Clinical Significance of Iodine-123-15-(p-Iodophenyl)-3-R, S-Methylpentadecanoic Acid Myocardial Scintigraphy in Patients With Aortic Valve Disease

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The present study sought to determine whether myocardial fatty acid metabolism as assessed with iodine-123-labeled 15-(p-iodophenyl)-3-R, S-methylpentadecanoic acid (BMIPP) scintigraphy is impaired in patients with aortic valve disease (AVD) and whether the degree of the metabolic abnormality reflects the severity of AVD. BMIPP scintigraphy was performed in 12 patients with aortic stenosis (AS), 14 patients with aortic regurgitation (AR), and 9 healthy volunteers, and from that the heart–mediastinum uptake ratio (H/M ratio) corrected by the left ventricular (LV) mass (U/Mass ratio) and the myocardial washout rate (WR) were obtained. The H/M ratio tended to be higher in patients than in healthy volunteers (3.3±0.7 for AS, 3.5±0.5 for AR, 3.0±0.3 for healthy volunteers), and the WR was significantly higher in patients than in healthy volunteers (42.8±9.1% for AS, 35.7±6.5% for AR, 19.6±9.1% for healthy volunteers, $p<0.01$). In the AS patients, the U/Mass ratio showed significant negative correlations ($r=-0.79$ to -0.90, all $p<0.01$) and the WR showed significant positive correlations ($r=0.61$ to 0.82, all $p<0.01$) with transaortic pressure gradient, LV wall thickness, and LV mass. Similarly, in AR patients these BMIPP parameters showed proportional changes to the LV volumes and LV mass ($r=-0.79$ to -0.83, all $p<0.01$ for U/Mass ratio, $r=0.55$ to 0.70, $p<0.05$ to <0.01 for WR). In the 9 patients who underwent aortic valve replacement, the BMIPP parameters tended to normalize with increasing U/Mass ratio ($0.90\pm0.41\times10^{-2}$/g to $1.34\pm0.59\times10^{-2}$/g, $p<0.05$) and decreasing WR (41.9±8.8% to 35.4±9.2%, $p<0.01$) after surgery. Myocardial fatty acid metabolism as assessed with BMIPP scintigraphy was impaired in patients with aortic valve disease and the U/Mass ratio and WR reflect the severity. These parameters may be useful for the noninvasive assessment of the myocardial metabolic abnormalities caused by hemodynamic overload. (*Circ J* 2002; **66:** 41–46)

Key Words: Cardiovascular disease; Echocardiography; Scintigraphy; Valves

The left ventricle in patients with aortic valve disease (AVD) is exposed to a long-standing significant hemodynamic burden either as pressure overload in aortic stenosis (AS) or as volume overload in aortic regurgitation (AR). Although these patients remain asymptomatic during a latent period because of left ventricular (LV) compensation (hypertrophy and/or dilatation),[1–5] their myocardial metabolism may be impaired by the chronic hemodynamic overload before the appearance of overt heart failure.[6,7] Therefore, it is important to assess myocardial metabolism in patients with AVD regardless of their symptoms.

About 75% of the energy metabolism in a human heart is based on β-oxidation of free fatty acids. Iodine-123-labeled 15-(p-iodophenyl)-3-R, S-methylpentadecanoic acid (BMIPP), a structurally modified fatty acid, accumulates in the triglyceride pool of the myocardium and remains there for some time because of its slow washout kinetics.[8,9] Therefore, BMIPP can assess myocardial fatty acid metabolism with gamma camera imaging.

Impairment of the myocardial fatty acid metabolism as assessed by BMIPP scintigraphy has been shown to be a sensitive marker of severe myocardial damage in ischemic heart disease[10–13] and hypertrophic cardiomyopathy,[14–17] it is unclear whether or not BMIPP scintigraphy can reveal myocardial damage in hemodynamically overloaded hearts. The present study was designed to determine whether myocardial fatty acid metabolism as assessed with BMIPP scintigraphy was impaired in patients with AVD, and to determine whether the degree of metabolic abnormality reflected the severity of the disease. In addition, we investigated whether BMIPP scintigraphy could detect improvement of the myocardial fatty acid metabolism resulting from reduction of chronic overload by aortic valve replacement (AVR).

