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Pulmonary Hypertension

Increased [^{18}F]Fluorodeoxyglucose Accumulation in Right Ventricular Free Wall in Patients With Pulmonary Hypertension and the Effect of Epoprostenol

Minako Oikawa, MD,* Yutaka Kagaya, MD, PHD,* Hiroki Otani, MD, PHD,* Masahito Sakuma, MD, PHD,* Jun Demachi, MD,* Jun Suzuki, MD, PHD,* Tohru Takahashi, MD, PHD,* Jun Nawata, MD, PHD,* Tatsuo Ido, PHD,† Jun Watanabe, MD, PHD,* Kunio Shirato, MD, PHD*
Sendai, Japan

OBJECTIVES We examined whether right ventricular (RV) [^{18}F]fluorodeoxyglucose (FDG) accumulation is increased in patients with pulmonary hypertension using gated positron emission tomography (PET) and whether RV FDG accumulation changes after therapy with epoprostenol.

BACKGROUND Myocardial glucose utilization is increased in animal models with ventricular pressure overload.

METHODS We performed gated FDG-PET in 24 patients with pulmonary hypertension. The RV standardized uptake value (SUV) of FDG was corrected for the partial volume effect based on the wall thickness measured by electron-beam computed tomography or magnetic resonance imaging.

RESULTS The corrected RV SUV of FDG was significantly correlated with the pulmonary vascular resistance, mean pulmonary artery pressure, right atrial pressure, RV wall stress, and plasma brain natriuretic peptide levels, but not with the RV wall thickness and mass. After pulmonary vasodilator therapy with epoprostenol for three months, the corrected RV SUV of FDG significantly decreased in the responders, but not in the non-responders, and the percentage change of the corrected RV SUV of FDG was significantly correlated with the percentage change of the pulmonary vascular resistance ($r = 0.78$; $p < 0.01$) and RV systolic wall stress ($r = 0.76$; $p < 0.05$).

CONCLUSIONS The RV FDG accumulation corrected for the partial volume effect was significantly increased in accordance with the severity of the RV pressure overload (i.e., the RV peak-systolic wall stress) in patients with pulmonary hypertension. Furthermore, the corrected RV FDG accumulation was decreased after the treatment with epoprostenol in accordance with the degree of reduction in the pulmonary vascular resistance and RV peak-systolic wall stress. (J Am Coll Cardiol 2005;45: 1849–55) © 2005 by the American College of Cardiology Foundation

Chronic ventricular pressure or volume overload has been shown to alter the myocardial preference for energy substrates (1–5). Our previous study and others (1–3) demonstrated that myocardial glucose uptake was increased, whereas free fatty acid analogue uptake was decreased, in animal models of chronic left ventricular (LV) pressure overload. In humans, myocardial fatty acid metabolism has been shown to be altered in hypertrophied LV myocardium induced by chronic hypertension (6). In right ventricular (RV) pressure overload due to pulmonary artery constriction in rats, we demonstrated not only that myocardial glucose utilization in the RV free wall increased, but the regional profiles of substrate utilization in the interventricular septum and the LV free wall were also altered (5). Our previous clinical study with positron emission tomography (PET) demonstrated that myocardial [^{18}F]fluorodeoxyglucose (FDG) accumulation was increased in the interventricular septum compared with the LV free wall in patients with chronic RV volume overload due to atrial septal defect, and that the FDG accumulation in the RV free wall was also increased in those patients compared with the control subjects, although we did not correct the radioactivity for the RV free wall thickness (7). However, it is unclear whether FDG accumulation in the RV free wall, corrected for the partial volume effect, which is derived from the relatively thin RV free wall thickness, increases in patients with chronic RV pressure overload. Furthermore, it is also unclear whether myocardial FDG accumulation in the RV free wall changes after treatment with epoprostenol, which has been shown to greatly improve the quality of life and prognosis of patients with primary pulmonary hypertension (8,9).

In the present study, we examined whether FDG accumulation in the RV free wall increases in patients with primary pulmonary hypertension and chronic thromboembolic pulmonary hypertension using gated PET with FDG. We also examined whether RV FDG accumulation changes after therapy with epoprostenol in patients with primary pulmonary hypertension.

METHODS

Study population. From among a total of 38 consecutive patients who were diagnosed as having precapillary pulmonary hypertension in our institute from March 2001 to June

From the *Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; and the †Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan.

