

Association between Abnormal Fatty Acid Metabolism and Myocardial Triglyceride Accumulation in Patients with Chronic Heart Failure: A Study Using ^{123}I -BMIPP and ^1H -MRS

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Abstract

Objective

Myocardial energy metabolism is impaired in heart failure (HF), but the in vivo relationship between myocardial triglyceride (MTG) accumulation and fatty acid utilization remains unclear. Proton magnetic resonance spectroscopy (^1H -MRS) quantifies MTG, while iodine-123- β -methyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) scintigraphy assesses myocardial fatty acid uptake and turnover (early heart-to-mediastinum ratio [H/M(e)] and washout rate [WR]). We investigated associations between MTG accumulation and ^{123}I -BMIPP-derived metabolic parameters in chronic HF patients.

Methods

Consecutive chronic HF patients ($n = 33$; mean age 62.8 ± 14.1 years) were prospectively enrolled between September 2020 and January 2024 during a stable phase. All patients underwent ^{123}I -BMIPP SPECT imaging (acquisition at 20 and 180 minutes post-injection) to calculate H/M(e) and WR, and cine cardiac MRI (1.5T) to measure left ventricular (LV) volumes, ejection fraction, and mass. MTG content was quantified by ^1H -MRS.

Results

WR did not correlate with any clinical or imaging parameters. In contrast, H/M(e) was significantly correlated with LV volume ($r = -0.402$, $p = 0.020$) and mass ($r = -0.427$, $p = 0.013$). MTG content was not related to ^{123}I -BMIPP-derived measures or LV function, but correlated significantly with immunoreactive insulin (IRI; $r = 0.641$, $p = 0.0002$) and HOMA-IR ($r = 0.589$, $p = 0.001$). No correlations were found among WR, H/M(e), and MTG.

Conclusions

Comprehensive assessment of myocardial fatty acid metabolism using ^{123}I -BMIPP scintigraphy and ^1H -MRS in patients with chronic heart failure suggested that WR, H/M(e), and MTG may reflect distinct metabolic stages. These parameters provide independent and complementary information and may contribute to a better understanding of heart failure pathophysiology, as well as to diagnostic support and prognostic assessment.

Introduction

Myocardial metabolism is profoundly influenced by obesity, systemic metabolic disorders, and nutritional status, and the underlying mechanisms are highly complex [1]. The heart has exceptionally

high energy demands and consumes large amounts of adenosine triphosphate (ATP); more than approximately 90% of this ATP is generated through mitochondrial oxidative phosphorylation, with the remainder derived from pathways such as glycolysis [2]. In the healthy heart, fatty acids account for approximately 70% of the substrates used for oxidative phosphorylation, while the remaining energy is obtained from the metabolism of glucose, lactate, ketone bodies, and other substrates [3]. This fatty acid–dominant metabolic profile is thought to reflect a prioritization of high efficiency in ATP production.

In contrast, in patients with heart failure, in whom the myocardium exists in a state of relative oxygen insufficiency, oxidative phosphorylation—the central pathway for cardiac energy production—is impaired. This impairment is attributable to a reduction in mitochondrial number and structural abnormalities, as well as decreased expression and activity of enzymes involved in oxidative phosphorylation, resulting in an overall reduction in myocardial ATP availability. In parallel, fatty acid oxidation is also reported to be suppressed through multiple mechanisms, including reduced expression and activity of enzymes involved in fatty acid oxidation, as well as inhibition of fatty acid uptake transporters such as CD36 and carnitine-dependent translocators, including carnitine palmitoyltransferase 1 [2].

Under physiological conditions, the myocardium possesses the capacity to flexibly switch metabolic substrates in response to energy demand and oxygen availability in order to maintain efficient ATP production. In heart failure, a metabolic shift from fatty acid metabolism toward greater reliance on glucose metabolism, which is more oxygen-efficient, is thought to occur [4–6]. However, in patients with heart failure, enhanced sympathetic nervous system activity and alterations in the endocrine milieu promote lipolysis in adipose tissue, leading to elevated circulating levels of free fatty acids (FFAs). The coexistence of excessive FFA supply and chronically impaired fatty acid metabolic capacity facilitates intracellular triglyceride accumulation within cardiomyocytes. Consequently, lipotoxicity may be induced, resulting in cellular membrane damage and ion channel dysfunction, thereby contributing to cardiomyocyte dysfunction [6–8]. Furthermore, insulin resistance, which frequently accompanies the progression of heart failure, not only suppresses glucose metabolism but also disrupts regulatory mechanisms that normally restrain fatty acid utilization, thereby further impairing myocardial energy metabolic efficiency. Collectively, these observations suggest that both impaired fatty acid utilization and myocardial lipid accumulation may contribute to the progression of heart failure pathophysiology, and that their assessment therefore has important clinical implications. Nevertheless, the precise mechanisms underlying these processes and their interrelationships have not yet been fully elucidated.

In recent years, imaging modalities enabling non-invasive assessment of abnormalities in fatty acid metabolism and myocardial lipid accumulation have been increasingly established. Iodine-123- β -methyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) myocardial scintigraphy is a nuclear imaging technique that reflects myocardial fatty acid uptake and utilization kinetics and is useful for detecting abnormalities in fatty acid metabolism [9]. In contrast, proton magnetic resonance spectroscopy (^1H -MRS) is the only non-invasive modality capable of quantifying myocardial triglyceride (MTG) content, thereby allowing direct assessment of myocardial lipid accumulation in the heart [10, 11]. However, the impact of fatty acid metabolic impairment and myocardial lipid accumulation, as detected by these

imaging modalities, on the pathophysiology of heart failure remains incompletely understood, and their interrelationship and clinical significance have yet to be fully elucidated. Therefore, in the present study, we aimed to evaluate the association between abnormalities in fatty acid metabolism and myocardial lipid accumulation in patients with chronic heart failure by performing ^{123}I -BMIPP scintigraphy and ^1H -MRS in close temporal proximity, and to investigate their clinical significance.