Methods

Patients

Twenty-six patients with AVD who underwent cardiac catheterization were studied: 12 patients had pure AS (7 men, 5 women; 50–75 years old, mean: 60±12 years) and 14 patients had pure AR (12 men, 2 women; 22–74 years old, mean: 50±15 years). The etiologies of the AVD included

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degenerative change in 10 patients, rheumatic changs in 7 patients, bicuspid aortic valve in 6 patients and aortic root dilatation in 3 patients. None of the patients had acute AR. Patients who had other concomitant valvular diseases or coronary artery disease were excluded, as were patients with a history of diabetes mellitus or hyperlipidemia, which might influence fatty acid metabolism. Aortic valve replacement (AVR) was subsequently performed in 22 of the 26 patients. Nine healthy volunteers (all men, 25–44 years old, mean: 31±7 years) were the control subjects. Informed consent for the procedure was obtained from each participant.

BMIPP Scintigraphy

On the day of examination, all subjects were deprived of food, liquids except water and exercise until completion of the study. Patients were supine and received an intravenous injection of ^{123}I-BMIPP (111 MBq/1.5 ml) (Nihon Medi-Physics Co, Ltd, Nishinomiya, Japan). A planar image was obtained using a single-head gamma camera system (GCA901A/HG, Toshiba Medical Co, Tokyo, Japan) with 512×512 matrix at 20 min (early image) and at 240 min (delayed image) after the tracer injection.

BMIPP Parameters

For the analysis of BMIPP uptake, regions of interest (ROIs) were set on the upper mediastinum and the LV myocardium on the planar images (Fig 1). The mean radionuclide count per pixel in each ROI was calculated and 2 indices of myocardial BMIPP accumulation were obtained. To evaluate the global myocardial accumulation of BMIPP, the heart–mediastinum uptake ratio (H/M ratio) was calculated as:

$$\text{H/M ratio} = [\text{H}]/[\text{M}]$$

where [H] = mean count of the LV myocardium and [M] = mean count of the upper mediastinum. Because the myocardial BMIPP uptake might be affected by LV mass, we also calculated the uptake/mass ratio (U/Mass ratio) as:

$$\text{U/Mass ratio (/g)} = \text{H/M ratio}/\text{LVM}$$

where LVM = LV mass derived by echocardiography. The H/M and U/Mass ratios were defined from the early images. The clearance of BMIPP from the myocardium (washout rate, WR) was calculated from the early and delayed images as:

$$\text{WR (\%)} = \{([\text{H}]-[\text{M}])_{\text{E}}-([\text{H}]-[\text{M}])_{\text{D}}\} / ([\text{H}]-[\text{M}])_{\text{E}}\times 100$$

where $([\text{H}] - [\text{M}])_{\text{E}}$ and $([\text{H}] - [\text{M}])_{\text{D}}$ are the differences of the mean BMIPP count between the LV myocardium and upper mediastinum on the early and the delayed images, respectively.

Hemodynamics and Echocardiography

All patients with AVD underwent cardiac catheterization and 2-dimensional echocardiography. We measured LV end-diastolic pressure (LVEDP), transaortic peak-to-peak pressure gradient, LV end-diastolic and end-systolic volumes and LV ejection fraction by catheterization, and the grade of AR was determined using aortography according to the criteria of Sellers et al.[18] From the 2-dimensional echocardiography images, we measured the thickness of the interventricular septum and the posterior wall, the diameter of the LV at end-diastole and end-systole, the fractional shortening, and the LV mass, according to the method of Devereux and Reichek.[19] The mean LV wall thickness was obtained as an average of the thickness of the interventricular septum and the posterior wall. LV wall stress was calculated at end-systole and end-diastole by the catheterization-derived and echocardiography-derived data as reported previously.[20]

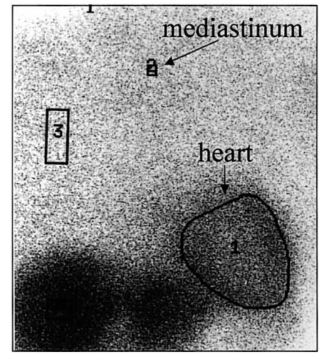


Fig 1. Regions of interest in the upper mediastinum and the LV myocardium on planar images.

