Impaired Regional Fatty Acid Uptake and Systolic Dysfunction in Hypertrophied Right Ventricle

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Little information is available regarding the determinants of systolic contractile function of the hypertrophied right ventricle (RV). The purpose of this study was to clarify the relationship between myocardial metabolism and contractile function in the hypertrophied RV due to pulmonary hypertension (PH). **Methods:** Iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) and ^{99m}Tc-sestamibi (MIBI) SPECT were performed to calculate the RV-to-left ventricle (LV) tracer uptake ratio (RV/LV) in 21 patients with PH (6 with primary PH and 15 with chronic thromboembolic PH). The patients also underwent electron-beam CT to assess RV ejection function (RVEF) and percentage systolic wall thickening (%SWT) and right heart catheterization to measure mean pulmonary arterial pressure (mPAP). **Results:** There were significant positive correlations between mPAP and MIBI-RV/LV ($r = 0.89$, $p < 0.001$) and between mPAP and BMIPP-RV/LV ($r = 0.86$, $p < 0.001$). However, 8 patients showed lower BMIPP-RV/LV than MIBI-RV/LV, indicating the impairment of myocardial fatty acid uptake in the RV. These patients had lower RVEF and %SWT compared to those with normal myocardial fatty acid uptake (RVEF = 28% ± 10% compared to 40% ± 9% and %SWT = 33% ± 27% compared to 74% ± 30%, respectively; $p < 0.05$ for both comparisons). Although mPAP did not differ between the groups, the RVEF-mPAP and %SWT-mPAP regression lines drawn from the patients with impaired myocardial fatty acid uptake were located below the lines from the patients with normal myocardial fatty acid uptake, suggesting disproportionately decreased RV myocardial contractility for a given mPAP in patients with impaired myocardial fatty acid uptake. The patients with the impaired fatty acid uptake in the RV had a significantly higher death rate (log-rank test, $p < 0.05$). **Conclusion:** The results from this preliminary study suggest that myocardial fatty acid uptake is impaired in the failing hypertrophied RV due to PH.

Key Words: pulmonary hypertension; myocardial metabolism; myocardial contraction; hypertrophy; iodine-123-BMIPP

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Myocardial hypertrophy is an adaptive response that results in the maintenence of normal systolic wall stress in face of an increased mechanical load, but excessive myocardial hypertrophy is often associated with myocardial failure (*1*). Although right ventricle (RV) hypertrophy is an important feature in patients with pulmonary hypertension (PH), the mechanisms of structural and functional changes leading to RV hypertrophy and failure, compared with the mechanisms of left ventricle (LV) hypertrophy, are not well understood. Recent studies have shown that myocardial metabolism is impaired in the hypertrophied LV due to systemic hypertension (*2*) or aortic stenosis (*3*), particularly in the failing hypertrophied LV. However, it remains unclear whether myocardial metabolism is impaired in the hypertrophied RV due to PH or whether there are metabolic differences between the compensated and the failing hypertrophied myocardium in the RV.

The measurement of RV mechanical function by conventional methods was difficult because of the complicated configuration of the RV. However, electron-beam CT has made it possible to evaluate RV volume and myocardial mass with a high degree of accuracy (*4–6*). In addition, ^{123}I-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) SPECT has recently been used for the detection of regional impairment of myocardial fatty acid uptake (*7–10*). Decreased ^{123}I-BMIPP uptake has been suggested to be due to deranged esterification to triglyceride (*8,11*), reduced myocardial adenosine triphosphate content (*12*) or impaired mitochondrial function (*13*), resulting in abnormal fatty acid uptake.

Thus, the purposes of this study were to investigate:

1. Whether myocardial fatty acid uptake is impaired in the hypertrophied RV due to PH;
2. How myocardial fatty acid uptake is related to RV systolic contractile function; and
3. Whether an impairment of myocardial fatty acid uptake is associated with the poor prognosis in patients with PH, using electron-beam CT and ^{123}I-BMIPP SPECT.