Methods

Study design and subjects

This was a prospective study. Among Japanese patients aged ≥ 20 years with stable chronic heart failure who were evaluated between September 2020 and January 2024, those with end-stage renal disease requiring dialysis, prior myocardial infarction, severe valvular heart disease, myocarditis, cardiac amyloidosis, cardiac sarcoidosis, Fabry disease, or hypertrophic cardiomyopathy were excluded. Both male and female patients were enrolled. Of the 43 patients who provided written informed consent, 4 withdrew during the study period, and 6 patients were excluded because MRS could not be performed or due to inadequate image quality. Consequently, a total of 33 consecutive patients were included in the final analysis (Fig. 1). All participants underwent ^{123}I -BMIPP scintigraphy and magnetic resonance imaging (MRI) using a 1.5-T MR scanner. For all subjects, the following clinical data were collected: age, sex, presence of diabetes mellitus, hypertension, dyslipidaemia, and anthropometric measurements (height and body weight). In addition, fasting blood samples were obtained to measure lipid parameters (triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), glucose-related parameters (fasting blood glucose [FBS], fasting immunoreactive insulin [IRI], and glycated haemoglobin [HbA1c]), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as follows:

fasting plasma glucose (mg/dL) $\times$ fasting plasma insulin ($\mu\text{U/mL}$) / 405.

Associations among ^{123}I -BMIPP- and MRS-derived parameters, as well as their relationships with left ventricular functional parameters assessed by MRI and patient background characteristics, were evaluated.

^{123}I -BMIPP Acquisition and Processing

^{123}I -BMIPP imaging was performed using a Symbia S gamma camera system (Siemens AG, Munich, Germany). A dose of 111 MBq of iodine-123- β -methyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) (Nihon Medi-Physics Co. Ltd., Tokyo, Japan) was administered intravenously. Single-photon emission computed tomography (SPECT) images were acquired at two time points: an early image obtained 20 minutes after injection of 111 MBq of ^{123}I -BMIPP and a delayed image obtained 3 hours after injection.

Planar images were acquired for calculation of the heart-to-mediastinum count ratio (H/M ratio). The H/M ratio was calculated using planar images obtained 20 minutes after injection (early phase). SPECT data acquisition was performed using a 180° rotation with 45 projections, an acquisition time of 20 seconds per step, a 64 × 64 matrix size, and a zoom factor of 1.45. An energy window centred at 158 keV with a width of 20% was applied. A low- to medium-energy general-purpose (LMEGP) collimator was used.

The acquired SPECT data were prefiltered using a Butterworth filter (cut-off frequency, 0.35 cycles/cm; power factor, 8) and subsequently reconstructed using a ramp filter with 360° filtered back-projection. Polar maps were generated from short-axis images using the Heart Risk View-S software (Nihon Medi-Physics, Tokyo, Japan). The ¹²³I-BMIPP washout rate (WR) was calculated using polar coordinate images obtained at 20 minutes and 3 hours after injection of ¹²³I-BMIPP. For planar image analysis, circular regions of interest (ROIs) were placed over the left ventricular (LV) myocardium and the upper mediastinum to measure myocardial ¹²³I-BMIPP activity. The H/M ratio at 20 min after ¹²³I-BMIPP injection was calculated by dividing the mean counts per pixel in the cardiac ROI by those in the upper mediastinal ROI (H/M(e)).

In addition, the washout rate (WR, %) was calculated using polar maps from the early and delayed images according to the following formula:

$$\text{WR (\%)} = [(\text{count at 20 min}) - (\text{count at 3 h} \times \text{Cf})] / (\text{count at 20 min}) \times 100$$

where $\text{Cf} = 1 / (1/2)^x$, $x = (\text{Td} - \text{Te}) / 13.2$, Td represents the time of delayed imaging, and Te represents the time of early imaging.

CMR Imaging

Cardiac MRI and ¹H-MRS were performed using a MAGNETOM Avanto 1.5-Tesla MRI system (Siemens Medical Solution, Erlangen, Germany). All participants were examined in the supine position at rest, with an abdominal belt applied over the upper abdomen to minimise respiratory motion. LV functional and morphological parameters were analysed on a separate workstation using dedicated software (Argus; Siemens Medical Systems, Erlangen, Germany). Endocardial and epicardial borders of the LV were manually traced on short-axis cine images obtained at end-diastole and end-systole. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and stroke volume (SV) were calculated using the Simpson method. In addition, peak LV ejection and filling rates were automatically derived from the LV volume–time curves.

To quantify myocardial triglyceride (TG) content, a voxel measuring 10 × 10 × 20 mm³ was positioned within the interventricular septum on cine dynamic images. Water and lipid spectra were acquired using the point-resolved spectroscopy (PRESS) technique with a repetition time (TR) of at least 4,000 ms and an echo time (TE) of 30 ms.

The myocardial TG signal was obtained at 1.4 ppm from water-suppressed spectra, whereas the water signal was obtained at 4.7 ppm from spectra acquired without water suppression. The areas under the curves of the water and lipid peaks were quantified using a standard linear fitting method (Siemens Syngo Spectroscopy®Siemens Medical Solution). Myocardial TG levels were expressed as the lipid-to-water ratio (%).

Statistical Analysis

Continuous variables with a normal distribution are presented as mean $\pm$ standard deviation, whereas non-normally distributed variables are expressed as median with interquartile range (IQR). Categorical variables are presented as the number of patients (and percentages) in each group. Correlations were analysed using Pearson's correlation coefficient when both variables were normally distributed, and Spearman's rank correlation coefficient when at least one variable was non-normally distributed.