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
EBCT = electron-beam computed tomography
ECG = electrocardiogram/electrocardiography
FDG = [^{18}F]fluorodeoxyglucose
LV = left ventricle/ventricular
MRI = magnetic resonance imaging
PET = positron emission tomography
ROI = region of interest
RV = right ventricle/ventricular
SUV = standardized uptake value

2004, seven patients were excluded from the present study due to diabetes mellitus or glucose intolerance, and seven patients were excluded due to unstable hemodynamic conditions. The remaining 24 patients were enrolled in the present study. Using right heart catheterization, a diagnosis of precapillary pulmonary hypertension was made if the mean pulmonary artery pressure was higher than 25 mm Hg at rest and the pulmonary capillary wedge pressure was ≤12 mm Hg (10,11). The classification into primary or secondary precapillary pulmonary hypertension was performed according to World Health Organization standards (12). Fifteen patients were diagnosed as having primary pulmonary hypertension and nine patients as having chronic thromboembolic pulmonary hypertension. Coronary angiography was also performed in all the patients to exclude coronary artery disease. Medications included calcium channel blockers (n = 15), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (n = 14), digoxin (n = 5), diuretics (n = 9), and nasal oxygen supplementation (n = 12) in various combinations. All nine patients with chronic thromboembolic pulmonary hypertension received anticoagulants. Right heart catheterization and the measurement of the plasma brain natriuretic peptide (BNP) level were performed within two weeks from the PET study. Continuous intravenous epoprostenol (Flolan, Glaxo-SmithKline, Middlesex, United Kingdom) was initiated in 10 patients with primary pulmonary hypertension because these patients were markedly symptomatic (New York Heart Association functional class III or class IV) despite optimal medical therapy. Epoprostenol was started at a dose of 0.5 ng/kg/min and gradually increased weekly by 1 ng/kg/min. We performed the second PET, magnetic resonance imaging (MRI) or electron-beam computed tomography (EBCT), and right heart catheterization after the treatment with epoprostenol for three months in the 10 patients treated with epoprostenol. The purpose and nature of the present study were approved by the Committee for the Administration of Radioactive Substances of Tohoku University School of Medicine. Written informed consent was obtained from all subjects before each study.

PET. Positron emission tomography was performed with an SET-2400W PET scanner (Shimadzu, Kyoto, Japan). The scanner had an axial and transverse field of view of 20 cm and 59 cm, respectively, yielding 63 contiguous transaxial slices to cover the whole cardiac region. Each patient fasted at least 8 h before the PET study. We injected FDG (185 MBq) intravenously as a bolus 30 min after 50 g of oral glucose. The emission scan was started 35 min after the FDG injection with an electrocardiogram (ECG)-gated two-dimensional acquisition. We obtained six to eight frames per cardiac cycle with a frame separation of 100 ms. We performed 10-min transmission scan for attenuation correction after the emission scan. Plasma concentrations of glucose, insulin, and free fatty acid were measured just before the injection of FDG and after the transmission scan. The images were reconstructed with a conventional filtered-back projection method using a Butterworth-ramp filter with a cutoff frequency of 1.25 cm^{-1}. The matrix size was 2.0 × 2.0 mm with 128 × 128 pixels, and the slice thickness was 3.125 mm.

Data analysis and phantom study. We placed 5 to 14 circular regions of interest (ROI, 78 mm^2/ROI) on the RV free wall, the interventricular septum, and the LV free wall of the end-diastolic transaxial image, and the standardized uptake value (SUV), which represents myocardial FDG uptake per unit volume, was calculated as:

$$\text{SUV} = \left[\text{mean ROI count (cps/pixel)} \times \text{body weight (kg)}\right] / \left[\text{injected dose (mCi)} \times \text{calibration factor (cps/mCi)}\right]$$

where cps is counts per second. To correct for the partial volume effect, a phantom experiment was performed with board phantoms of various thickness and the recovery coefficient curve was obtained. The corrected SUV was calculated by the following equation:

$$\text{Corrected SUV} = \text{SUV}/\text{recovery coefficient}$$

We also determined RV end-diastolic volume, RV end-systolic volume, and RV ejection fraction using RV short-axial slices of gated FDG-PET and Perfusion and Function Analysis for Gated SPECT software (pFAST, Sapporo Medical University, Sapporo, Japan) (13).

