Dynamic ^{123}I -BMIPP Single-Photon Emission Computed Tomography in Patients with Congestive Heart Failure: Effect of Angiotensin II Type-1 Receptor Blockade

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Summary

Background: Heart failure is a major and growing public health problem with a high mortality rate. Although recent studies have demonstrated that a variety of metabolic and/or neurohumoral factors are involved in the progression of this syndrome, the precise mechanisms responsible for this complex condition are poorly understood.

Hypothesis: To examine ^{123}I - β -methyl-iodophenylpentadecanoic acid (BMIPP) kinetics in the early phase soon after tracer injection in patients with congestive heart failure (CHF), we performed dynamic single-photon emission computed tomography (SPECT).

Methods: Twenty-six patients with CHF and eight control subjects were examined. The consecutive 15 images of 2-min dynamic SPECT were acquired for 30 min after injection. In the early phase after injection (0–4 min), a significant amount of radioactivity existed in the blood pool. After 6 min, the myocardial ^{123}I -BMIPP image was clear and thus the washout rate of ^{123}I -BMIPP from 6 to 30 min was calculated.

Results: The washout rate of ^{123}I -BMIPP from the myocardium was faster in patients with CHF than in the controls (8 ± 4 vs. $-5 \pm 3\%$, $p < 0.01$). The washout rate of ^{123}I -BMIPP demonstrated positive correlation with left ventricular (LV) end-diastolic volume index ($R = 0.54$, $p < 0.02$) and inverse correlation with LV ejection fraction ($R = 0.53$, $p < 0.02$). Patients were given the angiotensin II type-1 receptor antagonist candesartan for 6 months, and dynamic SPECT was repeated. The enhanced washout rate of ^{123}I -BMIPP in CHF was reduced after treatment with candesartan ($p < 0.05$).

Conclusion: These data suggest that (1) enhanced washout of ^{123}I -BMIPP was observed soon after injection in patients with CHF, (2) the activation of angiotensin II signaling pathway is involved as an intracellular mechanism for enhanced ^{123}I -BMIPP washout in heart failure, and (3) improvement in fatty acid metabolism may represent a new mechanism for beneficial effects of angiotensin II receptor blockade on cardiac function and survival in patients with heart failure. ^{123}I -BMIPP washout in the early phase obtained from dynamic SPECT may be a new marker for evaluating the severity of heart failure and the effects of medical treatment.

Key words: heart failure, angiotensin II receptor blockade, fatty acid metabolism, ^{123}I -BMIPP

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Introduction

Heart failure is a major and growing public health problem with a high mortality rate.¹ Although recent studies have demonstrated that a variety of metabolic and/or neurohumoral factors are involved in the progression of this syndrome, the precise mechanisms responsible for this complex condition are poorly understood.² Hypertrophy is a compensatory response to increased wall stress in the early stage. However, if the stimuli for pathologic hypertrophy are sufficiently intense and prolonged, decompensated hypertrophy ensues and ultimately leads to heart failure. Angiotensin II plays an important role in

the progression of cardiac hypertrophy and failure.^{2,3} Recent clinical studies have clearly demonstrated that treatment with angiotensin II receptor blocker improved survival of patients with congestive heart failure (CHF).⁴

Energy metabolic pathway reverts to a fetal pattern during the development of cardiac hypertrophy and heart failure;^{5,6} namely, a transition of energy substrate utilization occurs with reduced fatty acid oxidation and increased glucose utilization during the development of cardiac hypertrophy and in the failing heart. Sack *et al.* have reported that protein expression and activity of fatty acid oxidation enzymes are depressed in the failing myocardium of patients with end-stage heart failure.⁷ Recchia *et al.* have demonstrated in a pacing-induced heart failure model that cardiac fatty acid uptake is reduced and glucose uptake is complementarily increased in the failing heart.⁸ Kataoka *et al.*, in an animal model of heart failure by rapid ventricular pacing, recently reported that myocardial ^{123}I -BMIPP uptake is low and clearance is enhanced in the failing myocardium.⁹ In a clinical study, we have recently reported that fatty acid metabolic abnormality can be detected using ^{123}I -BMIPP in patients with CHF.¹⁰ We have shown that a heart-to-mediastinum ratio of ^{123}I -BMIPP is lower and washout of ^{123}I -BMIPP from 30 min early to 4 h delayed images is faster in patients with heart failure compared with normal controls.

