the increases in FDG uptake in reperfused myocardium observed clinically.

REFERENCES

1. Melin JA, Wijns W, Keyeux A, Gurne O, Cogneau M, Michel C, et al. Assessment of thallium-201 redistribution versus glucose uptake as predictors of viability after coronary occlusion and reperfusion. *Circulation* 77: 927–934, 1988.
2. Czernin J, Porenta G, Brunken R, Krivokapich J, Chen K, Bennett R, et al. Regional blood flow, oxidative metabolism, and glucose utilization in patients with recent myocardial infarction. *Circulation* 88: 884–895, 1993.
3. Tamaki N, Kawamoto M, Takahashi N, Yonekura Y, Magata Y, Nohara R, et al. Prognostic value of an increase in fluorine-18 deoxyglucose uptake in patients with myocardial infarction: Comparison with stress thallium imaging. *J Am Coll Cardiol* 22: 1621–1627, 1993.
4. Gould KL, Yoshida K, Hess MJ, Haymie M, Mullani N, Smalling RW. Myocardial metabolism of fluorodeoxyglucose compared to cell membrane integrity for the potassium analogue rubidium-82 for assessing infarct size in man by PET. *J Nucl Med* 32: 1–9, 1991.
5. Pierard LA, DeLandsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 15: 1021–1031, 1990.
6. Bianco JA, Bakanauskas J, Carlson M, Jones S, Moring A, Alpert JS, et al. Augmented uptake of 2-C-14-D-deoxyglucose in reversibly injured myocardium. *Eur J Nucl Med* 13: 557–562, 1988.
7. Schoeder H, Friedrich M, Topp H. Myocardial viability: What do we need? *Eur J Nucl Med* 20: 792–803, 1993.
8. Kusuoka H, Weisfeldt M, Zweier JL, Jacobus WE, Marban E. Mechanism of early contractile failure during hypoxia in intact ferret heart: evidence for modulation of maximal Ca^{2+}-activated force by inorganic phosphate. *Circ Res* 59: 270–282, 1986.
9. Sokoroff L, Reivich M, Kennedy C, Rosiers MH, Patlak CS, Pettigrew KD, et al. [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 28: 897–916, 1977.
10. Camici P, Araujo LI, Spinks T, Lammertsma AA, Kaski JC, Shea MJ, et al. Increased uptake of ^{18}F-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. *Circulation* 74: 81–88, 1986.
11. Corretti MC, Koretsune Y, Kusuoka H, Chacko VP, Zweier JL, Marban E. Glycolytic inhibition and calcium overload as consequences of exogenously generated free radicals in rabbit hearts. *J Clin Invest* 88: 1014–1025, 1991.
12. Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrates and lipids. *Proc Cardiovasc* 15: 289–329,

1972.
13. Neely JR, Morgan HE. Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle. *Annu Rev Physiol* 36: 413–459, 1974.
14. Liedtke AJ. Alterations of carbohydrate and lipid metabolism in acutely ischemic heart. *Prog Cardiovasc Dis* 23: 321–336, 1981.
15. Schwaiger M, Neese RA, Araujo L, Wyns W, Wisneski JA, Sochor H, et al. Sustained nonoxidative glucose utilization and depletion of glycogen in reperfused canine myocardium. *J Am Coll Cardiol* 13: 745–754, 1989.
16. Wijns W, Melin JA, Leners N, Ferrant A, Keyeux A, Rahier J, et al. Accumulation of polymorphonuclear leukocytes in reperfused ischemic canine myocardium: Relation with tissue viability assessed by fluorine-18-2-deoxyglucose uptake. *J Nucl Med* 29: 1826–1832, 1988.