Different Mechanisms for Changes in Glucose Uptake of the Right and Left Ventricular Myocardium in Pulmonary Hypertension

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In patients with pulmonary hypertension (PH) the right ventricular (RV)–to–left ventricular (LV) ratio of fatty acid uptake is reduced. In animal studies, such a finding was combined with an increased glucose uptake in RV myocardium. The aim of this study was to measure the metabolic rates of glucose uptake for the RV and LV myocardium in patients in relationship to parameters of RV and LV function. **Methods:** Thirty patients with PH underwent PET with ^{18}F-FDG and SPECT with ^{99m}Tc-tetrofosmine. The metabolic rate of glucose uptake was determined for RV and LV myocardium using the method of Patlak. A right heart catheter, thermodilution, and Doppler sonography were used to characterize RV and LV function. From these methods, the stroke work of both ventricles and the RV Tei index were calculated. **Results:** RV-to-LV ratios of ^{18}F-FDG-uptake increased with rising pulmonary arteriolar resistance (PAR). With increasing PAR, the metabolic rate of glucose uptake of the left ventricle decreased ($r = -0.547$; $P < 0.01$) together with LV stroke work ($r = -0.838$; $P < 0.001$). The metabolic rate of glucose uptake of the right ventricle, however, correlated neither with RV stroke work ($r = 0.124$) nor with PAR ($r = 0.189$) but with the Tei index ($r = 0.78$; $P < 0.001$). **Conclusion:** Increasing right-to-left ratios of glucose uptake with an increasing pressure load in the right ventricle in PH are caused mainly by a significant reduction in the LV metabolic rate of glucose uptake. This is obviously due to a reduced energy demand of the LV myocardium caused by reduced stroke work. An increased metabolic rate of glucose uptake in the right ventricle presumably indicates RV impairment, correlating with the Tei index, which is an established prognostic parameter for cardiac dysfunction and poor survival.

Key Words: pulmonary heart disease; glucose; nuclear cardiology and PET

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Pulmonary hypertension (PH) is a life-threatening disease with a median survival rate of 2.8 y (*1*). The mortality is associated with right ventricular (RV) hemodynamic dysfunction (*1,2*). However, the natural history of the disease varies, with substantial differences in the tendency to develop RV failure (*3*). So far, the most important investigations to evaluate PH have been right heart catheterization and echocardiography. The Tei index is an echocardiographic index that combines information on systolic and diastolic RV function. This noninvasive parameter reflects the efficiency of RV function and correlates well with prognosis in patients with primary PH (*4,5*).

The recent literature contains evidence that heterogeneity in clinical course is caused by polymorphic variation in gene expression and that energy substrate metabolism forms the link between gene expression and contractile function of the heart (*6*).

The changes in myocardial metabolism with RV pressure overload are poorly understood. To our knowledge, no study has systematically analyzed glucose metabolism in patients with PH.

The aim of the present study was to initially investigate myocardial glucose use and perfusion in RV and left ventricular (LV) myocardium in a hemodynamically well-characterized group of patients with PH. In particular, we addressed the questions of whether RV or LV glucose uptake shows systemic changes with increasing severity of PH and whether RV or LV glucose uptake correlates with hemodynamic parameters.

MATERIALS AND METHODS

Patients

This prospective study included 30 consecutive patients (11 men and 19 women; mean age ± SD, 51.0 ± 14.5 y) who were referred to our center for treatment of PH. This group consisted of 13 patients with primary PH (according to the criteria of the National Institutes of Health Registry on Primary Pulmonary Hypertension (*7*)), 13 patients with chronic thromboembolic PH, 2

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patients with PH due to collagenosis, and 2 patients with PH due to Eisenmenger's complex. In all patients, significant LV disorders such as coronary artery disease, primary valvular disease, or myocardial disease were excluded on the basis of history, clinical findings, echocardiography findings, and electrocardiography findings. Further exclusion criteria were diabetes mellitus (fasting blood glucose level ≥7.0 mmol/L) and systemic arterial hypertension (blood pressure >140/90 mm Hg). The local ethics committee approved the study. All patients provided written informed consent. All clinical, hemodynamic, and imaging data were obtained within 3 wk after the patients had been included into the study.