All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. All statistical analyses were performed using JMP pro 14.2 (SAS institute INC., Cary, NC, USA).

Results

Baseline characteristics

A total of 33 patients were included in the analysis. Data for IRI and HOMA-IR were unavailable in 5 patients; therefore, analyses of these parameters were performed in 28 patients. The mean age was 62.8 ± 14.1 years, and men accounted for 70% of the study population.

The mean interval between ^{123}I -BMIPP scintigraphy and MRI was 2 [0–7] days. The mean WR was 5.6 [1.4–13.9] %, H/M(e) ratio was 2.6 ± 0.3 , and MTG assessed by MRS was 1.3 [0.5– 2.1] %. Diabetes mellitus was present in 48% of patients; HbA1c was 6.5 [5.7–6.9] %, and IRI was 5.2 [3.1–8.8] $\mu\text{U/mL}$. Heart failure with reduced ejection fraction (HFrEF) accounted for 79% of the cohort. Atrial fibrillation was observed in 8 of 33 patients. Baseline characteristics of the patients are summarised in Table 1.

Table 1

Study population characteristics (n = 33) BMI, body mass index; LVEF, left ventricle ejection fraction; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; IRI, Immunoreactive Insulin; NT-proBNP, N-terminal pro B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass; MTG, myocardial triglyceride; Avg., average. IRI and HOMA-IR were available in 28 patients.

Age, years	62.8 ± 14.1	¹²³ I-BMIPP	
Male, n (%)	23 (70)	WR (%)	5.6 [1.4–13.9]
BMI, kg/m ²	24.4 ± 5.3	H/M ratio(e)	2.6 ± 0.3
Complication		MRI	
Hypertension, n (%)	18 (55)	LVEDV (mL)	170.2 ± 63.1
Diabetes mellitus, n (%)	16 (48)	LVEDVI	98.7 ± 34.0
Dyslipidemia, n (%)	18 (55)	LVESV (mL)	126.9 ± 61.1
NYHA		LVESVI	73.5 ± 35.1
NYHA I-II	28 (85)	SV (mL)	40 [32.5–51.1]
NYHA III-IV	5 (15)	SVI	25.3 ± 8.5
Baseline laboratory findings		LVEF (%)	23.6 [18.5–35.6]
HDL (mg/dL)	48.1 ± 11.5	LV mass (g)	119.7 ± 45.1
LDL (mg/dL)	108.0 ± 30.1	LV mass index	69.2 ± 21.1
TG (mg/dL)	99 [80.5–134.5]	MTG (%)	1.3 [0.5–2.1]
FBS (mg/dL)	94 [87–117]	Echography	
HbA1c (%)	6.5 [5.7–6.9]	LVEDV (mL)	173.9 ± 61.1
IRI (μU/mL) (n = 28)	5.2 [3.1–8.8]	LVESV (mL)	121.0 ± 57.1
HOMA-IR (n = 28)	1.2 [0.9–2.1]	e'(avg.)	5.9 [4.4–7.7]
NT-proBNP (ng/L)	724 [388–2640]	E/e'(avg.)	12.2 ± 3.7
HFrEF, n (%)	26 (79)	LVEF (%)	30 [24–38]

Correlation between WR and clinical parameters

Correlations between the WR and various clinical parameters are shown in Table 2. WR showed no significant correlations with age, body mass index (BMI), MRI-derived parameters, or laboratory measurements.

Table 2
Association between WR and all parameters (n = 33)

Age (y.o)	r	p value		r	p value
	0.136	0.450	MRI		
BMI (kg/m ²)	0.137	0.448	LVEDV (mL)	0.074	0.681
Complication			LVEDVI	0.036	0.844
Hypertension, n (%)	0.194	0.278	LVESV (mL)	0.082	0.651
Diabetes mellitus, n (%)	0.194	0.278	LVESVI	0.047	0.795
Dyslipidemia, n (%)	0.099	0.582	SV (mL)	-0.002	0.993
Baseline laboratory findings			SVI	-0.032	0.858
HDL (mg/dL)	0.199	0.266	LVEF (%)	-0.002	0.991
LDL (mg/dL)	0.015	0.934	LV mass (g)	0.007	0.968
TG (mg/dL)	-0.094	0.603	LV mass index	-0.038	0.832
FBS (mg/dL)	0.069	0.704	MTG (%)	0.287	0.105
HbA1c (%)	0.082	0.648	Echography		
IRI (μU/mL) (n = 28)	-0.105	0.594	LVEDV (mL)	0.102	0.571
HOMA-IR (n = 28)	-0.108	0.583	LVESV (mL)	0.061	0.734
NT-proBNP (ng/L)	-0.260	0.144	e'(avg.)	-0.214	0.240
¹²³ I-BMIPP			E/e'(avg.)	0.241	0.183
H/M ratio (e)	0.211	0.238	LVEF (%)	0.032	0.860
BMI, body mass index; LVEF, left ventricle ejection fraction; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; IRI, Immunoreactive Insulin; NT-proBNP, N-terminal pro B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass; MTG, myocardial triglyceride; Avg., average. IRI and HOMA-IR were available in 28 patients. Pearson correlation coefficients were used for normally distributed variables, and Spearman rank correlation coefficients were used for non-normally distributed variables.					

Correlation between early H/M ratio and clinical parameters

Correlations between H/M(e) and various clinical parameters are shown in Table 3. H/M(e) showed significant correlations with age (r = 0.356, p = 0.042), LVEDV (r=-0.417, p = 0.016), LVEDV index (LVEDVI) (r=-0.402, p = 0.020), LVESV (r=-0.362, p = 0.038), LV mass (r=-0.400, p = 0.021), and LV mass index

($r=-0.427$, $p = 0.013$) as measured by MRI, as well as LVEDV(TTE) ($r=-0.429$, $p = 0.013$), LVESV(TTE) ($r=-0.446$, $p = 0.009$), and LVEF ($r = 0.353$, $p = 0.044$) as assessed by transthoracic echocardiography.