Experimental studies have shown that fatty acids are rapidly metabolized after intravenous injection into the cardiomyocyte.^{11,12} Therefore, the present study was undertaken to examine whether dynamic single-photon emission computed tomography (SPECT) could detect abnormalities in ^{123}I -BMIPP kinetics in the early phase soon after tracer injection in patients with CHF. We also examined the effects of the angiotensin II type-1 receptor antagonist candesartan on ^{123}I -BMIPP kinetics in patients with heart failure.

Methods

Subjects and Study Protocol

We studied 26 patients (18 men, 8 women, mean age 57 years, range 43–80) with CHF. We used eight normal subjects (four men, four women, mean age 59 years) as controls. The etiologies for CHF were idiopathic dilated cardiomyopathy ($n = 20$), ischemic cardiomyopathy ($n = 2$), valvular heart disease ($n = 2$), and hypertensive heart disease ($n = 2$). The characteristics of the study subjects are summarized in Table I. There were 5 patients with New York Heart Association (NYHA) functional class I, 9 patients with class II, 10 patients with class III, and 2 patients with class IV heart failure. Left ventricular (LV) fractional shortening obtained by echocardiography was lower in patients with CHF than in the controls ($p < 0.01$). Left ventricular end-diastolic dimension was larger in CHF than in the controls ($p < 0.01$). Written informed consent was obtained from all patients, and the Institutional Review Board on human research approved the study protocol.

In 16 of 26 patients with CHF, the angiotensin II type-1 receptor antagonist candesartan (8 mg/day), was given for 6

TABLE I Characteristics of subjects

	Controls ($n = 8$)	Heart failure ($n = 26$)
Age (years)	59 ± 11	57 ± 10
Gender (M/F)	4/4	18/8
NYHA (I/II/III/IV)	—	5/9/10/2
LVFS (%)	41 ± 4	22 ± 6^a
LVEDD (mm)	43 ± 5	61 ± 5^a
CI (l/min/m ²)	N/A	2.3 ± 0.5
PCWP (mmHg)	N/A	12 ± 2
LVEDP (mmHg)	N/A	11 ± 2

^a $p < 0.05$ vs. controls.

Abbreviations: M = male, F = female, NYHA = New York Heart Association, LVFS = left ventricular fractional shortening, LVEDD = left ventricular end-diastolic dimension, CI = cardiac index, PCWP = pulmonary capillary wedge pressure, LVEDP = left ventricular end-diastolic pressure, N/A = not available.

months, and ^{123}I -BMIPP dynamic SPECT was repeated. The etiologies of heart failure in this subgroup were idiopathic dilated cardiomyopathy in 12 patients, valvular heart disease in 2 patients, and hypertensive heart disease in 2 patients.

Dynamic ^{123}I -BMIPP Single-Photon Emission Computed Tomography Imaging

A dose of 148 MBq of ^{123}I -BMIPP (Nihon Medi-Physics Co. Ltd., Tokyo, Japan) was rapidly administered with 20 ml saline under resting supine conditions after an overnight fast. All images were acquired using a three-head rotating gamma camera equipped with a low-energy, high-resolution collimator (Multispect 3, Siemens Medical Systems, Chicago, Ill., USA) as previously reported.^{13–15} Data acquisition was performed in the continuous rotation mode, in which the three detector heads make an alternating motion in a 120° range with a cycle of 2 min. The 15 consecutive 2-min dynamic SPECT images were obtained for 30 min after the tracer injection. Energy discrimination was provided by a 15% window centered on the 159 keV photopeak. The data were stored on a 64×64 matrix. Data processing was performed on a nuclear medicine computer system (Icon, Siemens Medical Systems). A series of contiguous transaxial 6 mm thick images were reconstructed by means of a filtered back-projection algorithm without attenuation correction. These transaxial images were then reoriented in the short axis and vertical long axis of the left ventricle.