MATERIALS AND METHODS

Patients

We studied 21 patients (9 men, 12 women; age range 21–73 yr; mean age 47 ± 12 yr) with PH [mean pulmonary arterial pressure (mPAP) ≥20 mmHg]. Six had primary PH, and 15 had chronic thromboembolic PH. Primary PH was defined as PH unexplained by any secondary cause, based on the criteria of National Institutes of Health registry on primary PH (*14*). Chronic thromboembolic PH was identified by radionuclide perfusion lung scans and pulmonary angiography (*15,16*). Seven patients (33%) were classified as New York Heart Association functional class II, 11 (53%) were classified as class III and 3 (14%) were classified as class IV. None of them had clinical evidence of significant LV diseases, such as primary myocardial, valvular or coronary artery disease, which was confirmed by echocardiography as well as by cardiac catheterization. In addition to hemodynamic studies, coronary angiography was performed in all patients to exclude subclinical coronary artery disease. No patient had hyperlipidemia or diabetes mellitus, which might influence ^{123}I-BMIPP kinetics. All patients gave informed consent.

Hemodynamic Studies

Mean pulmonary arterial pressure, right ventricular end-diastolic pressure, mean right atrial pressure, pulmonary capillary wedge pressure and mean systemic arterial pressure were measured at end-expiration in all patients by right heart catheterization. Cardiac output was measured by Fick's method. Total pulmonary resistance was calculated as mPAP/cardiac output.

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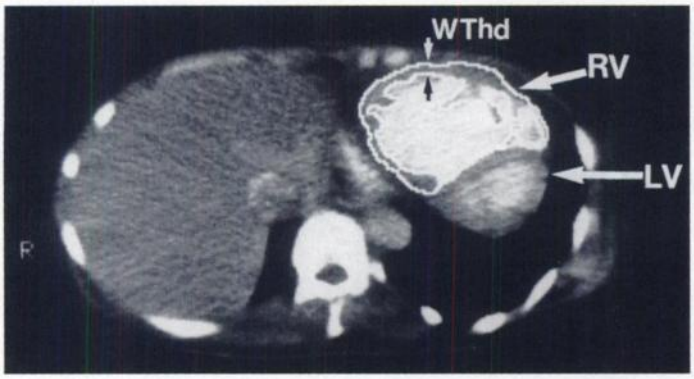

FIGURE 1. Photograph showing typical short-axis computed tomogram at midventricular level in patient with primary pulmonary hypertension. Endocardial and epicardial border lines of right ventricular cavity are drawn to calculate right ventricular ejection fraction, volume and myocardial mass at corresponding level. Wall thickness in lateral regions of right ventricle (RV) was also measured at end-diastole (WThd) and end-systole. LV = left ventricle.

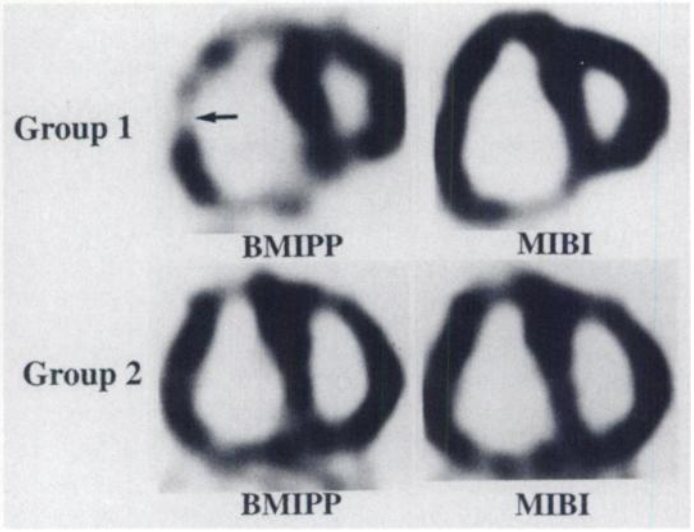

FIGURE 2. (Top) Representative patient with impaired myocardial metabolism in right ventricle (RV) (Group 1). Patient exhibited more reduced ^{123}I-BMIPP uptake than ^{99m}Tc-MIBI uptake in RV. RV function was disproportionately reduced for a given mean pulmonary arterial pressure (mPAP) [mPAP = 57 mmHg, right ventricular ejection fraction (RVEF) = 14%, percentage systolic wall thickening (%SWT) = 4%]. (Bottom) Representative patient with normal myocardial metabolism in RV (Group 2). Patient exhibited equal distributions of ^{123}I-BMIPP and ^{99m}Tc-MIBI in RV. RV function was relatively well maintained, despite severe pulmonary hypertension (mPAP = 59 mmHg, RVEF = 32%, %SWT = 61%).