Clinical Investigation and Hemodynamic Studies

The clinical investigations included assessment of New York Heart Association functional class and of clinical signs of right heart failure. Hemodynamic variables, such as arterial blood pressure, mean pulmonary artery pressure (PAP), mean right atrial pressure, and RV end-diastolic pressure, were measured by means of right heart catheterization. Cardiac output was determined using a standard thermodilution technique (values are given as the mean of 4 separate injections). Pulmonary arteriolar resistance (PAR) was calculated by dividing mean PAP by cardiac output. RV and LV stroke work was calculated using the following established formulas: RV stroke work = cardiac output/heart frequency × (mean PAP –RAP) × 0.0136 × 1,000, and LV stroke work = cardiac output/heart frequency × (mean RR –LAP) × 0.0136 × 1,000, where RAP = right atrial pressure, RR = arterial blood pressure, and LAP = left atrial pressure.

Doppler echocardiography was used to measure the Tei index, which is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time.

Isovolumetric contraction time and isovolumetric relaxation time were obtained by registering the tricuspid inflow velocity pattern recorded in the 4-chamber view. Ejection time was measured using the RV outflow velocity pattern in the parasternal short axis.

PET

PET scans were obtained using a high-resolution scanner (ECAT EXACT HR+; Siemens). Patient preparation included overnight fasting and administration of a single 250-mg oral dose of acipimox (Olbemox; Pharmacia and Upjohn) and a 50-g oral glucose load in aqueous solution (2 h and 1 h before the ^{18}F-FDG application, respectively). Immediately after transmission scanning for accurate localization of the patient and attenuation correction, 370 MBq of ^{18}F-FDG were administered intravenously and emission scanning began. The plasma concentration of glucose was measured 0, 30, and 60 min after injection. The image sequence consisted of 6 frames of 30 s, 4 of 60 s, 4 of 120 s, and 9 of 300 s, for a total imaging time of 60 min. All data were corrected for dead time, decay, scatter and measured photon attenuation. Images were reconstructed with filtered backprojection using a Hann filter with a cutoff of 0.3 Nyquist.

SPECT

Images were acquired 1 h after intravenous application of 400 MBq of ^{99m}Tc-tetrofosmine. A dual-head camera (Vertex; ADAC Laboratories) equipped with ultra-high-resolution collimators and two ^{153}Gd line sources was used. Thirty-two views were recorded for 80 s each from 45° left posterior oblique to 45° right anterior oblique. Images were reconstructed by use of an iterative reconstruction algorithm (maximum-likelihood method) with attenuation and scatter correction. The PET and SPECT studies were performed within 3 d of each other.

Data Analysis

The obtained image data were analyzed semiquantitatively (PET and SPECT data) using an established region-of interest (ROI) method and, for PET studies only, an absolute quantification technique.

ROI Analysis. Twelve ROIs were manually drawn over the RV, LV, and septal myocardium on 1 apical, 1 midventricular, and 1 basal short-axis slice (Fig. 1). For this relative analysis, the SPECT images and PET images, which were created by adding the last 6 frames (31–60 min of acquisition), were used. The arithmetic mean of the mean count densities (SPECT study) and mean standardized uptake values (PET study) was obtained for all RV and LV ROIs. From these values were calculated the ratio of mean standardized uptake values in RV versus LV myocardium in ^{18}F-FDG PET studies and the ratio of mean counts in RV versus LV myocardium in ^{99m}Tc-tetrofosmine SPECT studies.

Absolute Analysis. The metabolic rate of glucose uptake was calculated from the PET studies by using the equation MR (μmol/min/g) = $K_{PAT} \times C_P/LC$, where K_{PAT} represents the macroparameter for the influx of ^{18}F-FDG derived from the Patlak graphical analysis (*8,9*), C_P represents the mean plasma glucose concentration during scanning, and LC is the lumped constant (0.67 (*10,11*)). The calculation was performed using PETER software (Research Center Rossendorf). The arterial input function, necessary for calculation of $K_{PAT,}$ was derived noninvasively from LV blood pool time–activity curves generated from an ROI in a midventricular plane. The resulting parametric images containing the obtained metabolic rates of glucose uptake on a pixelwise basis were stored and used to determine the mean metabolic rate of glucose uptake in 12 ROIs in the same wall areas as the ROI set, which was used the for semiquantitative analysis but with a width of only 2 pixels in the center of the ventricular walls.