Table 3
Association between H/M(e) and all parameters (n = 33)

Age (y.o)	r	p value		r	p value
	0.356	0.042	MRI		
BMI (kg/m ²)	-0.103	0.569	LVEDV (mL)	-0.417	0.016
Complication			LVEDVI	-0.402	0.020
Hypertension, n (%)	0.311	0.078	LVESV (mL)	-0.362	0.038
Diabetes mellitus, n (%)	0.099	0.583	LVESVI	-0.342	0.052
Dyslipidemia, n (%)	0.311	0.078	SV (mL)	-0.235	0.188
Baseline laboratory findings			SVI	-0.342	0.052
HDL (mg/dL)	0.104	0.563	LVEF (%)	0.263	0.139
LDL (mg/dL)	-0.080	0.656	LV mass (g)	-0.400	0.021
TG (mg/dL)	-0.038	0.832	LV mass index	-0.427	0.013
FBS (mg/dL)	0.241	0.192	MTG (%)	0.172	0.340
HbA1c (%)	0.288	0.104	Echography		
IRI (μU/mL) (n = 28)	-0.119	0.545	LVEDV (mL)	-0.429	0.013
HOMA-IR (n = 28)	-0.051	0.797	LVESV (mL)	-0.446	0.009
NT-proBNP (ng/L)	-0.131	0.466	e'(avg.)	0.044	0.811
			E/e'(avg.)	0.058	0.754
			LVEF (%)	0.353	0.044

BMI, body mass index; LVEF, left ventricle ejection fraction; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; IRI, Immunoreactive Insulin; NT-proBNP, N-terminal pro B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass; MTG, myocardial triglyceride; Avg., average. IRI and HOMA-IR were available in 28 patients. Pearson correlation coefficients were used for normally distributed variables, and Spearman rank correlation coefficients were used for non-normally distributed variables.

Correlation between MTG and clinical parameters

Correlations between MTG and various clinical parameters are shown in Table 4. MTG showed no significant correlations with age, BMI, or MRI-derived parameters, but demonstrated significant correlations with circulating IRI ($r = 0.641$, $p = 0.0002$) and HOMA-IR ($r = 0.589$, $p = 0.001$).

Table 4
Association between MTG and all parameters (n = 33)

Age (y.o)	r	p value		r	p value
	-0.251	0.159	MRI		
BMI (kg/m ²)	0.008	0.966	LVEDV (mL)	-0.166	0.356
Complication			LVEDVI	-0.199	0.266
Hypertension, n (%)	-0.151	0.402	LVESV (mL)	-0.200	0.265
Diabetes mellitus, n (%)	0.061	0.734	LVESVI	-0.220	0.219
Dyslipidemia, n (%)	-0.151	0.402	SV (mL)	0.105	0.562
Baseline laboratory findings			SVI	0.111	0.538
HDL (mg/dL)	0.051	0.777	LVEF (%)	0.270	0.129
LDL (mg/dL)	0.173	0.335	LV mass (g)	-0.229	0.200
TG (mg/dL)	0.258	0.147	LV mass index	-0.328	0.063
FBS (mg/dL)	0.141	0.449	Echography		
HbA1c (%)	-0.166	0.357	LVEDV (mL)	-0.239	0.180
IRI (μ U/mL) (n = 28)	0.641	0.0002	LVESV (mL)	-0.331	0.060
HOMA-IR (n = 28)	0.589	0.001	e'(avg.)	0.119	0.517
NT-proBNP (ng/L)	-0.270	0.129	E/e'(avg.)	-0.272	0.132
			LVEF (%)	0.294	0.096
BMI, body mass index; LVEF, left ventricle ejection fraction; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; IRI, Immunoreactive Insulin; NT-proBNP, N-terminal pro B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass; Avg., average. IRI and HOMA-IR were available in 28 patients. Pearson correlation coefficients were used for normally distributed variables, and Spearman rank correlation coefficients were used for non-normally distributed variables.					

Correlations among WR, H/M(e), and MTG

No significant correlations were observed among WR, H/M(e), and MTG (WR vs. H/M(e): $r = 0.211$, $p = 0.238$; WR vs. MTG: $r = 0.287$, $p = 0.105$; H/M(e) vs. MTG: $r = 0.172$, $p = 0.340$).

Representative Case

Case 1

A 73-year-old woman with no notable past medical history was referred to our hospital for first-onset heart failure. After medical treatment and stabilization, transthoracic echocardiography revealed reduced LVEF 23%. Coronary angiography showed no significant coronary artery stenosis. The WR was 14.7%, and the H/M(e) was 2.17.

Cardiac MRI demonstrated left ventricular dilatation and increased myocardial mass, with LVEDV index of 97.6 mL/m², LVESV index of 75.3 mL/m², and LV mass index of 105.3 g/m². MTG was 1.16%, which was within the normal range (Fig. 2).

Case 2

A 62-year-old man with a history of diabetes mellitus and dyslipidaemia was referred to our hospital for his first episode of heart failure in 2007. Thereafter, serial transthoracic echocardiography demonstrated progressive left ventricular systolic dysfunction (LVEF 17%), and he was hospitalized for decompensated heart failure in 2021. Coronary angiography revealed no significant coronary artery stenosis. The HOMA-IR, indicating insulin resistance, was 3.0. During the stable phase, WR was 10.0%, and H/M(e) was 2.28. On cardiac MRI, LVEDV index was 104.8 mL/m², LVESV index was 87.5 mL/m², and LV mass index was 54.6 g/m². MTG was elevated at 2.34%, suggesting MTG accumulation (Fig. 3).