The serial short-axis images were reconstructed as shown in Figure 1A, and regions of interest were defined for the entire left ventricle and LV cavity on the short-axis image as shown in the left panel of Figure 1B. The radio activities in the regions of interest were plotted as a function of time for every 2 min, and the time-activity curves from 0 to 30 min were generated for the entire left ventricle and LV cavity, as shown in the right

FIG. 1 Serial short-axis images of ^{123}I -BMIPP obtained from dynamic single-photon emission computed tomography (SPECT) (A). The 15 consecutive 2-min dynamic SPECT images were obtained for 30 min after the tracer injection. Regions of interest were defined for the entire left ventricle and left ventricular (LV) cavity on the short-axis image (B). The time-activity curves for the entire left ventricle and LV cavity were generated.

panel of Figure 1B. The time-activity curve for the LV myocardium was obtained by subtracting the time activity curve of the LV cavity from that of the entire left ventricle, as shown in Figure 2. The count densities in the myocardium were approximately 100 counts per pixel.

As shown in Figure 1A, a significant amount of radioactivity exists in the blood pool soon after tracer injection on 0–2 and 2–4 min images. Therefore, the washout rate of BMIPP from 6–8 to 28–30 min images was calculated with physical decay correction. The analyses of ^{123}I -BMIPP washout were repeated in 10 patients by the same observer and by a second observer on a separate day to determine intra- and interobserver variability. The calculation of ^{123}I -BMIPP washout was reliable because excellent correlations were obtained from repeated analyses ($r = 0.96$, $p < 0.0001$ by the same observer; $r = 0.95$, $p < 0.0001$ by the second observer).

Echocardiography

Echocardiography was carried out using a Hewlett-Packard Sonos 2500 ultrasound system with 2.5 MHz transducer (Hewlett-Packard Co., Andover, Mass., USA) as previously described.^{15,16} The patients were studied in the left lateral decubitus position in the resting state. The parasternal long-axis and short-axis views and the apical four- and two-chamber views were recorded in all patients. All echocardiographic data were recorded on an S-VHS videotape for subsequent analysis. M-mode tracings were recorded at 100 mm/s, on which LV chamber size and the thickness of the interventricular septum and the posterior wall were measured. Three cardiac cycles were averaged, and the fractional shortening (% FS) was calculated as $(\text{LVDd} - \text{LVDs}) / \text{LVDd} \times 100$ (LVDd = LV dimension at end-diastole, LVDs = LV at end-systole).

FIG. 2 Time-activity curves for the left ventricular myocardium were generated from serial short-axis images by subtracting the left ventricular cavity from the entire left ventricle. There were two patterns of time-activity curves for the left ventricular myocardium: retention and washout types.

Cardiac Catheterization

Selective coronary arteriography and biplane left ventriculography were performed in all patients using a standard percutaneous technique. Biplane left ventriculography was performed before coronary arteriography. Left ventricular ejection fraction was measured by Simpson's method from ventriculograms in the right anterior oblique view as $(LVEDV - LVESV) / LVEDV \times 100$ ($LVEDV$ = LV end-diastolic volume, $LVESV$ = LV end-systolic volume).

Statistics

Data were presented as mean $\pm$ 1 standard deviation. Continuous variables were compared by a paired or unpaired *t*-test. Differences in proportion were examined by chi-square test for independence. A value of $p < 0.05$ was considered significant.