Statistical Analysis

After validation of normal distribution (Kolmogorov–Smirnov test, $P < 0.05$), differences between groups were analyzed by the Student *t* test for unpaired samples and differences among multiple groups, by unifactorial ANOVA. Regression analyses were performed, and Pearson correlation coefficients were calculated. Statistical significance was accepted at a level of $P < 0.05$.

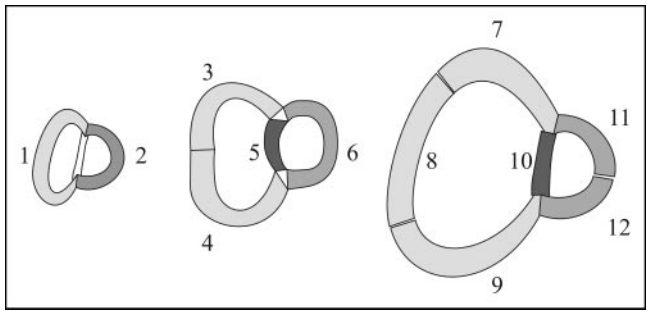

FIGURE 1. Set of 12 ROIs manually drawn on apical, midventricular, and basal short-axis slices. ROIs 1, 3, 4, 7, 8, and 9 represent RV myocardium, ROIs 2, 6, 11, and 12 represent LV myocardium, and ROIs 5 and 10 represent interventricular septum.

TABLE 1
Clinical and Hemodynamic Characteristics of Patients with PH of Various Causes

Characteristic	Primary PH (n = 13)	Thromboembolic PH (n = 13)	PH of other cause (n = 4)
Mean pulmonary artery pressure (mm Hg)	60.8 ± 19.1	48.6 ± 12.5	49.5 ± 24.8
RV end-diastolic pressure (mm Hg)	88.4 ± 30.3	78.9 ± 17.5	69.8 ± 29.5
PAR (dyn × s × cm^{-5})	1,302 ± 715	987 ± 469	1,002 ± 460
Mean arterial blood pressure (mm Hg)	93.8 ± 10.7	96.1 ± 13.7	94.3 ± 16.2
Cardiac output (L/min)	4.00 ± 1.80	4.12 ± 1.58	3.78 ± 1.33
Heart frequency (beats/min)	89.4 ± 12.2	83.1 ± 11.0	93.0 ± 9.8
RV stroke work	30.3 ± 12.0	28.2 ± 8.8	25.3 ± 19.2
LV stroke work	54.5 ± 28.9	66.6 ± 41.9	53.0 ± 29.8
RV Tei index	0.67 ± 0.19	0.77 ± 0.17	0.75 ± 0.22
New York Heart Association class	2.7 ± 0.5	2.8 ± 0.7	3.2 ± 0.5
Walking distance within 6 min (m)	384 ± 78	342 ± 145	242 ± 180
Patients with right heart failure (n)	8/13	7/13	2/2

Data are mean ± SD, with no significant differences, or number of patients.

For investigation of the influence of different etiologies on the correlation between imaging and clinical data, the 95% confidence intervals of the regression lines were compared between subgroups.

RESULTS

Table 1 shows clinical and hemodynamic characteristics of the patient groups with different etiologies of PH. No significant differences were found.

In our patients, PAR and mean PAP correlated positively ($r = 0.872$; $P < 0.01$). As a consequence, in this study PAR was applied as the main parameter for characterization of the severity of PH.

The relationships between PAR and relative count densities in the free RV wall (in relation to the free LV wall) are presented in Figure 2. Relative RV radiotracer uptake increased in ^{18}F-FDG studies as the severity of PH increased, from a mean right-to-left ratio of 0.5 at a PAP of 260 dyn × s × 10^{-5} to a ratio of 1.2 at 2,000 dyn × s × 10^{-5}. In contrast, in the perfusion studies no correlation was found.

The quantitative analysis results for the ^{18}F-FDG studies are illustrated in Figure 3. No correlation was found between RV glucose uptake and PAR ($r = 0.189$; not statistically significant). In contrast to the right ventricle, a significant negative correlation was found between PAR and the metabolic rate of glucose uptake in the left ventricle ($r = -0.547$; $P < 0.01$) and septal myocardium ($r = -0.613$; $P < 0.01$). According to the linear regression analysis, the mean LV metabolic rate of glucose uptake was 30.7 μmol/100 g/min at a PAR of 100 dyn × s × 10^{-5} and decreased to about 14.2 μmol/100 g/min in patients with a PAR of 2,000 dyn × s × 10^{-5} due to PH. Therefore, the observed PAR-dependent changes in right-to-left-ratios of ^{18}F-FDG studies are caused mainly by changes in the LV myocardium. Figure 4 shows 3 typical examples of rapidly decreasing ^{18}F-FDG uptake with increasing PAR in LV myocardium.