Discussion

In the present study, we simultaneously performed ¹²³I-BMIPP scintigraphy and ¹H-MRS during the stable phase of chronic heart failure to visualize myocardial fatty acid metabolism, which represents the primary energy source of the heart, and to investigate the clinical significance of imaging-based assessment of fatty acid metabolic dynamics in patients with heart failure. As a result, the present study demonstrated the following findings.

- (1) The WR derived from ¹²³I-BMIPP showed no significant correlations with any patient characteristics or clinical parameters.
- (2) H/M(e) was significantly correlated with age, LVEDV, LVEDV index, LVESV, LV mass, and LV mass index measured by MRI, as well as with LVEDV, LVESV, and LVEF assessed by transthoracic echocardiography.
- (3) MTG quantified by ¹H-MRS showed significant correlations with serum insulin levels and HOMA-IR, an index of insulin resistance.

(4) No significant correlations were observed among WR and H/M(e) measured by ^{123}I -BMIPP, or MTG measured by ^1H -MRS.

In the present study, WR derived from ^{123}I -BMIPP showed no significant correlations with any patient-related parameters. After myocardial uptake, ^{123}I -BMIPP enters cardiomyocytes following kinetics similar to those of free fatty acids and is subsequently incorporated predominantly into the intracellular lipid pool as storage-form fatty acids, such as triglycerides. Thereafter, ^{123}I -BMIPP undergoes lipolysis and is transported into mitochondria via the carnitine shuttle, in a manner analogous to long-chain fatty acids. Under physiological conditions, fatty acids are utilized for energy production through mitochondrial β -oxidation. However, ^{123}I -BMIPP contains a methyl group at the β -position, which makes it resistant to β -oxidation. As a result, ^{123}I -BMIPP remains within cardiomyocytes for a prolonged period as a storage-form fatty acid. Therefore, the WR of ^{123}I -BMIPP is considered to primarily reflect the degradative capacity of myocardial metabolism acting on ^{123}I -BMIPP once it has been incorporated into the triglyceride pool.

Regarding abnormalities in triglyceride degradation, a disease entity known as triglyceride deposit cardiomyovasculopathy (TGCV) has been proposed in recent years. TGCV is characterized by intracellular metabolic dysfunction of long-chain fatty acids, leading to lipotoxicity caused by excessive accumulation of triglycerides and concomitant energy failure due to insufficient availability of long-chain fatty acids for energy production. This condition is associated with a poor prognosis, with a reported 5-year survival rate of 71.8% [12].

TGCV is classified into primary and idiopathic forms. In primary TGCV, the underlying etiology is a genetic deficiency of adipose triglyceride lipase (ATGL), an essential enzyme for intracellular triglyceride hydrolysis. Impaired triglyceride degradation results in excessive myocardial triglyceride infiltration, which markedly compromises cardiac function.

In contrast, the number of patients with idiopathic TGCV is estimated to be approximately 40,000–50,000 in Japan; however, many aspects of its pathogenesis, mechanisms of disease progression, and prevalence among patients with heart failure remain unclear [13]. In both primary and idiopathic TGCV, WR is markedly reduced, and because this feature has not been reported in conditions other than TGCV, a WR of $< 10\%$ has been established as an essential diagnostic criterion [14]. In addition, it has been reported that WR does not correlate with serum triglyceride levels or other patient-related parameters.

In the present study, WR was not associated with serum triglyceride levels or other patient-related background factors, a finding that is consistent with previous reports. In patients with heart failure, prior studies have reported both increased and decreased WR values [12, 15–17], and thus its behavior has not been consistently characterized. This inconsistency may be attributable to the fact that WR reflects abnormalities in triglyceride degradation capacity independent of heart failure severity.

In our study, WR tended to be lower than values considered within the normal range ($6.9 \pm 8.6\%$). Moreover, in our previous report, approximately 66% of patients with heart failure of unknown etiology exhibited a $WR \leq 10\%$, suggesting that patients with impaired triglyceride degradation may be more prevalent than previously assumed. In addition, our prior study demonstrated that WR was a significant predictor of prognosis [17]. Therefore, further investigation is warranted to clarify the clinical significance of WR in patients with heart failure.

In contrast, in the present study, H/M(e) showed significant correlations with age and with LVEDV, LVEDV index, LVESV, LV mass, and LV mass index measured by MRI, as well as with LVEDV, LVESV, and LVEF assessed by transthoracic echocardiography. Negative correlations were observed between H/M(e) and LVEDV, LVESV, and LV mass, indicating that lower H/M(e) values were associated with greater left ventricular volumes.

The clinical significance of the H/M ratio has not been extensively investigated. However, animal studies have suggested that early myocardial uptake of ^{123}I -BMIPP reflects myocardial ATP content [18, 19]. In heart failure, the myocardium is in an energy-deficient state, which is largely attributed to mitochondrial dysfunction, particularly abnormalities in metabolic pathways involved in ATP production and impaired oxygen supply [2]. At present, most human studies investigating myocardial energy metabolic abnormalities in heart failure have relied on phosphorus magnetic resonance spectroscopy (^{31}P -MRS), using the phosphocreatine-to-ATP ratio (PCr/ATP ratio) as an index. Previous studies employing this approach have demonstrated that myocardial ATP levels tend to decline with the progression of heart failure, and that the degree of ATP depletion correlates with New York Heart Association (NYHA) functional class and systolic function [1, 20, 21].