TABLE II Incidence of retention and washout types in patients with congestive heart failure and normal subjects

	Normal controls	Heart failure		
		I/II	III/IV	Total
Retention type	8	13	4	25
Washout type	0	1	8	9
Total	8	14	12	34

$\chi^2 = 15.528$, $p < 0.001$.

Results

Patterns of Time Activity Curves and the Severity of Heart Failure

Time activity curves for the LV myocardium were generated from serial dynamic ^{123}I -BMIPP SPECT images. We found that there were two patterns of time-activity curves for the LV myocardium, retention and washout types, as shown in Figure 2. The majority of study subjects had time activity curves of retention type (25 of 34 subjects, Table II). All eight normal controls showed retention type; however, eight of nine patients with washout type had moderate to severe CHF with NYHA functional class III and IV ($p < 0.001$).

Early ^{123}I -BMIPP Washout from 6 to 30 Min and Cardiac Function

The washout rate of ^{123}I -BMIPP from 6 to 30 min was compared between patients with retention and washout types. As shown in Figure 3, the washout rate was faster in patients with washout type than in those with retention type ($p < 0.01$). The NYHA functional class was more severe in patients with washout type than in those with retention type ($p < 0.01$).

Left ventricular end-diastolic volume index was larger in the washout type than in the retention type ($p < 0.05$, Fig. 4). Patients with washout type had lower LV ejection fraction ($p < 0.01$) and lower FS ($p < 0.01$) than those with retention type. As shown in Figure 5, the washout rate of ^{123}I -BMIPP from 6 to 30 min demonstrated positive correlation with LV end-diastolic volume index ($R = 0.54$, $p < 0.02$) and inverse correlation with LV ejection fraction ($R = 0.53$, $p < 0.02$).

Effect of Angiotensin II Receptor Blockade on ^{123}I -BMIPP Washout

Patients with CHF ($n = 16$) were given the angiotensin II type-1 receptor antagonist candesartan (8 mg/day) for 6 months, and ^{123}I -BMIPP imaging was repeated. The enhanced washout rate of ^{123}I -BMIPP in patients with heart failure was reduced af-

FIG. 3 Comparisons of washout rate (6–30 min) and New York Heart Association (NYHA) functional class between patients with retention and washout types. ** $P < 0.01$.

FIG. 4 Comparisons of left ventricular end-diastolic volume index (LVEDVI), left ventricular ejection fraction (LVEF), and fractional shortening (%FS) between patients with retention and washout types. * $P < 0.05$, ** $p < 0.01$.

FIG. 5 Correlations of ¹²³I-BMIPP washout rate (6–30 min) with left ventricular end-diastolic volume index (LVEDVI) and left ventricular ejection fraction (LVEF).

ter treatment with candesartan (Fig. 6, $p < 0.05$). Among those patients, there were six, eight, and two with NYHA functional class II, III, and IV, respectively, before treatment. After treatment with candesartan, NYHA functional class improved (10, 4, and 2 patients in NYHA class I, II, and III, respectively). Left ventricular end-diastolic dimension was reduced from 59 ± 6 to 56 ± 7 mm, and FS was increased from 23 ± 8 to $28 \pm 10\%$, but these changes were not statistically significant.

Discussion

We performed dynamic ¹²³I-BMIPP SPECT in patients with CHF and found that an enhanced washout of ¹²³I-BMIPP

FIG. 6 Changes in ¹²³I-BMIPP washout rate (6–30 min) after angiotensin II receptor blockade with candesartan. * $P < 0.05$.

was observed soon after tracer injection. The ¹²³I-BMIPP washout from 6 to 30 min demonstrated positive correlation with LV end-diastolic volume index and inverse correlation with LV ejection fraction. Enhanced washout of ¹²³I-BMIPP in CHF was reduced after angiotensin II receptor blockade. These data suggest that the angiotensin II receptor signaling pathway is involved in intracellular mechanisms for the increased washout of ¹²³I-BMIPP in CHF.