A close correlation was found between PAR, cardiac output, and LV stroke work (Fig. 5). As a result, the LV metabolic rate of glucose uptake correlated not only with

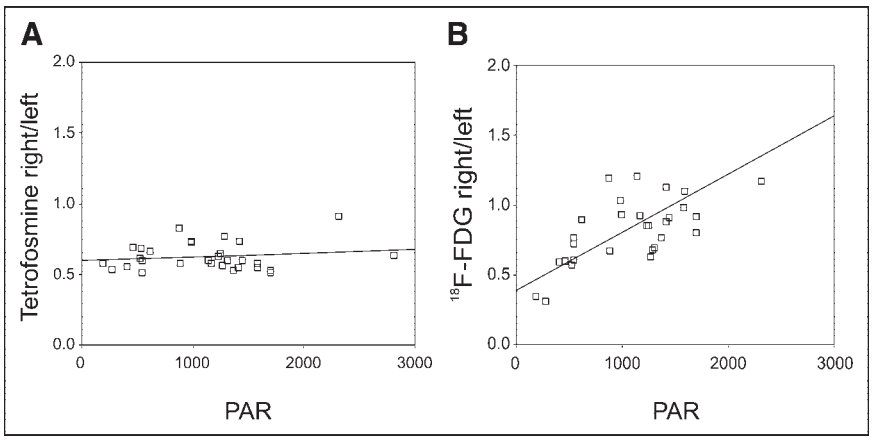

FIGURE 2. Relationship between mean PAR (dyn × s × 10^{-5}) and right-to-left counting rate ratios in ^{99m}Tc-tetrofosmine studies (A) and ^{18}F-FDG studies (B). Significant correlation was found for regional ^{18}F-FDG uptake ($r = 0.767$; $P < 0.001$; y = 0.391 + 0.416E-03x) but not for regional perfusion ($r = 0.16$; not statistically significant).

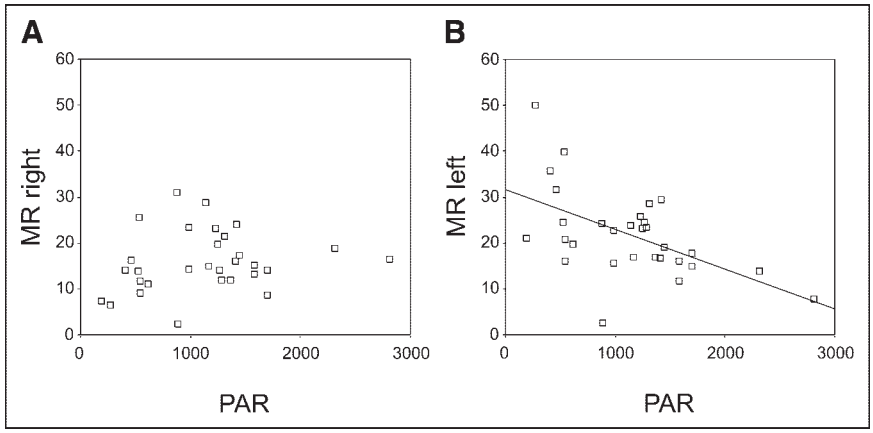

FIGURE 3. Relationship between mean PAR (dyn × s × 10^{-5}) and metabolic rate of glucose uptake in free RV myocardium (A) and LV myocardium (B). There was no correlation in right ventricle ($r = 0.189$; not statistically significant) but significant negative correlation in free LV wall ($r = -0.547$; $P < 0.01$; y = 31.59 − 8.68E-03x). MR = metabolic rate of glucose uptake.

PAR but also with both cardiac output ($r = 0.52$; $P < 0.01$) and LV stroke work ($r = 0.58$; $P < 0.01$; Fig. 6B).

RV metabolic rate of glucose uptake was independent of both PAR (Fig. 3A; $r = 0.189$) and RV stroke work (Fig. 6A; $r = 0.124$) but correlated positively with the RV Tei index (Fig. 7C; $r = 0.78$; $P < 0.001$). We also observed a weak correlation between the RV metabolic rate of glucose uptake and New York Heart Association class ($r = 0.47$; $P < 0.01$). The 2 examples shown in Figures 7A and 7B illustrate the large interindividual differences in RV ^{18}F-FDG uptake corresponding to differences in Tei indices and New York Heart Association class, despite relatively small differences in pressure load and LV parameters between these patients.