Electron-Beam CT

RV systolic function and wall thickness were measured using electron-beam CT within 1 mo of cardiac catheterization. There was no change in clinical status or medication regimen between the CT and cardiac catheterization studies. Electron-beam CT was performed with a C-150 scanner (Imatron, San Francisco, CA) as described previously (*17*). Cine-mode scanning (scanning time, 50 msec) was performed after the administration of 40–50 ml nonionic contrast medium (Iopamidol 370; Nippon Schering, Osaka, Japan). The scanner table was rotated 25° in a clockwise horizontal direction to obtain near short-axial views of the heart. Eight-level (10 contiguous images per level) or 10-level (8 contiguous images per level) cine-mode scans of the heart were obtained with electrocardiography gating. The data acquisition system performs image reconstruction that is composed of 256 × 256 pixels. With a 35-cm reconstruction circle, each pixel represents an area of 1.868 mm^2.

The end-diastolic (R wave on the electrocardiogram) and end-systolic (the smallest chamber volume during the cardiac cycle) frames were identified at each tomographic level. Wall thickness in the lateral regions of the RV at a midventricular level was measured at end-diastole and end-systole. The endocardial and epicardial borders of the ventricles were determined using the previously described methods (*4–6*) of edge detection for electron-beam CT (Fig. 1). We used a modified version of Simpson's method to obtain multisection cine-mode scans.

The following parameters were calculated for each subject:

1. RV end-diastolic wall thickness (WThd) and end-systolic wall thickness (WThs);
2. Percentage systolic wall thickening (%SWT) = (WThs − WThd) × 100/WThd;
3. RV end-diastolic volume index;
4. RV stroke volume index;
5. RV ejection fraction (RVEF); and
6. RV mass index.

Radiopharmaceuticals

The ^{123}I-BMIPP used in this study was a commercially available product. Its radiochemical purity was >98%, and 111 MBq ^{123}I-BMIPP (1.5 ml) contained 0.6 mg of carrier BMIPP (*18*).

Iodine-123-BMIPP and Technetium-99m-MIBI Imaging

Iodine-123-BMIPP and ^{99m}Tc-sestamibi (MIBI) SPECT imaging were performed on two separate days within 2 wk of cardiac catheterization. There was no change in clinical status or medication regimen between the SPECT and cardiac catheterization studies. Iodine-123-BMIPP (111 MBq) was intravenously injected from the antecubital vein under resting condition after an overnight fast. Data were acquired 15 min after injection using a three-head gamma camera (Multi SPECT 3; Siemens, Hoffman Estates, IL) equipped with a low-energy, high-resolution collimator. Forty projections (64 × 64 pixel matrix, 40 sec/projection) were obtained over 240° in the 159-keV photopeak with a 20% window. No attenuation or scatter correction was used. Technetium-99m-MIBI (740 MBq) was injected intravenously during resting condition after an overnight fast. Data acquisition was performed 1 hr after injection in the same manner as in the ^{123}I-BMIPP study, except that the photopeak was 140 keV and that the acquisition time was 20 sec/projection to obtain similar count density as in the ^{123}I-BMIPP study.

Iodine-123-BMIPP and ^{99m}Tc-MIBI images were analyzed using the short-axis tomogram. A square region of interest (ROI) of 2 × 2 pixels was placed over the center of each lateral wall of the RV and LV at a midventricular level to assess tracer activities. The following parameters were obtained in each subject:

1. BMIPP-RV/LV, defined as the ratio of ROI count in the RV to that in the LV for ^{123}I-BMIPP;
2. MIBI-RV/LV, defined as the ratio of ROI count in the RV to that in the LV for ^{99m}Tc-MIBI; and
3. (MIBI-RV/LV − BMIPP-RV/LV) × 100%, which is an index of the magnitude of the abnormalities in RV myocardial fatty acid uptake relative to myocardial perfusion normalized for LV.