In contrast, left ventricular volume and left ventricular mass have been frequently reported to be associated with the presence and severity of heart failure. An increase in left ventricular mass has been shown to be independently associated with heart failure and other cardiovascular events [22], and patients with higher NT-proBNP levels have been reported to exhibit larger LVEDV, LVESV, and LV mass [23]. Although the underlying mechanisms have not been fully elucidated, myocardial fibrosis and scar formation secondary to myocardial injury, as well as impaired myocardial perfusion, have been proposed as contributing factors [22]. Taken together with these previous reports, the observed negative correlation between H/M(e) and LVEF in the present study suggests that hearts with larger left ventricular volumes and mass—namely, those with advanced left ventricular remodeling—may exhibit impaired mitochondrial function. This mitochondrial dysfunction may, in turn, lead to reduced ATP production capacity and contribute to the progression of left ventricular systolic dysfunction, which is indirectly reflected by lower H/M(e) values.

At present, there is no established method for directly assessing myocardial ATP concentration in vivo. Therefore, if an imaging-based parameter such as H/M(e) derived from ^{123}I -BMIPP scintigraphy reflects myocardial ATP production capacity, its clinical significance would be substantial.

With regard to MTG quantified by ^1H -MRS, the present study demonstrated significant correlations with IRI and with HOMA-IR, an index of insulin resistance. The concept of diabetic cardiomyopathy has been proposed since the 1970s, describing a condition that develops independently of other cardiovascular risk factors such as coronary artery disease and hypertension and leads to myocardial dysfunction as a consequence of progressive hyperglycemia. The pathogenesis of diabetic cardiomyopathy is thought to involve impairment of insulin signaling pathways associated with insulin resistance and hyperinsulinemia, enhanced formation of advanced glycation end products (AGEs) driven by hyperglycemia, and increased fatty acid supply under diabetic conditions. In addition, upregulation of peroxisome proliferator-activated receptor- α (PPAR- α) in the myocardium promotes triglyceride accumulation, which is considered to contribute to myocardial dysfunction [24]. Myocardial lipid accumulation has also been reported to be increased in patients with obesity and diabetes compared with healthy individuals [25, 26]. In patients with heart failure, myocardial substrate utilization is generally characterized, particularly in the early stages, by reduced β -oxidation and decreased fatty acid utilization, accompanied by a compensatory increase in glucose metabolism and reduced fatty acid uptake. However, in advanced stages of heart failure, hyperinsulinemia frequently develops and exacerbates systemic insulin resistance [1]. Under insulin-resistant conditions, myocardial glucose uptake is impaired, and intracellular insulin signaling is disrupted, leading to increased activity of enzymes involved in fatty acid metabolism and a preferential shift toward lipid utilization as the myocardial energy substrate. This metabolic shift increases myocardial oxygen consumption and promotes excessive intracellular triglyceride accumulation, resulting in lipotoxicity [25]. Lipotoxicity-induced cardiomyocyte apoptosis has been implicated as a mechanism contributing to myocardial dysfunction [8].

The significant association observed between insulin resistance and MTG in the present study may be attributable to these pathophysiological mechanisms. In contrast, the lack of association between MTG and the presence of diabetes or BMI suggests that myocardial lipid accumulation in heart failure is influenced by a complex interplay of factors, including disease severity, the underlying systemic metabolic milieu, and inflammatory processes. These findings indicate that myocardial triglyceride accumulation based on insulin resistance in heart failure is not solely attributable to cardiomyopathy related to diabetes or obesity, but rather reflects a broader metabolic derangement intrinsic to heart failure.

In the present study, no significant correlations were observed among WR, H/M(e), and MTG. Based on the underlying mechanisms of ^{123}I -BMIPP scintigraphy and ^1H -MRS, WR is considered to reflect the capacity for intracellular triglyceride degradation, H/M(e) represents early myocardial fatty acid uptake proportional to myocardial ATP production capacity, and MTG reflects the extent of intracellular triglyceride accumulation. Accordingly, the absence of correlations between ^{123}I -BMIPP-derived WR and H/M(e), as well as between ^{123}I -BMIPP and MRS-derived parameters, is physiologically plausible. Notably, no significant correlation was observed between WR and MTG. Although impaired triglyceride degradation and the resulting reduction in fatty acid utilization may promote a positive feedback loop of fatty acid uptake, thereby facilitating myocardial lipid accumulation, the actual extent of myocardial fatty

acid accumulation may be determined by a balance between supply and demand of fatty acids, which is influenced by heart failure stage and insulin resistance. Understanding the distinct pathophysiological significance of each imaging-derived parameter may enable a multifaceted assessment of the etiology and pathophysiology of heart failure. Further studies are warranted to elucidate the clinical implications of each parameter.

Limitation

This study has several limitations. First, this was a single-center, cross-sectional study with a relatively small sample size, and the results should therefore be interpreted with caution. Second, owing to the limited number of participants, we were unable to adequately distinguish between patients with HFrEF and those with heart failure with preserved ejection function (HFpEF), and potential differences in metabolic profiles between these phenotypes may not have been fully captured in the present analysis.

Conclusion

Using ^{123}I -BMIPP scintigraphy and ^1H -MRS to comprehensively evaluate myocardial fatty acid metabolism in patients with chronic heart failure, we demonstrated that WR, H/M(e), and MTG reflect distinct metabolic stages, including triglyceride degradation capacity, ATP production capacity, and myocardial lipid accumulation associated with insulin resistance, respectively. These parameters provide complementary and independent information and may be useful for improving the understanding of heart failure pathophysiology, as well as for diagnostic support and prognostic assessment.

Declarations

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Board of our hospital. The study was registered with H16-0224.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors confirm that written informed consent was obtained from all individual participants for publication of the images and associated data.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

S.F. received a research grant from Nihon Medi-Physics Co., Ltd. The other authors have no relationships with industry relevant to the content of this article.