The described results were independent of the cause of PH in individual patients.

DISCUSSION

This study demonstrated (a) that the ratio of glucose uptake in RV versus LV myocardium increased with increasing severity of PH independently of changes in perfusion distribution, (b) that this effect was caused by a systematic decrease in LV glucose uptake concordant with decreasing cardiac output and LV stroke work, (c) that RV glucose uptake did not correlate with the severity of PH or RV stroke work, (d) that RV glucose uptake increased with increasing Tei index.

(i) To our knowledge, no reported studies have systematically analyzed myocardial glucose uptake in patients with PH. Myocardial fatty acid uptake, however, has been investigated by various groups. Matsushita et al. found that, with increasing pressure load in PH, right-to-left ratios increased more slowly for fatty acid uptake than for perfusion (*12*). For patients showing a reduction in RV contractile function, Nagaya et al. described a decrease in this right-to-left ratio that was independent of the individual pressure load (*13*). In these SPECT studies, it was not possible to quantify fatty acid metabolism absolutely. Therefore, it was not possible to attribute the findings directly to the right or the left ventricle. Both groups hypothesized that the decrease in right-to-left ratios was caused by impaired fatty acid uptake in the hypertrophied RV myocardium. This assumption is supported by experimental findings in dogs and rats (*14,15*). After banding of the pulmonary artery, these authors observed a regional decrease in fatty acid uptake and an increase in glucose uptake in the right ventricle. Our study

PAR	405 dyn * s * 10^{-5}	1412 dyn * s * 10^{-5}	3119 dyn * s * 10^{-5}
CO	4.94 l/min	2.72 l/min	2.36 l/min
SW left	92.7 ml * mmHg	32.5 ml * mmHg	30.85 ml * mmHg
MR left	35.7 μmol/100 g/min	16.7 μmol/100 g/min	7.8 μmol/100 g/min
MR right	14.0 μmol/100 g/min	16.0 μmol/100 g/min	16.5 μmol/100 g/min

FIGURE 4. Characteristic short-axis slices from ^{18}F-FDG PET images of 3 patients with different severities of PH. From left to right, images show increasing degree of PAR and decreasing LV metabolic rate of glucose uptake. CO = cardiac output; SW = stroke work; MR = metabolic rate of glucose uptake.

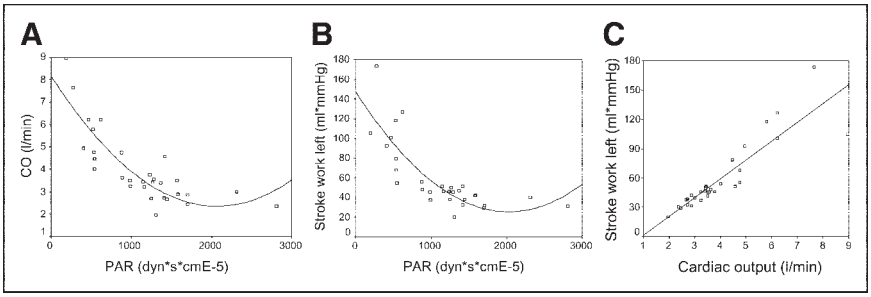

FIGURE 5. Correlations between cardiac output, LV stroke work, and PAR: cardiac output vs. PAR (nonlinear; $y = 112.733x^{-0.4949}$; $r = -0.828$; $P < 0.001$) (A), stroke work vs. PAR (nonlinear; $y = 4922.29x^{-0.6615}$; $r = -0.838$; $P < 0.001$) (B), and stroke work vs. cardiac output (linear; $y = -18.091 + 19.3088x$; $r = 0.938$; $P < 0.001$) (C). CO = cardiac output.

showed an increase in right-to-left ratios of glucose uptake with increasing severity of PH, a finding that—at first view—is concordant with the cited literature supporting a switch from fatty acid to glucose use in the overloaded RV myocardium. Thus, by applying the described PET technique to absolutely quantify ^{18}F-FDG uptake in RV and LV myocardium, we could obtain initial clinical evidence supporting this assumption.