Patients were divided into two groups according to the magnitude of the impairment of RV myocardial fatty acid uptake assessed by ^{123}I-BMIPP and ^{99m}Tc-MIBI (Fig. 2): patients with impaired myocardial fatty acid uptake, which was defined as having values of (MIBI-RV/LV − BMIPP-RV/LV) × 100% that were ≥4% (Group 1, n = 8) and the remaining patients (Group 2, n = 13). The cutoff point of 4% was arbitrarily used because the mean value for this measure was 4% ± 6% in all patients.

Reproducibility of these measurements was assessed in 8 patients who were selected at random. The mean differences between the measurements in each patient were BMIPP-RV/LV of 3% ± 2% and MIBI-RV/LV of 2% ± 2%.

Survival Estimates

To determine whether the impairment of myocardial fatty acid uptake in the RV is associated with the patients' prognosis, we investigated the prognosis of 18 patients with PH (6 with primary PH and 12 with chronic thromboembolic PH), excluding those who underwent surgical treatment. All patients received anticoagulant therapy, and 89% of them were treated with a long-term orally active prostacyclin analog, beraprost sodium. Survival was defined as the period from the date of the ^{123}I-BMIPP study to March 10, 1997, or the death of the patient. The mean follow-up period was 18 mo (range 5–31 mo), and the follow-up rate was 100%.

Statistical Analysis

Data are presented as mean ± s.d. Comparisons of parameters between the two groups were made by Fisher's exact test or the unpaired Student's t-test. Correlation coefficients between two parameters were determined by linear regression analysis. Analysis of covariance was performed to assess slope and elevation differences in RVEF–mPAP or %SWT–mPAP regression lines between the two groups. Survival curves were derived using the Kaplan-Meier method and compared using log-rank tests. A p value of <0.05 was considered statistically significant.

RESULTS

There were significant positive correlations between mPAP and MIBI-RV/LV ($r = 0.89$, $p < 0.001$) and between mPAP and BMIPP-RV/LV ($r = 0.86$, $p < 0.001$) (Fig. 3). As indicated by the arrows in Figure 3, 8 of the 21 (38%) patients with PH showed a lower BMIPP-RV/LV (by less than 4 points) than MIBI-RV/LV (Group 1). These results imply that RV myocardial fatty acid uptake is impaired in a substantial percentage of patients with PH relative to myocardial flow distribution.

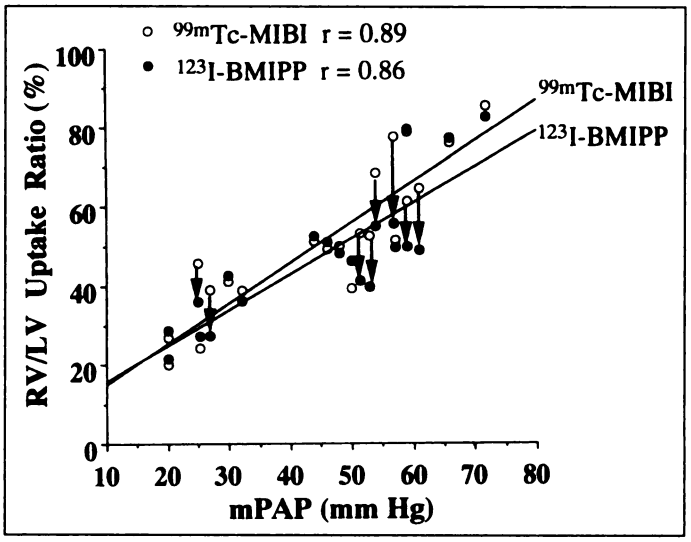

FIGURE 3. Relationships between mean pulmonary arterial pressure (mPAP) and right ventricle-to-left ventricle (RV-to-LV) uptake ratio of ^{99m}Tc-MIBI (MIBI-RV/LV) and between mPAP and RV-to-LV uptake ratio of ^{123}I-BMIPP (BMIPP-RV/LV) in patients with pulmonary hypertension. As indicated by the arrows, 8 patients showed lower BMIPP-RV/LV than MIBI-RV/LV (Group 1), indicating impairment of myocardial fatty acid metabolism in RV.