Fatty Acid Metabolism in Cardiac Hypertrophy and Heart Failure

Cardiac hypertrophy is a major risk factor for the development of CHF and death.^{1,2} Although hypertrophy is a compensatory response to increased wall stress in the early stage, decompensated hypertrophy ensues and ultimately leads to heart failure if the stimulus for pathologic hypertrophy is sufficiently intense and prolonged. Cardiac hypertrophic responses involve a reversion to the fetal gene program.¹⁷ Re-expression of atrial natriuretic factor (ANF) and the fetal isoforms of the sarcomeric proteins are demonstrated in hypertrophied myocardium. Recapitulation of fetal genes probably is an adaptive response to relatively hypoxic environment. Energy metabolic pathway also reverts to a fetal pattern during development of cardiac hypertrophy and failure.^{5–7} The fetal heart primarily uses glucose and pyruvate as substrates for ATP production, and a rapid transition to fatty acid β -oxidation occurs postnatally.¹⁸ During the development of cardiac hypertrophy and in the failing heart, a transition of energy substrate utilization occurs with reduced fatty acid oxidation and increased glucose utilization.^{5–7} Recchia *et al.* demonstrated in an animal model of heart failure by rapid ventricular pacing that fatty acid uptake was reduced and glucose uptake was complementarily increased in the failing heart.⁸

Long-chain acyl-CoA synthetase (LCAS) is the cytosolic enzyme, which catalyzes the formation of fatty acyl-coenzyme A thioesters from fatty acids entering the cardiomyocyte (Fig. 7). Carnitine palmitoyltransferase I (CPT I) is the mitochondrial membrane-bound protein, which catalyzes the import of long-chain acyl-CoA into mitochondria. Long-chain acyl-CoA dehydrogenase (LCAD), medium-chain acyl-CoA dehydrogenase (MCAD), and long-chain 3-OH acyl-CoA dehydrogenase (LCHAD) are mitochondrial enzymes for the fatty acid β -oxidation. It has been demonstrated that gene expressions of LCAS, CPT, LCAD, MCAD, and LCHAD were decreased in animal models of cardiac hypertrophy and failure by pressure-overload.^{5,6} In addition, Sack *et al.* reported that protein expression and enzyme activity of MCAD were depressed in human failing myocardium with end-stage heart failure.⁷ These biochemical changes may account for the reduced fatty acid utilization in the failing myocardium.

Possible Mechanisms for Faster Washout of ¹²³I-BMIPP in Heart Failure

Kataoka *et al.* have recently demonstrated that impaired fatty acid metabolism can be detected with ¹²³I-BMIPP in a dog

FIG. 7 A schema for BMIPP kinetics and long-chain fatty acid metabolism in the cardiomyocyte. FA = fatty acid, FAT = fatty acid translocase, FABP = fatty acid binding protein, LCAS = long-chain acyl-CoA synthetase, CPT = carnitine palmitoyltransferase, LCAD = long-chain acyl-CoA dehydrogenase, MCAD = medium-chain acyl-CoA dehydrogenase, LCHAD = long-chain 3-OH acyl-CoA dehydrogenase.