(ii) In contrast to the cited results of animal experiments, the systematic increase in right-to-left ratios of ^{18}F-FDG uptake in our study was not based on increasing RV glucose uptake but on decreasing LV glucose uptake.

It is well known that, because of an impaired blood supply to the left atrium and ventricles, not only the overloaded right but also the left ventricle plays an important role in the pathomechanism of PH. Consequently, end-diastolic and stroke volumes and wall tension in the left ventricle are reduced (*16,17*). The results of our study confirmed these findings by showing close inverse correlations between PAR and the cardiac output and stroke work of the left ventricle. Along with these changes, the ^{18}F-FDG uptake of the LV myocardium decreased with increasing PAR. We hypothesize that this reduction in glucose uptake with increasing severity of PH could be due to the reduced energy demand in cases of reduced stroke work. Alternatively, a decrease in LV contractility (*18*) or hypoxemia (*19*) could play a role. A reduced count recovery due to a partial-volume effect is unlikely to account for the observed considerable decrease in LV counting rates in the ^{18}F-FDG studies, especially since no systematic alterations of the LV wall thickness have been reported in the literature on PH patients and since the right-to-left ratios in the perfusion scans increased only in the ^{18}F-FDG studies, not in the perfusion studies, with increasing severity of PH.

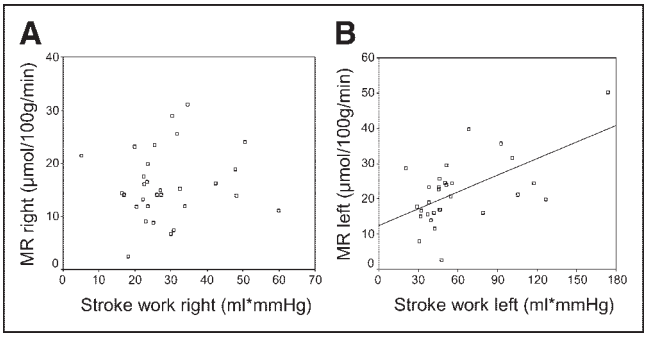

FIGURE 6. Relationships between metabolic rate of glucose uptake in free RV wall and RV stroke work ($r = 0.124$; not statistically significant) (A) and metabolic rate of glucose uptake in free LV wall and LV stroke work ($y = 12.457 + 0.1572x$; $r = 0.518$; $P < 0.01$) (B).

(iii) In experimental studies on rats (*15*), dogs (*14*), and swine (*20*), an acute or chronic pressure load on the right ventricle enhanced glucose uptake, despite unaltered or decreased fatty acid uptake of the RV myocardium. Similar findings have been reported for the LV myocardium in cases of LV pressure overload (*21,22*). From these results, we initially expected a systematic increase in RV glucose uptake with increasing severity of PH in our patient group. However, our results showed a large interindividual variability in the RV metabolic rate of glucose uptake but no correlation with PAR. This discrepancy could be due to different metabolic conditions: Whereas the cited animal studies were performed under basal conditions, our PET studies were performed after administration of an oral glucose load and inhibition of serum fatty acids. In support of this possibility, Uehara et al. found enhanced ^{18}F-FDG uptake in the LV myocardium of hypertrophic cardiomyopathy patients only when they were fasting, not after they had received a glucose load (*23*). On the other hand, because of the development of various degrees of tricuspid regurgitation in patients with PH, the strong correlation between PAR and RV stroke work is overridden. This fact might also influence the correlation between PAR and RV glucose uptake.

(iv) Our study showed a highly significant positive correlation between RV glucose uptake and the sonographic RV Tei index in patients with PH. The Tei index was initially developed as a noninvasive way to measure the combined systolic and diastolic function of the left ventricle (*24*). Over the past several years, it has become established as a powerful and independent predictor of poor clinical outcome in patients with symptomatic heart failure and severe LV systolic dysfunction (*25*). Tei and colleagues showed also for the right ventricle that the Tei index is a strong predictor of clinical status and survival in patients with primary PH (*4*), independent of RV pressure, RV dilation, or tricuspid regurgitation. In a study of Yeo et al., the RV Tei index was the only independent predictor of