Groups 1 and 2 had similar age and mPAP, but Group 1 had a longer disease period than Group 2 (Table 1). RVEF and %SWT were significantly lower in Group 1 than in Group 2

TABLE 1
Differences in Clinical Characteristics, Hemodynamics and Cardiac Function of Patients with Pulmonary Hypertension According to the Presence of Impaired Fatty Acid Metabolism in the Right Ventricle

Parameter	Group 1	Group 2	Group 1 versus Group 2
Age (yr)	44 ± 18	48 ± 17	NS
Sex (M/F)	4/4	5/8	NS
Disease entity (PPH/PTE)	2/6	4/9	NS
Disease period (mo)	80 ± 50	36 ± 28	$p < 0.05$
mPAP (mmHg)	48 ± 14	44 ± 17	NS
CO (liter/min)	3.7 ± 1.1	3.8 ± 1.4	NS
TPR (wood units)	15 ± 7	13 ± 8	NS
RVEDP (mmHg)	12 ± 7	6 ± 4	$p < 0.05$
RAP (mmHg)	9 ± 6	5 ± 4	NS
PCWP (mmHg)	8 ± 3	9 ± 3	NS
mSAP (mmHg)	82 ± 31	83 ± 25	NS
RVEDVI (ml/m^2)	108 ± 25	85 ± 34	NS
RVSVI (ml/m^2)	28 ± 7	33 ± 10	NS
RVEF (%)	28 ± 10	40 ± 9	$p < 0.05$
RV mass index (g/m^2)	43 ± 18	40 ± 22	NS
WThd (mm)	5 ± 2	4 ± 2	NS
WThs (mm)	7 ± 2	8 ± 2	NS
%SWT (%)	33 ± 27	74 ± 30	$p < 0.05$
PaO_2 (torr)	67 ± 12	73 ± 7	NS
$PaCO_2$ (torr)	33 ± 4	36 ± 4	NS
O_2 saturation (%)	91 ± 4	94 ± 2	NS
1-yr survival rate (%)	57	100	$p < 0.05$

Group 1 = patients with more reduced ^{123}I-BMIPP uptake than ^{99m}TC-MIBI uptake in the right ventricle (RV); Group 2 = those with equal distributions of ^{123}I-BMIPP and ^{99m}Tc-MIBI in the RV; PPH = primary pulmonary hypertension (PH); PTE = chronic thromboembolic PH; mPAP = mean pulmonary arterial pressure; CO = cardiac output; TPR = total pulmonary resistance; RVEDP = RV end-diastolic pressure; RAP = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; mSAP = mean systemic arterial pressure; RVEDVI = RV end-diastolic volume index; RVSVI = RV stroke volume index; RVEF = right ventricle ejection fraction; WThd = end-diastolic wall thickness; WThs = end-systolic wall thickness; %SWT = percentage systolic wall thickening; NS = not significant.

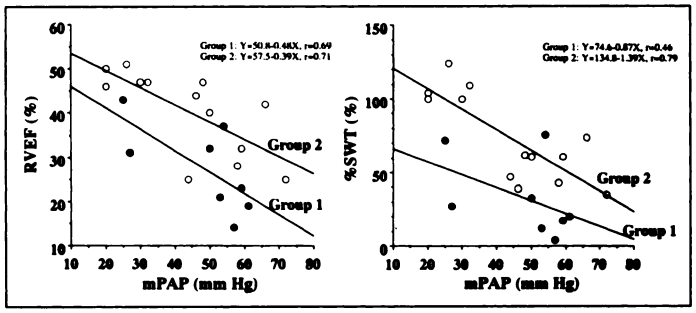

FIGURE 4. Relationships between mPAP and RVEF (left) and between mPAP and SWT (right) in patients with or without impaired myocardial metabolism in RV. RVEF–mPAP and %SWT–mPAP regression lines in patients with impaired myocardial metabolism (Group 1, ●) were located significantly downward ($p < 0.01$ by analysis of covariance) than those in patients with normal myocardial metabolism (Group 2, ○).

(both $p < 0.05$), although mPAP, total pulmonary resistance, RV mass index and WThd did not differ significantly between the groups.