heart failure model by rapid ventricular pacing.⁹ They showed that myocardial ^{123}I -BMIPP uptake was reduced and washout of ^{123}I -BMIPP from the myocardium was faster in heart failure. In clinical studies, we have reported that metabolic abnormalities in human heart failure can be detected as decreased myocardial ^{123}I -BMIPP uptake and enhanced washout of ^{123}I -BMIPP from the myocardium.¹⁰ The washout rate from 30 min early to 4 h delayed images was faster in patients with heart failure than in normal controls. In the present study, ^{123}I -BMIPP washout from 6 min to 30 min was also faster in patients with heart failure compared with normal controls. The precise mechanism for enhanced washout of ^{123}I -BMIPP in heart failure is still unknown. The BMIPP kinetics and long-chain fatty acid metabolism in the cardiomyocyte are shown in Figure 7.^{5, 6, 12, 19} Some possible mechanisms for decreased uptake and enhanced washout of ^{123}I -BMIPP in heart failure are suggested. First, depressed expression of LCAS in the failing heart may contribute to impaired cellular retention of ^{123}I -BMIPP;^{5, 6} BMIPP becomes hydrophilic and can be held in the cardiomyocyte by converting to acyl-CoA with LCAS.¹² Therefore, decreased level of LCAS in the failing myocardium may cause the reduced conversion of BMIPP to acyl-CoA and thus impair the retention of BMIPP in the cardiomyocyte.¹⁹ Second, triglyceride turnover is enhanced in the failing heart.^{20, 21} Since BMIPP is partly trapped into triglyceride fraction in the cardiomyocyte,¹² enhanced triglyceride turnover may increase BMIPP washout from the myocardium. Third, the depressed level of fatty acid-binding protein may cause decreased BMIPP uptake and enhanced BMIPP washout in the early phase soon after tracer injection.¹⁹ The fatty acid-binding protein is necessary for BMIPP uptake and retention by the cardiomyocyte.^{22, 23} It has been reported that expression of myocardial fatty acid-binding protein is reduced in the hypertrophied heart induced by pressure overload.²⁴

Angiotensin II and Fatty Acid Metabolism in the Failing Heart

It has been widely accepted that angiotensin II plays a pivotal role in the progression of cardiac hypertrophy and failure.^{2, 3} Recent clinical studies have shown that angiotensin II

receptor blockade improves the prognosis of patients with heart failure.⁴ In the present study, we showed that angiotensin II receptor blockade with candesartan reduced ^{123}I -BMIPP washout in heart failure. These data suggest that the enhanced washout rate of ^{123}I -BMIPP in heart failure is, at least in part, angiotensin II receptor dependent. This is supported by the experimental data showing that angiotensin II enhances lipid hydrolysis in the cardiomyocyte.²⁵ It has been reported that angiotensin-converting enzyme (ACE) inhibition improves ^{123}I -BMIPP uptake in patients with acute myocardial infarction, who had received successful coronary revascularization.²⁶ We and others have also reported that ACE inhibition reduces enhanced ^{123}I -BMIPP washout in heart failure.^{10, 27} Taken together, these data implicate that improvement in fatty acid metabolism may contribute to improved cardiac function and survival by angiotensin II blockade in patients with CHF. Basic experimental studies to support these findings are currently underway in our laboratory.

Technical Considerations and Limitations of the Study

Tracer activity in the blood may affect myocardial tissue clearance rate; however, in the present study, the activity of ^{123}I -BMIPP in the LV cavity were not different between patients with CHF and normal controls. The initial myocardial uptake of ^{123}I -BMIPP was also similar between patients with heart failure and normal controls.

Plasma substrate concentrations affect myocardial fatty acid metabolism. Unfortunately, the data for plasma substrates were not available in the present study. However, patients were examined after overnight fast in resting condition, and plasma levels of glucose, free fatty acids, and lactate were considered to be low. In addition, we have previously reported that myocardial uptake of ^{123}I -BMIPP was not affected by plasma levels of glucose, insulin, and free fatty acids.²⁸

Conclusions

We conclude that the activation of angiotensin II signaling pathway is involved as an intracellular mechanism for en-

hanced ^{123}I -BMIPP washout in heart failure, and that the improvement in fatty acid metabolism may represent a new mechanism for beneficial effects of angiotensin II receptor blockade on cardiac function and survival in patients with heart failure. The ^{123}I -BMIPP washout in the early phase obtained from dynamic SPECT may be a new marker for evaluating the severity of heart failure and effects of medical treatment.

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