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Figures

Fig. 1

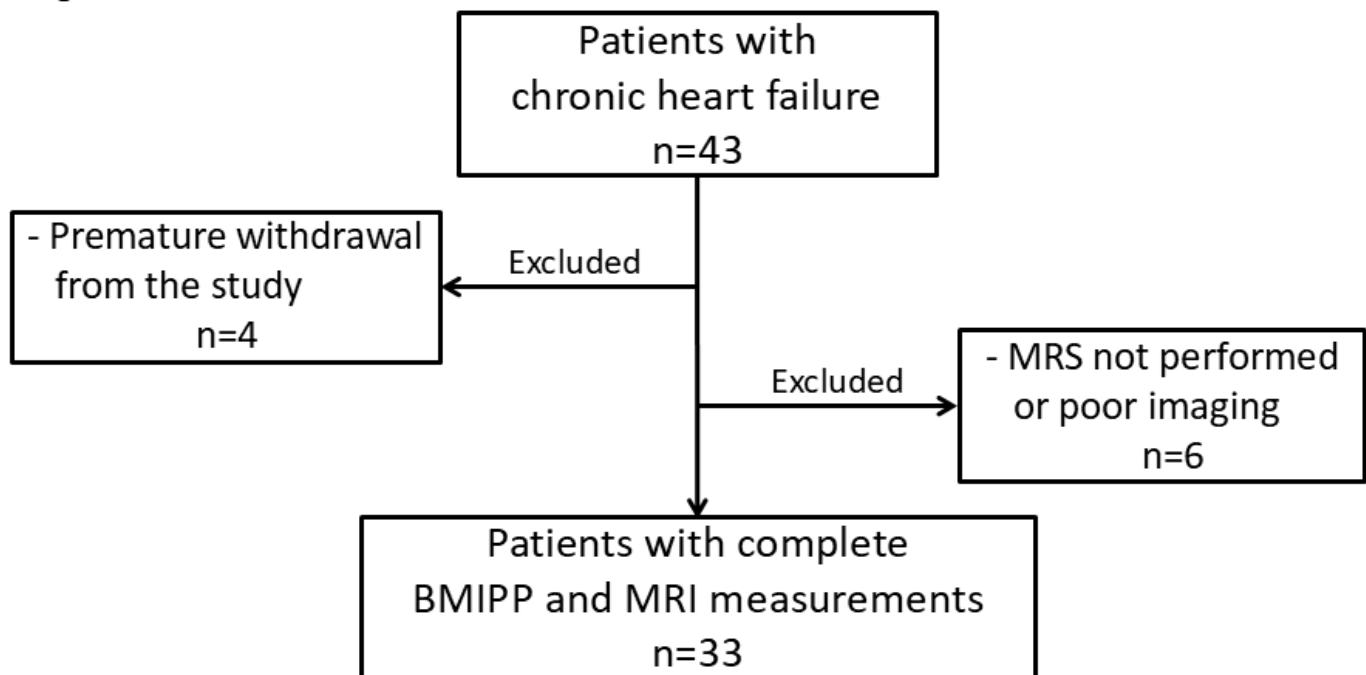


Figure 1

Flow chart of target patients

Among Japanese patients aged ≥ 20 years with stable chronic heart failure who were evaluated between September 2020 and January 2024. Of the 43 patients who provided written informed consent, 4 withdrew during the study period, and 6 patients were excluded because MRS could not be performed or due to inadequate image quality. Consequently, a total of 33 consecutive patients were included in the final analysis