Statistics

Data are expressed as mean ± SD. The BMIPP parameters were compared among the patients with AS and AR, and the healthy volunteers using analysis of variance. The BMIPP parameters were correlated with the hemodynamic and echocardiographic data using linear regression analysis. A p value less than 0.05 was considered statistically significant.

Results

Comparison of Patients and Healthy Volunteers

The patients' characteristics and echocardiographic, hemodynamic and electrocardiographic data are shown in Table 1. All patients had a moderate to severe grade of AS or AR. Preoperative coronary angiography showed that none of the patients had significant coronary stenosis (>50%). Representative planar images from the early phase are shown in Fig 2. The H/M ratio in patients with AVD tended to be higher than that in healthy volunteers (3.3±0.7 for AS, 3.5±0.5 for AR, 3.0±0.3 for healthy volunteers, p=NS). The U/Mass ratio in AS patients tended to be higher than that in AR patients ($1.1\pm0.5\times10^{-2}$/g for AS, $0.8\pm0.3\times10^{-2}$/g for AR, p=NS). The WR was significantly higher in patients with AVD than in healthy volunteers (42.8±9.1% for AS, 35.7±6.5% for AR, 19.6±9.1% for healthy volunteers, p<0.01).

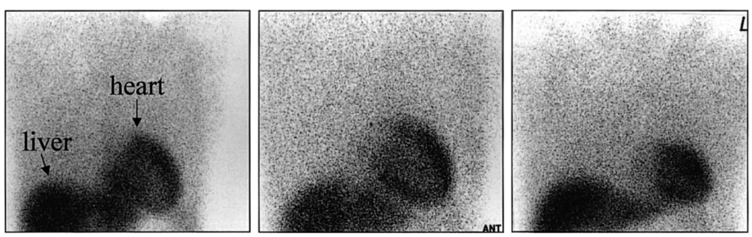
Relationships Between BMIPP Parameters and Hemodynamics

The H/M ratio did not show a significant correlation with hemodynamic parameters in either group of patients, but in the patients with AS the U/Mass ratio and WR both showed a significant correlation with transaortic pressure gradient (r=–0.83, p<0.01 for U/Mass ratio, r=0.67, p<0.01 for WR), mean LV wall thickness (r=–0.90, p<0.01 for U/Mass ratio, r=0.82, p<0.05 for WR) and LV mass (r=–0.79, p<0.01 for U/Mass ratio, r=0.61, p<0.01 for WR) (Fig 3). The U/Mass ratio in the AS patients also showed a significant negative correlation with LV end-diastolic volume (r=–0.83, p<0.01)

Table 1 Hemodynamic Variables

	AS (n=12)	AR (n=14)
Age (years)	60±12	50±15
NYHA functional class (I/II/III) (n)	4/6/2	5/9/0
Echocardiographic data		
LV diastolic diameter (mm)	50±5	70±8
LV systolic diameter (mm)	34±7	49±9
LVFS (%)	32±9	30±7
LVWT (mm)	14±2	11±2
LV mass (g)	344±136	449±176
Catheterization data		
LVEDP (mmHg)	22±8	16±9
LVEDV (ml)	127±54	311±110
LVESV (ml)	54±32	169±57
LVEF (%)	58±9	44±6
PG (mmHg)	101±40	–
AR grade	1.0±1.0	3.5±0.5
Electrocardiology		
SV_1+RV_5 (mm)	50±14	56±13
Negative T in V_5 or V_6 (n)	8	6

AS, aortic stenosis; AR, aortic regurgitation; NYHA, New York Heart Association; LV, left ventricular; FS, fractional shortening; WT, wall thickness; EDP, end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; PG, transaortic pressure gradient.