EBCT, MRI, and RV wall stress. All patients underwent EBCT or MRI to determine RV free wall thickness, RV volume, and mass within two weeks from the PET study. The decision to employ EBCT or MRI for the measurement was predominantly based on their availability. Eleven patients underwent EBCT (C-150XP, GE Imatron, San Francisco, California). The images were acquired in cine mode with contrast medium by triggering on the peak of the R-wave of the ECG. Two contiguous 7-mm-thick tomographic images were produced per target ring, with a 3-mm gap between images from the adjacent target ring. At each of the 12 levels, 6 to 10 images per cardiac cycle were produced in order to cover the total cardiac cycle (each image was acquired in 50 ms). End-diastole was defined as the scan acquired just before the peak of the R wave on the ECG. We visually selected the transaxial slices correspond-

Table 1. Clinical Characteristics of the Patients With Pulmonary Hypertension (n = 24)

			Normal Range
Age (yrs)	45 ± 19	(16–76)	
Gender (M/F)	7/17		
Body mass index	21.7 ± 3.2	(14.8–26.3)	
Etiology of pulmonary hypertension			
Primary/chronic thromboembolic	15/9		
NYHA functional class (II/III/IV)	8/12/4		
Brain natriuretic peptide (pg/ml)	216 ± 228	(8–743)	
Mean pulmonary artery pressure (mm Hg)	52 ± 14	(30–81)	9–19*
RV systolic pressure (mm Hg)	85 ± 22	(42–126)	15–30*
Right atrial pressure (mm Hg)	6 ± 4	(2–14)	1–5*
Pulmonary vascular resistance (Wood units)	14 ± 6	(4–31)	0.3–1.6*
Cardiac index (l/min/m^2)	2.2 ± 0.5	(1.2–3.5)	2.5–3.5†
RV end-diastolic volume index (ml/m^2)	103 ± 41	(55–233)	75 ± 13‡
RV ejection fraction (%)	35 ± 13	(11–58)	61 ± 7†
RV mass index (g/m^2)	68 ± 25	(27–117)	26 ± 5†

Values are mean ± SD. The ranges are shown in the parentheses. The normal values are from references 15 (*), 16 (†), and 17 (‡).
NYHA = New York Heart Association; RV = right ventricular.

ing to the PET slices based on the tomographic shape of the RV and LV and measured the wall thickness of the RV free wall, the interventricular septum, and the LV free wall at end-diastole.

Thirteen patients underwent MRI. The entire left ventricle was covered by transaxial tomograms with a 10-mm slice thickness. The ECG signal was transmitted by telemetry to a remote receiver to trigger the acquisition of the images by the R-wave of the ECG. The flow-compensated gradient-echo sequence employed a flip angle of 30° and gradient-refocused echoes with an echo time of 12 ms and a repetition time of 28 ms. Therefore, the temporal resolution for the individual slices was 56 ms. We visually selected the transaxial slices corresponding to the PET slices on the basis of the tomographic shape of the RV and LV and measured the wall thickness of the RV free wall, the interventricular septum, and the LV free wall at end-diastole.

We also estimated the RV meridianal peak systolic wall stress according to the following equation (14):

$$\text{RV meridianal peak systolic wall stress} = 1.35DP/4T \times (1 + [T/D])$$

where D is end-systolic RV cavity diameter, P is peak-systolic RV pressure, and T is end-systolic RV free wall thickness, measured from right heart catheterization and MRI or EBCT.

Statistical analysis. All values are expressed as mean ± SD. Statistical analysis of differences between groups was done by unpaired Student *t* test or paired Student *t* test where appropriate. Correlations between the two parameters were determined by simple linear regression analysis. Statistical significance was accepted at a level of $p < 0.05$.