Fig. 2

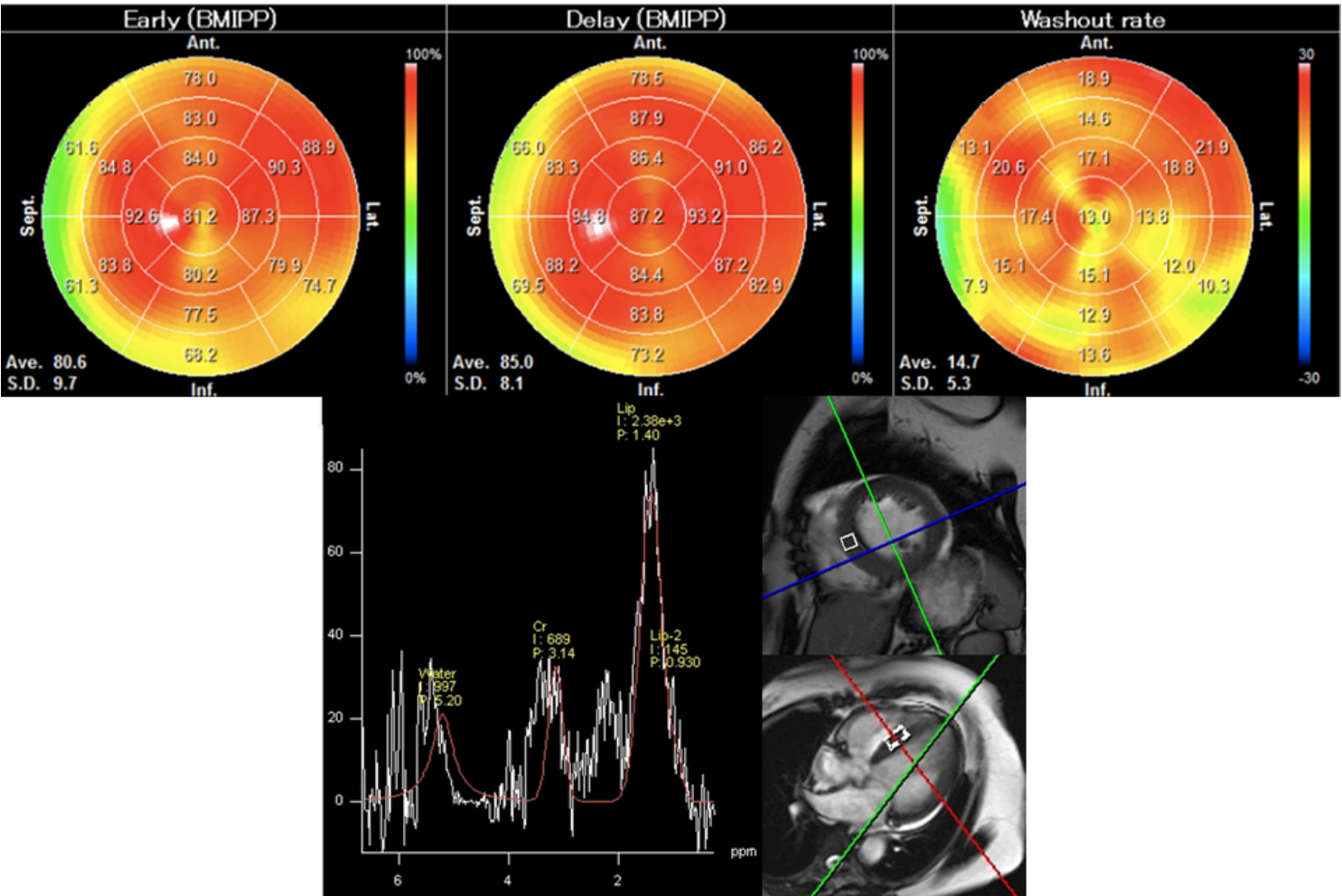


Figure 2

Representative myocardial fatty acid metabolic imaging findings in Case 1

Upper panels show early and delayed iodine-123 β -methyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) single-photon emission computed tomography (SPECT) images for evaluation of myocardial fatty acid uptake and washout rate (WR). Lower panels show proton magnetic resonance spectroscopy (^1H -MRS) of the left ventricular myocardium used to quantify myocardial triglyceride (MTG) content

Fig. 3

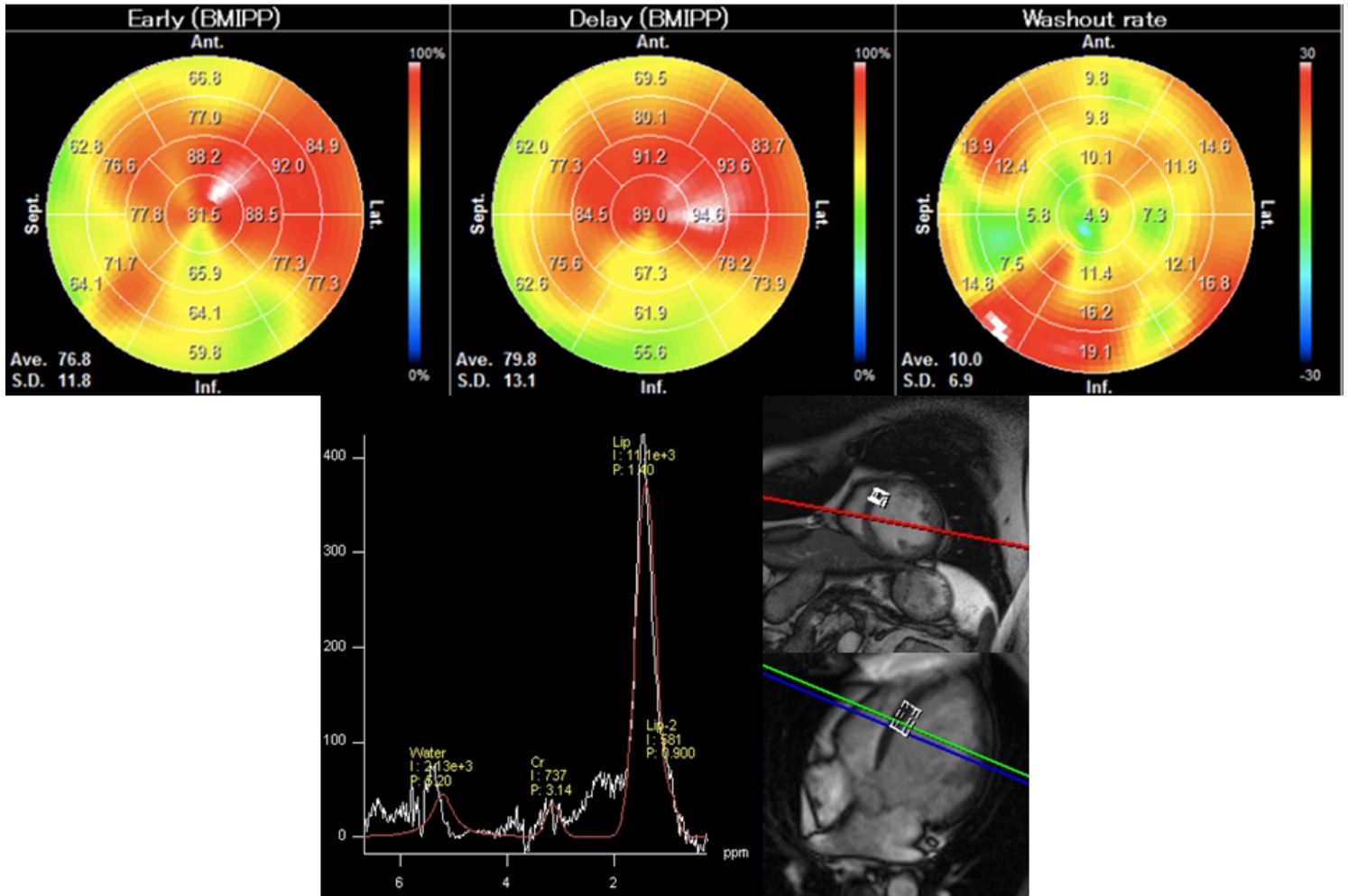


Figure 3

Representative myocardial fatty acid metabolic imaging findings in Case 2

Upper panels show early and delayed ^{123}I -BMIPP SPECT images assessing myocardial fatty acid uptake and washout characteristics. Lower panels show ^1H -MRS of the left ventricular myocardium for assessment of MTG content