Aortic stenosis
H/M = 2.62
U/Mass = 0.51

Aortic regurgitation
H/M = 3.38
U/Mass = 0.49

Normal
H/M = 3.42

Fig 2. Representative planar images from the early phase.

and LV end-systolic volume (r=–0.79, p<0.01). Thus, the U/Mass ratio dcreased and the WR increased in proportion to the severity of AS.

Similarly, the U/Mass ratio and WR had proportional changes with disease severity in the patients with AR (Fig 4 shows the relationships between LV end-diastolic volume, LV end-systolic volume, LV mass and the BMIPP parameters). In these patients, the U/Mass ratio and WR both showed a significant correlation with LV volume (U/M ratio; r=–0.79, p<0.01 for LV end-diastolic volume, r= –0.83, p<0.01 for LV end-systolic volume, WR; r=0.55, p<0.05 for LV end-diastolic volume, r=0.68, p<0.05 for LV end-systolic volume), and LV mass (r=–0.80, p<0.01 for U/Mass ratio, r=0.70, p<0.01 for WR). The WR showed a positive relation with LV systolic wall stress (r=0.60, p<0.05). Thus, the U/Mass ratio decreased and the WR increased in proportion to the severity of AR.

The BMIPP parameters did not show significant correlations with the other hemodynamic and echocardiographic parameters.

Effects of Surgery on BMIPP Parameters

Nine patients had BMIPP scintigraphy 6 months after AVR (5 patients with AS and 4 patients with AR). The U/Mass ratios significantly increased (from $0.90\pm0.41\times10^{-2}$/g to $1.34\pm0.59\times10^{-2}$/g, p<0.05) and WR significantly decreased after AVR (from 41.9±8.8% to 35.4±9.2%, p<0.01). However, the H/M ratio did not change substantially (from 3.4±0.7 to 3.0±0.3, p=NS).

Discussion

BMIPP scintigraphy is a relatively new method of noninvasively assessing fatty acid metabolism in the myocardium and is considered to sensitively identify myocardial injury in various diseases.[10–17,21,22] In the present study, we showed that there was abnormal myocardial fatty acid metabolism in patients with AVD, and that the degree of abnormality was proportional to the severity. To the best of our knowledge, this is the first study to demonstrate the clinical relevance of BMIPP in patients with valvular heart disease. Aortic valve disease is characterized by a significant pressure overload in AS or a significant volume overload in AR. Therefore, we can interpret the present results as showing the effects of hemodynamic overload on myocardial fatty acid metabolism.

BMIPP in AVD

The H/M ratio tended to be higher in patients with AVD than in the healthy volunteers, whereas the U/Mass ratio, which corrected the uptake counts by the quantity of LV mass, reflected the severity of aortic valve disease. Therefore, we consider that the U/Mass ratio is more suitable than the H/M ratio for assessing the impairment of fatty acid metabolism, especially in patients with LV hypertrophy. A previous animal study demonstrated that glucose