RESULTS

Table 1 shows the baseline clinical characteristics, right heart catheterization data, and EBCT or MRI data. The mean pulmonary artery pressure, RV systolic pressure, pulmonary vascular resistance, and plasma BNP were highly increased compared with the normal values (15,16), although the scatter of the plasma BNP was rather large. Right ventricular end-diastolic volume and RV mass index were increased and RV ejection fraction was decreased, because the reported normal RV end-diastolic volume, RV ejection fraction, and RV mass are 75 ± 13 ml/m^2, 61 ± 7 % and 26 ± 5 g/m^2 (17). Figure 1 shows the representative midventricular transaxial PET images of patients with mild (Fig. 1A) and severe (Fig. 1B) primary pulmonary hypertension. The SUV of FDG corrected for the partial volume effect in the RV free wall was significantly correlated with the mean pulmonary artery pressure ($r = 0.78$; $p < 0.001$; Fig. 2A), right atrial pressure ($r = 0.50$; $p < 0.05$; Fig. 2B), pulmonary vascular resistance ($r = 0.67$; $p < 0.01$; Fig. 2C), wall stress in the RV free wall ($r = 0.74$; $p < 0.001$; Fig. 2D), and plasma BNP level ($r = 0.54$; $p < 0.01$; Fig. 2E). Among these five independent variables, the mean pulmonary artery pressure and wall stress in the RV free wall were correlated tightly with the RV SUV of FDG, and those two independent variables were also significantly correlated with each other ($r = 0.58$, $p < 0.01$). The SUV of FDG corrected for the partial volume effect in the RV free wall did not correlate with the cardiac index, RV end-diastolic volume index, RV ejection fraction, or RV mass index. Although the RV SUV of FDG that was not corrected for the partial volume effect was significantly correlated with the

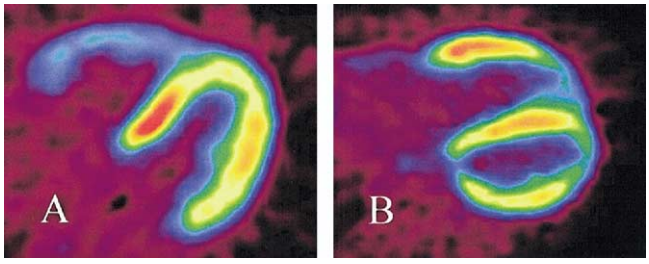

Figure 1. The midventricular transaxial [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) images of the patients with mild (**A**, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (**B**, mean pulmonary artery pressure, 81 mm Hg). In each image, the right ventricular (RV) free wall is at **upper left**, the interventricular septum at **middle**, and the left ventricular (LV) free wall at **lower right.** In the patients with severe pulmonary hypertension, the RV FDG accumulation increased compared with that in the patients with mild pulmonary hypertension. The RV standardized uptake value of FDG corrected for the partial volume effect was 6.6 and 12.7 in the patients with mild and severe pulmonary hypertension, respectively.

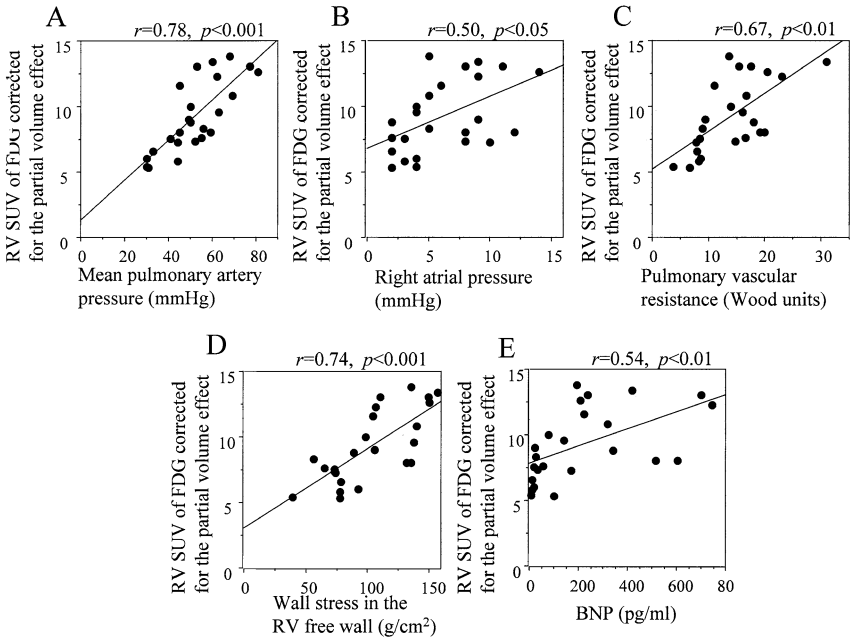

Figure 2. Correlations between the right ventricular (RV) standardized uptake value (SUV) of [^{18}F]fluorodeoxyglucose (FDG) corrected for the partial volume effect and mean pulmonary artery pressure **(A)**, right atrial pressure **(B)**, pulmonary vascular resistance **(C)**, wall stress in the RV free wall **(D)**, and plasma brain natriuretic peptide (BNP) level **(E)**.