To assess the differing influences of RV afterload and myocardial fatty acid uptake on RV systolic function, the relationship between RVEF or %SWT and mPAP was plotted for both groups (Fig. 4). There were inverse correlations both between RVEF and mPAP and between %SWT and mPAP in both groups. Analysis of covariance indicated no slope difference in the RVEF–mPAP and %SWT–mPAP regression lines between Groups 1 and 2, whereas it indicated a significant downward shift of the regression line of each relation for Group 1. These results suggest that patients in Group 1 had a disproportionately reduced systolic function of the RV for a given RV afterload.

During the follow-up period, 7 patients (3 with primary PH and 4 with chronic thromboembolic PH) died. Right-sided heart failure was the cause of death in all patients. The Kaplan–Meier survival curves according to the presence of an impaired myocardial fatty acid uptake in the RV are shown in Figure 5. Patients with more reduced ^{123}I-BMIPP uptake than ^{99m}Tc-MIBI uptake in the RV (Group 1) had a significantly higher death rate than in those with equal distributions of them (Group 2) (log-rank test, $p < 0.05$).

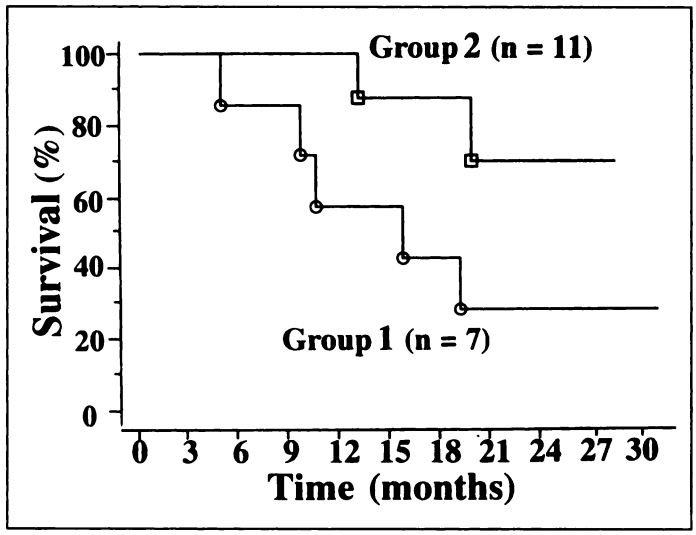

FIGURE 5. Kaplan–Meier survival estimates of 18 patients with pulmonary hypertension. Patients with more reduced ^{123}I-BMIPP uptake than ^{99m}Tc-MIBI uptake in right ventricle (Group 1) had significantly higher death rate than those with equal distributions of them (Group 2) (log-rank test, $p < 0.05$).

DISCUSSION

This study demonstrated that:

1. Myocardial fatty acid uptake in the hypertrophied RV was impaired in a substantial percentage of patients with PH;
2. The patients with impaired myocardial fatty acid uptake had similar age and mPAP but a long disease period compared with those with normal fatty acid uptake;
3. The impaired myocardial fatty acid uptake in the RV was associated with a disproportionate reduction of RV contractile function for a given mPAP; and
4. The patients with impaired fatty acid uptake in the RV had unfavorable prognosis.

These results suggest that impaired myocardial fatty acid uptake may be closely related to systolic dysfunction in the RV and to the poor prognosis in patients with PH.

Discrepancy Between Iodine-123-BMIPP and Technetium-99m-MIBI Scintigraphy

Recently, the structurally modified fatty acid, ^{123}I-BMIPP, has been proposed as a fatty acid probe for myocardial fatty acid utilization (*7–11*). Iodine-123-BMIPP uptake in the myocardium has been reported to correlate positively with the amount of myocardial adenosine triphosphate (*12*) that is required for the enzymatic conversion of fatty acids to acyl-CoA. Thus, the accumulation of ^{123}I-BMIPP mainly reflects the initial energy-dependent metabolic sequestration and retention of fatty acid. In contrast, ^{99m}Tc-MIBI has been used as a myocardial blood flow tracer, a substitute for ^{201}Tl (*19*). We used ^{99m}Tc-MIBI in this study to limit the problems of differential attenuation and scatter in ^{201}Tl SPECT.