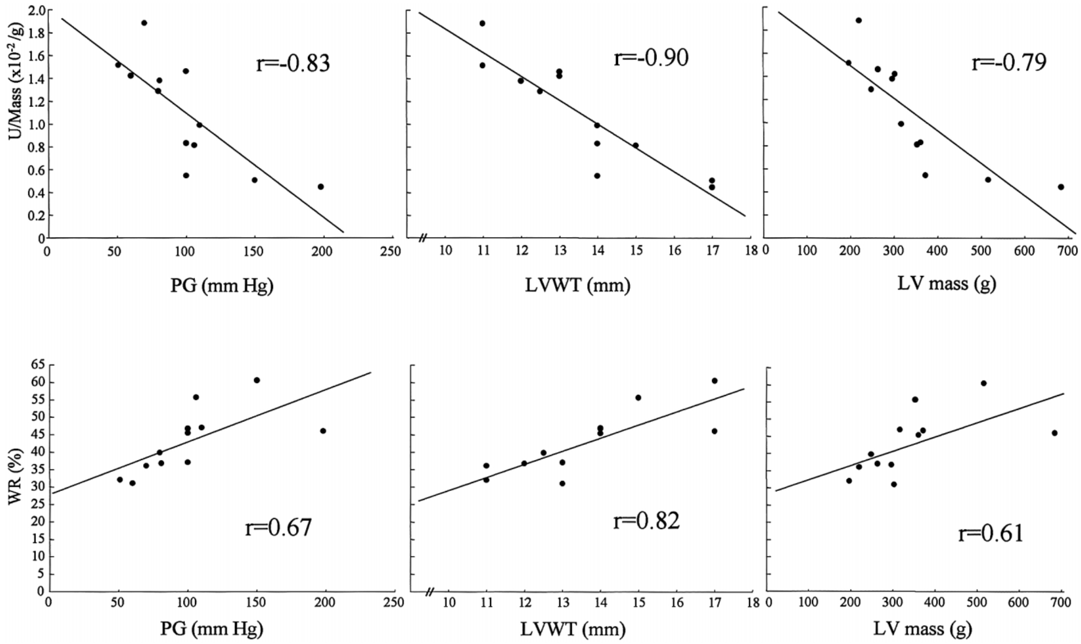


Fig 3. Relationships between BMIPP parameters (U/Mass ratio in the Upper panel and WR in the Lower panel) and hemodynamic parameters in patients with aortic stenosis. PG, transaortic pressure gradient; LVWT, mean left ventricular wall thickness; LV mass, left ventricular mass.

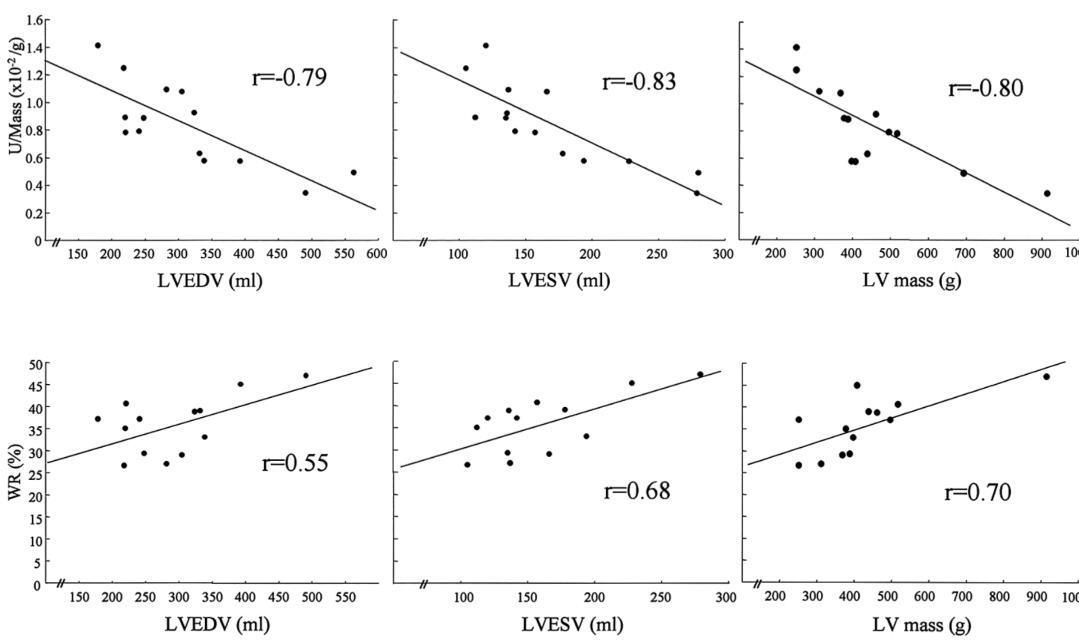


Fig 4. Relationships between BMIPP parameters (U/Mass ratio in the Upper panel and WR in the Lower panel) and hemodynamic parameters in patients with aortic regurgitation. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LV mass, left ventricular mass.

utilization was increased whereas fatty acid analogue uptake was decreased in long-term pressure overloaded hearts.[23] The decreased U/Mass ratio in the present study may therefore reflect an alteration in the energy substrate.