wall thickness of the RV free wall ($r = 0.58$; $p < 0.01$; Fig. 3A), the correlation was not significant after the RV SUV of FDG was corrected for the partial volume effect (Fig. 3B). The RV end-diastolic volume index ($r = 0.94$; $p < 0.001$; Fig. 4A) and RV end-systolic volume index ($r = 0.93$; $p < 0.001$; Fig. 4B) determined by pFAST were closely correlated with those determined by EBCT or MRI, although pFAST analysis was impossible in three patients because their FDG accumulation in the RV free wall was too low. The correlation between the RV ejection fraction and that determined by pFAST and that by EBCT or MRI was weaker ($r = 0.48$; $p < 0.05$; Fig. 4C).

Insulin, glucose, and free fatty acid concentrations. Table 2 shows the plasma concentrations of insulin, glucose, and free fatty acids during the initial PET study performed in the 24 patients. The plasma concentrations of insulin, glucose, and free fatty acids both 30 min and 80 min after 50 g oral glucose did not correlate with the SUV of FDG corrected for the partial volume effect in the RV free wall (data not shown).

Change of RV SUV of FDG corrected for the partial volume effect after the pulmonary vasodilator therapy. In 10 patients with primary pulmonary hypertension treated with epoprostenol for three months, FDG-PET, EBCT or MRI, and right heart catheterization were performed before and after the three-month treatment. The average dose of epoprostenol was 15 ± 2 ng/kg/min. We divided those patients into responders and nonresponders according to whether or not the pulmonary vascular resistance was reduced by >30% after the treatment with epoprostenol for three months. This was because a reduction of the pulmonary vascular resistance by <30% after epoprostenol treatment for three months has been reported to be an independent predictor of poor survival by Sitbon et al. (18). According to the results of the second right heart catheterization after the three-month epoprostenol treatment, five patients were classified into the responder group and the other five patients into the nonresponder group.

Figures 5A and 5B show the midventricular transaxial PET images of a responder before and after the treatment with epoprostenol for three months. In the responder group, whose pulmonary vascular resistance was significantly reduced by 10.1 ± 1.9 Wood units, the RV SUVs of FDG corrected for the partial volume effect, BNP, mean pulmonary artery pressure, cardiac index, RV ejection fraction, and RV meridianal peak systolic wall stress were significantly improved after the treatment with epoprostenol for three months. However, the RV volume, RV mass index, and RV

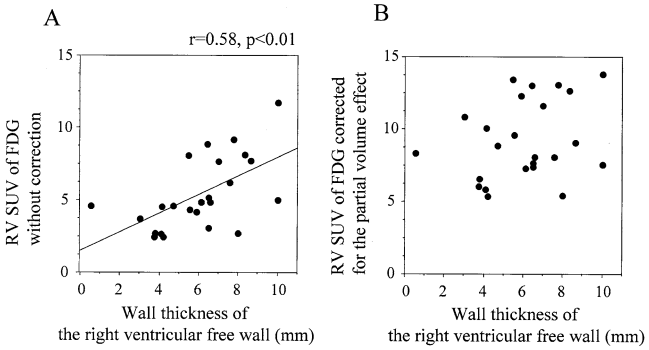

Figure 3. Correlations between the RV wall thickness and the RV SUV of FDG when not corrected for the partial volume effect **(A)** and the RV SUV of FDG corrected for the partial volume effect **(B)**. Abbreviations as in Figures 1 and 2.