Clinically, less ^{123}I-BMIPP uptake compared to ^{201}Tl or ^{99m}Tc-MIBI uptake is found in the ischemic but viable myocardium after acute myocardial infarction (*20,21*) or in the LV of patients with hypertrophic cardiomyopathy (*22*). Tamaki et al. (*23*) reported that myocardial regions with less ^{123}I-BMIPP uptake compared to ^{201}Tl uptake showed an enhanced uptake of fluorodeoxyglucose with PET, suggesting that the mismatched uptake of ^{123}I-BMIPP and ^{201}Tl could be used to identify the transition of fatty acid metabolism to glucose metabolism in diseased myocardium. Thus, the lower BMIPP-RV/LV than MIBI-RV/LV (Fig. 3) may indicate impaired myocardial fatty acid uptake in the hypertrophied RV due to PH.

Electron-Beam CT

Precise measurements for RV volume, systolic function and myocardial mass are more difficult than those for the LV because the configuration of the RV is far more complex and is not well approximated by any simple geometric formulation. Although a variety of imaging methods such as cine angiography (*24*), radionuclide ventriculography (*25*) and echocardiography (*26*) have been used to estimate these parameters, each has some shortcomings. Recently, however, electron-beam CT has allowed the accurate and reproducible measurements of the RV parameters with an excellent spatial resolution (*4–6*). Thus, in this study, a combination of electron-beam CT and metabolic imaging was used to assess the relationship between RV systolic function and myocardial metabolism.

Mechanism of Right Ventricle Contractile Dysfunction

It is well known that RV systolic function such as RVEF linearly decreases in proportion to the increase in mPAP (*27*). This finding does not necessarily imply the presence of myocardial failure due to PH because myocardial fiber shortening is directly dependent on afterload (afterload–shortening relationship) (*28*). However, in this study, analysis of covariance indicated a significant downward shift of the RVEF–mPAP and

%SWT–mPAP regression lines in Group 1 (Fig. 4), implying a disproportionate reduction in myocardial contractility of the RV for a given afterload in these patients. These results suggest that RV contractile function is closely related to the myocardial metabolic process in addition to RV afterload.

Ross (*29*) showed that the contractile function of ischemic myocardium is dependent on the degree of myocardial perfusion and proposed the concept of perfusion–contraction matching. However, in this study, RV myocardial ischemia as a cause of RV contractile dysfunction can be ruled out on the basis of the result of ^{99m}Tc-MIBI uptake. Thus, the impairment of myocardial fatty acid uptake may be another determinant of RV contractile function other than the afterload–shortening relationship and perfusion–contraction matching.

Whether the impairment of myocardial metabolism is the primary cause or a result of the RV contractile dysfunction remains unclear. Nonetheless, it is interesting to speculate that the impaired fatty acid uptake may be the result of long-term dysfunction, because patients with impaired myocardial fatty acid uptake had a longer disease period than patients with normal fatty acid uptake. Further study is needed to solve this issue.

Clinical Implication

The combination of ^{123}I-BMIPP and ^{99m}Tc-MIBI may distinguish failing myocardial hypertrophy from compensated myocardial hypertrophy of the RV in the presence of PH. This study suggests that such differentiation is possible, regardless of the level of mPAP and the disease period. Furthermore, the mismatched uptake of ^{123}I-BMIPP and ^{99m}Tc-MIBI in the RV may be used as an indicator of poor prognosis in patients with PH.

Study Limitations

First, patients with biventricular dysfunction, such as Eisenmenger syndrome, might have apparently normal BMIPP-RV/LV and MIBI-RV/LV despite severely depressed RV function. However, the uptakes of ^{123}I-BMIPP and ^{99m}Tc-MIBI in the lateral wall of the LV is unlikely affected in patients with primary or thromboembolic PH (*30*). Second, the limited number of patients for prognostic study should be noted as a limitation. Systematic trials including large number of patients are necessary.

CONCLUSION

Using radionuclide imaging and electron-beam CT, we have demonstrated that myocardial fatty acid uptake is impaired in the failing hypertrophied RV due to PH. Mismatching of ^{123}I-BMIPP and ^{99m}Tc-MIBI uptake may distinguish failing myocardial hypertrophy from compensated myocardial hypertrophy of the RV in the presence of PH.

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