The WR in patients with AVD was higher than that in the healthy volunteers and it increased with the severity of disease. In spite of the decreased BMIPP uptake, patients with severe AVD have an increased WR, which suggests that the uptake and the washout of BMIPP represent different pathways of fatty acid metabolism and is in accord with previous studies.[24–27] BMIPP accumulates in the triglyceride pool in the myocardium and remains in the myocardium for a long period because of its slow washout kinetics. BMIPP uptake depends on myocardial ATP content[24] and mitochondrial function.[25] A recent study using a canine pacing model showed that the energy store and uptake of BMIPP into heart failure myocardium decreased, suggesting mitochondrial dysfunction.[28] On the other hand, BMIPP is metabolized in the heart through α-oxidation and decarboxylation followed by β-oxidation with little BMIPP back-diffusion.[26,27] Myocardial BMIPP washout by back-diffusion is frequent during the very early stage after tracer injection. The WR in the present study represents the washout by α-oxidation followed by β-oxidation, not by back-diffuison, and the high myocardial WR is caused by the increased myocardial work load. Thus, the decreased U/Mass ratio and the rapid WR in AVD respectively demonstrate the decreased utility and the enhanced metabolism of BMIPP in hemodynamically overloaded hearts.

In the present study, the U/Mass ratio in AR patients tended to be lower than in AS patients, and the WR in AS patients tended to be higher than in AR patients, which may mean that the utility of BMIPP relatively decreases in the volume overloaded heart and the metabolism of BMIPP is relatively enhanced in the pressure overloaded heart. Because the BMIPP WR does not depend on myocardial flow volume, it may be more suitable than the U/Mass ratio for assessing myocardial metabolism in patients with LV hypertrophy.

Effect of AVR

Aortic valve disease induces myocardial damage by pressure and/or volume overload, which significantly affects morbidity and mortality. Therefore, AVR at the optimal timing is necessary to improve prognosis.[4,29–32] However, changes in myocardial metabolism as a result of AVR have not been well demonstrated. In the present study, both the U/Mass ratio and WR significantly improved in patients after AVR, which suggests that it normalized the energy metabolism and utilization of fatty acid through reduction of the hemodynamic overload. The BMIPP parameters are sensitive markers of myocardial metabolic abnormalities in pressure- or volume-overloaded hearts and may be a useful noninvasive assessment of the effects of medical and surgical treatment.

Study Limitations

The small number of patients in the present study is a limitation, but we selected only patients with pure AS or pure AR as models of pressure overload and volume overload, respectively. Further, the results from the measurements were consistent among all patients. Therefore, it seems unlikely that the present results would be significantly altered by a larger number of patients.

AS patients with severely reduced LV contraction were not included. Some patients in the terminal stage of AS have reduced LV contraction and in such cases, the transaortic pressure gradient and mean LV wall thickness would decrease and there would not be a linear relationship between BMIPP parameters and these indices. However, in such patients, fatty acid metabolism would be significantly impaired and therefore, we believe the BMIPP parameters are still useful for assessing myocardial damage.

Clinical Implications

Both the U/Mass ratio and WR correlated well with the catheterization-determined severity of AVD. Although there are many invasive and noninvasive methods for assessing the severity of AVD, BMIPP scintigraphy is a unique and useful alternative from the viewpoint of myocardial metabolism. Hemodynamic overload from AVD induces progressive myocardial damage before the appearance of overt LV dysfunction and BMIPP scintigraphy can be used to detect myocardial damage at an early stage for initiation of appropriate treatment.

Determining the optimal timing of aortic valve surgery is sometimes still difficult clinically[4,28–31] and ideally should be performed before irreversible LV dysfunction occurs. The BMIPP method reported here can assess the myocardial damage and help determine the best timing for surgery. The present patients showed improvement in the U/Mass ratio and WR after AVR, and it would be useful to know how much myocardial damage can be reversed by the surgery. Further studies are needed to show the feasibility of BMIPP parameters as determinants of the timing of aortic valve surgery or as prognostic indicators.

Conclusions

Myocardial fatty acid metabolism as assessed with BMIPP scintigraphy was impaired in patients with AVD and the decreased myocardial accumulation and accelerated WR of BMIPP reflect the severity. These parameters are a useful noninvasive assessment of myocardial metabolic abnormalities caused by hemodynamic overload.

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