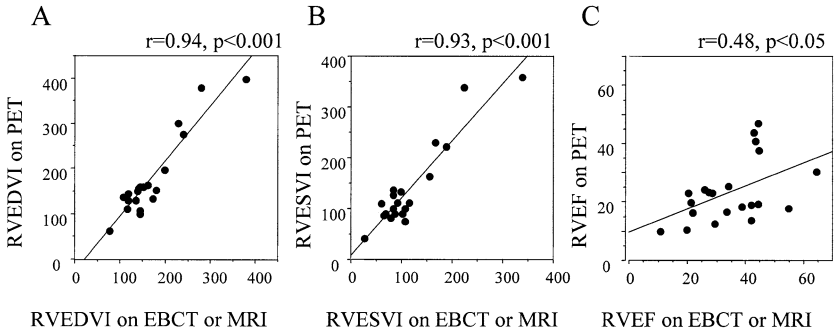

Figure 4. The RV end-diastolic volume index (RVEDVI) **(A)** and RV end-systolic volume index (RVESVI) **(B)** determined by perfusion and function analysis for gated SPECT software (pFAST) were closely correlated with those determined by electron-beam computed tomography (EBCT) or magnetic resonance imaging (MRI), although pFAST analysis was impossible in three patients because their FDG accumulation in the RV free wall was too low. The correlation between the RV ejection fraction (RVEF) **(C)** determined by pFAST and that by EBCT or MRI was weaker. Other abbreviations as in Figures 1 and 2.

wall thickness did not change (Table 3). In the 10 patients treated with epoprostenol, the percentage change of the corrected RV SUV of FDG was significantly correlated with the percentage change of the pulmonary vascular resistance (Fig. 6A) and wall stress in the RV free wall (Fig. 6B). The plasma concentrations of insulin, glucose, and free fatty acids both 30 min (insulin: 54 ± 33 μIU/ml vs. 55 ± 44 μIU/ml; glucose: 132 ± 24 mg/dl vs. 131 ± 23 mg/dl; free fatty acids: 0.47 ± 0.34 mEq/l vs. 0.45 ± 0.16 mEq/l) and 80 min (insulin: 23 ± 14 μIU/ml vs. 34 ± 16 μIU/ml; glucose: 109 ± 23 mg/dl vs. 128 ± 31 mg/dl; free fatty acids: 0.21 ± 0.31 mEq/l vs. 0.16 ± 0.14 mEq/l) after 50 g oral glucose were not significantly different between the first and the second PET studies, respectively.

DISCUSSION

Correlation between the FDG accumulation in RV free wall and RV pressure overload. First, the increased wall thickness in the patients with pulmonary hypertension might affect the recovered count through the partial volume effect. In the present study, however, we corrected for the partial volume effect based on the RV free wall thickness measured by EBCT or MRI and the recovery coefficient derived from the phantom study and found that the RV SUV of FDG corrected for the partial volume effect was correlated with the severity of the RV pressure overload. It is unlikely, therefore, that the increased RV FDG accumulation can be explained by the increased RV free wall thickness.

Second, myocardial ischemia has been shown to accelerate myocardial glucose uptake (19). A recent scintigraphic study by Gomez et al. (20) demonstrated perfusion abnormalities in the RV free wall in patients with severe primary pulmonary hypertension. Although all patients in the present study showed normal coronary arteriographies, we cannot exclude the possibility that myocardial ischemia due to severe RV hypertrophy might have increased the RV FDG accumulation (21).

Third, the myocardial preference for energy substrates is shifted from free fatty acids toward glucose in the development of cardiac hypertrophy. Our previous animal study showed that glucose utilization in rats was increased, whereas free fatty acid utilization was decreased or unchanged in the hypertrophied myocardium because of long-term LV or RV pressure overload (1,5). Although we did not investigate free fatty acid metabolism in the present study, the shift of the preference for energy substrates from free fatty acids to glucose in hypertrophied myocardium might be responsible for the increased RV FDG accumulation.

Finally, the increased RV workload would also explain the increased FDG accumulation in the RV free wall. Gertz et al. (22) reported that myocardial glucose utilization increases with exercise in humans. Camici et al. (23) reported that both myocardial oxygen consumption and glucose uptake increased linearly during incremental atrial

Table 2. Plasma Concentration of Insulin, Glucose, and Free Fatty Acids During PET Study

Time After 50 g Oral Glucose	30 min	80 min
Insulin (μIU/ml)	41 ± 28	29 ± 16
Glucose (mg/dl)	139 ± 23	139 ± 46
Free fatty acids (mEq/l)	0.55 ± 0.32	0.14 ± 0.22

Values are mean ± SD.
PET = positron emission tomography.