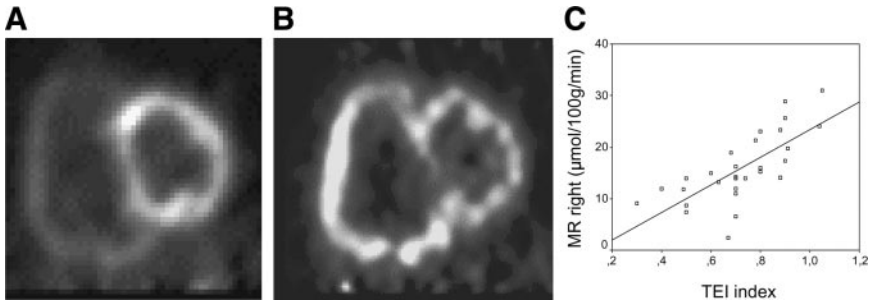

FIGURE 7. Relationship between RV metabolic rate of glucose uptake and Tei index is shown in C. Characteristic short-axis slices from ^{18}F-FDG PET images of 2 patients with different Tei indices are shown in A and B. Parameters for A vs. B: Tei index, 0.49 vs. 1.05; metabolic rate of glucose uptake, right, 11.75 vs. 31 μmol/100 g/min; metabolic rate of glucose uptake, left, 20.75 vs. 24.3 μmol/100 g/min; PAP, 39 vs. 55 mm Hg; PAR, 540 vs. 874 dyn × s × 10^{-5}; stroke work, right, 20.5 vs. 34.7; stroke work, left, 54.4 vs. 55.5; New York Heart Association class, II vs. III; right heart failure, no vs. yes. (C) y = −3.3343 + 26.7048x; $r = 0.78$; $P < 0.001$. MR = metabolic rate of glucose uptake.

outcome in patients with primary PH (*5*). We therefore presume that an increased RV glucose uptake could also be associated with a poor outcome in patients with PH. The observed strong correlation between the sonographic prognostic index and the RV metabolic rate of glucose uptake (whereby both parameters were independent of the individual severity of PH) may be a step toward understanding the substantial differences in prognosis of patients with PH.

Several methodologic issues need to be addressed to allow correct interpretation of our study results: First, in the present study, PAR was used to characterize the severity of PH. PH is caused by an increase in pulmonary vascular resistance followed by an increase in pressure in the pulmonary artery and the right heart. Therefore, PAR is the most direct parameter for characterizing disease severity. The initially close correlation between PAR and PAP is compromised by tricuspid regurgitation, which occurs in about 80% of patients with severe PH (*26*). Therefore, PAP determines the degree of pathologic pressure load of the right heart but may underestimate the severity of PH in patients with high PAR, severe tricuspid insufficiency, and low cardiac output.

Second, in our study, glucose uptake and perfusion were evaluated using different imaging modalities with different spatial resolutions (full width at half maximum, 4.5–6 mm in PET vs. 11 mm in SPECT). Therefore, we cannot exclude the possibility that differences in recovery coefficients affected the right-to-left count ratios in both investigations. The ventricular wall thickness in our patients was not systematically evaluated. However, a linear correlation is known to exist between the thickness of the RV free wall and the degree of pathologic pressure load in PH. Frank et al., for instance, performed cardiac MRI and found a mean wall thickness of 4 mm at a mean PAP of 40 mm Hg and a mean wall thickness of 9 mm at a mean PAP of 70 mm Hg. In contrast, free LV wall thickness is not affected by PH (*27*). Therefore, the observed systematic decrease in the metabolic rate of glucose uptake in the LV myocardium with increasing severity of PH could not have been caused by partial-volume effects. One cannot exclude, however, that a potential decrease in glucose uptake by the RV myocardium with increasing severity of PH could have been masked by a decrease in the influence of the partial-volume effect with increasing wall thickness (*28*).

The third methodologic consideration is that the present study lacked a control group. Because of the low impulse densities in the RV myocardium of healthy subjects in both ^{99m}Tc-tetrofosmine SPECT and ^{18}F-FDG PET studies, the chosen semiquantitative or quantitative analyses were not practicable in control subjects.

CONCLUSION

Increasing right-to-left ratios of glucose uptake with an increasing pressure load of the right ventricle in PH are caused mainly by a significant reduction in the LV metabolic rate of glucose uptake. This is obviously due to a reduced energy demand in the LV myocardium caused by reduced stroke work. An increased metabolic rate of glucose uptake in the right ventricle presumably indicates RV impairment, correlating with the Tei index, which is an established prognostic parameter for cardiac dysfunction and poor survival.

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