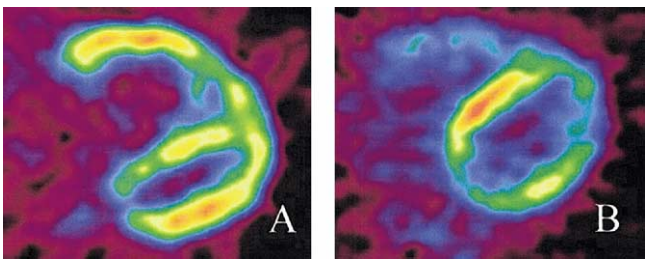

Figure 5. Representative midventricular transaxial FDG PET images of a patient with primary pulmonary hypertension before and after the pulmonary vasodilator therapy with epoprostenol for three months. Before the pulmonary vasodilator therapy, the RV FDG accumulation was highly increased and the corrected RV SUV of FDG was 13.4 **(A)**. After the therapy, the corrected RV SUV of FDG markedly decreased to 7.5 **(B)**. Abbreviations as in Figures 1 and 2.

Table 3. Paired Data Before and After Pulmonary Vasodilator Therapy of the Responder and Nonresponder Groups

	Responder (n = 5)			Nonresponder (n = 5)		
	Before Therapy	After Therapy	p Value	Before Therapy	After Therapy	p Value
Pulmonary vascular resistance (Wood units)	20.1 ± 7.0	10.1 ± 1.9	<0.05	15.2 ± 4.3	14.8 ± 5.2	NS
Mean pulmonary artery pressure (mm Hg)	64.4 ± 3.9	55.0 ± 6.6	<0.05	63.4 ± 14.5	64.0 ± 12.4	NS
RV systolic pressure (mm Hg)	100 ± 6	93 ± 7	NS	103 ± 21	103 ± 24	NS
Right atrial pressure (mm Hg)	6.4 ± 2.4	4.8 ± 3.4	NS	8.4 ± 4.2	7.8 ± 1.5	NS
Cardiac index (l/min/m^2)	2.1 ± 0.6	3.1 ± 0.4	<0.05	2.4 ± 0.7	2.5 ± 0.6	NS
RVEDVI (ml/m^2)	110 ± 23	105 ± 28	NS	111 ± 42	121 ± 52	NS
End systolic RV cavity diameter (mm)	53 ± 4	48 ± 10	NS	53 ± 17	46 ± 9	NS
RV ejection fraction (%)	27 ± 9	41 ± 9	<0.05	34 ± 10	36 ± 7	NS
RV mass index (g/m^2)	76 ± 30	74 ± 27	NS	86 ± 29	92 ± 43	NS
RV wall thickness (mm)	6.0 ± 2.5	5.7 ± 2.5	NS	5.4 ± 3.2	5.5 ± 3.0	NS
RV meridianal peak systolic wall stress (g/cm^2)	135 ± 18	101 ± 20	<0.05	113 ± 40	107 ± 40	NS
Brain natriuretic peptide (pg/ml)	362 ± 238	54 ± 59	<0.05	249 ± 267	176 ± 143	NS
RV SUV of FDG corrected for the partial volume effect	12.0 ± 1.8	7.2 ± 2.2	<0.01	11.4 ± 2.1	11.8 ± 1.9	NS

Values are mean ± SD.
FDG = [^{18}F]fluorodeoxyglucose; RV = right ventricular; RVEDVI = right ventricular end-diastolic volume index; SUV = standardized uptake value.

pacing in humans. In the present study, the RV wall stress was significantly increased in the patients with pulmonary hypertension owing to the increased RV diameter and RV systolic pressure. The increased RV wall stress may have increased myocardial oxygen consumption and energy substrate demand, and may explain the increased RV FDG accumulation in the patients with pulmonary hypertension. This notion might be supported by the fact that the corrected RV SUV of FDG was significantly correlated with the wall stress in the RV free wall, but not with the degree of RV hypertrophy, and also by the fact that the corrected RV SUV of FDG was significantly decreased in the responders to the epoprostenol treatment, although the RV hypertrophy did not regress.

Effects of pulmonary vasodilator therapy on FDG accumulation in RV free wall. In the present study, 5 of 10 patients treated with epoprostenol showed improvements in pulmonary vascular resistance compared with the baseline after the 3-month treatment with epoprostenol. In these five responders, the corrected RV FDG accumulation as well as mean pulmonary vascular resistance, mean pulmonary artery pressure, and RV meridianal peak systolic wall stress were significantly decreased, although the RV end-diastolic volume, the RV mass index, and the RV wall thickness measured by EBCT or MRI did not change significantly. Our findings regarding the RV volume and RV wall motion are concordant with the echocardiographic study by Hinderliter et al. (24) showing that although the RV end-diastolic area was unchanged, the RV wall motion improved after epoprostenol therapy for three months. Furthermore, as discussed in the previous section, the increased RV FDG accumulation at baseline in the patients with primary pulmonary hypertension can possibly be explained by the increased wall stress due to RV pressure overload rather than RV hypertrophy itself, because the RV FDG accumulation decreased according to the degree of reduction in the RV wall stress without a regression of the RV mass index after the epoprostenol therapy for three months. The RV metabolic change, therefore, may not necessarily be associated with a structural alteration if the heart is able to alter substrate accumulation with more alacrity than it is able to alter structure. Whether RV myocardial metabolic changes may contribute to the functional changes and whether myocardial metabolic modulation may improve the mortality and morbidity of patients with pulmonary hypertension remain to be elucidated.

Intravenous prostacyclin has been shown to increase the insulin sensitivity of the skeletal muscles (25). Therefore, decreased RV FDG accumulation by epoprostenol might simply reflect an increase in insulin sensitivity and resultant increase in FDG accumulation peripherally. To examine this possibility, we calculated FDG accumulation in the brachial muscles using the same PET images as those used for the measurement of myocardial FDG accumulation in five patients who showed a decrease in RV FDG accumulation after epoprostenol for three months. The SUV of FDG in the biceps brachii muscle after the epoprostenol therapy was not significantly different from that at the

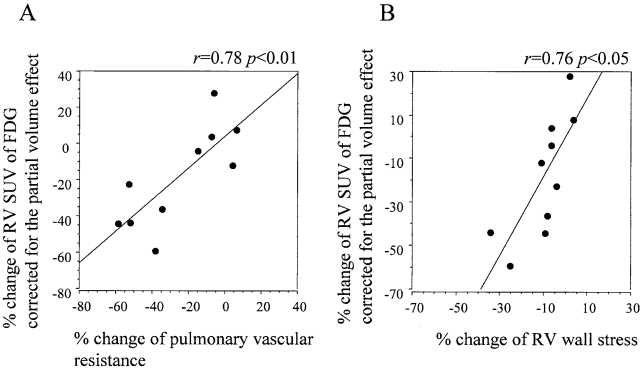

Figure 6. Correlations between the percentage change of RV SUV of FDG corrected for the partial volume effect and the percentage change of the pulmonary vascular resistance and peak-systolic wall stress in the RV free wall. Abbreviations as in Figures 1 and 2.

baseline (0.68 ± 0.25 vs. 0.70 ± 0.15, respectively). Therefore, the increased FDG accumulation in the peripheral skeletal muscle would be unlikely to explain the decreased RV FDG accumulation in our patients.

Study limitations. We measured the BNP level and RV and right atrial structural and functional data within two weeks of the PET study, but not on the day of the PET study. This may be a limitation because these parameters might have changed during the two weeks. It may be also a limitation to use EBCT and MRI for the measurement of RV structure because of a possible difference in the measurement between the two different modalities. We did not measure plasma sympathetic hormones in the present study. Sympathetic hormones would increase myocardial workload and oxygen consumption (26). The myocardial substrate preference would also be affected by sympathetic stress hormones. Finally, we did not perform myocardial perfusion imaging in the present study. Therefore, we do not know whether myocardial blood flow in the RV free wall increases in accordance with the severity of RV pressure overload. Further study using myocardial perfusion imaging with correction for the partial volume effect is required to answer this question.

Conclusions. The RV FDG accumulation corrected for the partial volume effect was significantly increased in accordance with the severity of RV pressure overload (i.e., the RV peak-systolic wall stress) in patients with pulmonary hypertension. Furthermore, the corrected RV FDG accumulation was decreased after the treatment with epoprostenol in accordance with the degree of reduction in the pulmonary vascular resistance and RV peak-systolic wall stress.

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Reprint requests and correspondence: Dr. Yutaka Kagaya, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. E-mail: kagaya@cardio.med.tohoku.ac.jp.

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