Role of ^{123}I-BMIPP and serum B-type natriuretic peptide for the evaluation of patients with heart failure

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INTRODUCTION Myocardial scintigraphy with ^{123}I-15-(p-iodophenyl)-3-methyl pentadecanoic acid (^{123}I-BMIPP) is used to evaluate impaired fatty acid metabolism. B-type natriuretic peptide (BNP), which is secreted by the ventricular myocardium on stretching and/or pressure overload, is a useful cardiac biomarker. This study aimed to evaluate the usefulness of ^{123}I-BMIPP imaging and serum BNP levels in patients with heart failure (HF).

METHODS 113 patients with HF were enrolled. There were 68 patients with ischaemic heart disease (IHD) and 22 with overt HF. Cardiac scintigraphy was performed 7 ± 3 days after admission, and heart-to-mediastinum (H/M) count ratios on early and delayed images and washout rates (WR) of ^{123}I-BMIPP were recorded. Serum BNP levels were recorded on the day of ^{123}I-BMIPP imaging. The ejection fraction (EF) was calculated just before cardiac scintigraphy using conventional echocardiography.

RESULTS The mean BNP level and EF were 282 pg/mL and 47%, respectively, with significant correlation between them. The mean H/M count ratios on early and delayed images were 2.29 and 1.93, respectively, showing significant positive correlations with EF ($r = 0.31$, $p = 0.0006$). The WR was significantly correlated with EF ($r = -0.36$, $p < 0.0001$) and BNP levels ($r = 0.33$, $p = 0.003$), and mean WR was significantly higher in patients with overt HF compared to those without ($p < 0.001$). Patients with IHD had significantly higher EFs than those with non-IHD ($p = 0.03$).

CONCLUSION The evaluation of impaired myocardial metabolism using ^{123}I-BMIPP scintigraphy and serum BNP levels appears to be useful for the evaluation of severity of HF.

Keywords: B-type natriuretic peptide, cardiac scintigraphy, heart failure, myocardial fatty acid metabolism
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INTRODUCTION

Heart failure (HF) is not an isolated clinical entity, but a complex clinical syndrome resulting from structural and/or functional cardiac disorder that adversely affects the ventricular filling and/or ejection of blood.[1] Glucose and free fatty acids are the major energy sources of the myocardium. Long chain fatty acids are rapidly metabolised by β-oxidation and are designated as the principal energy source for the normal myocardium. However, in ischaemia, the main energy substrate changes from free fatty acids to glucose as the energy metabolism shifts to an anaerobic environment.[2] The radiolabelled fatty acid, ^{123}I-15-(p-iodophenyl)-3-methyl pentadecanoic acid (^{123}I-BMIPP) is widely used in the imaging of myocardial aerobic metabolism,[3] and this sophisticated imaging technique has been playing a promising role in the assessment of the pathophysiology and evolution of HF.[2] At the same time, new biomarkers for evaluating cardiac diseases are being identified by molecular cell biology studies. B-type natriuretic peptide (BNP), which is produced by the ventricular myocytes and triggered by increased volume and transluminal pressure, is one such cardiac biomarker.[4] Left ventricular (LV) pressure and/or volume overload stimulates the production and release of BNP, and therefore, increased plasma levels of BNP reflect a common pathology in patients with LV dysfunction irrespective of aetiology.[5]

The purpose of this study was two-fold: (1) to unravel the role of planar images and the washout rate (WR) of ^{123}I-BMIPP from a polar map in predicting the severity of HF due to either ischaemic heart disease (IHD) or non-ischaemic heart disease (NIHD); and (2) to ascertain the relationship between various parameters of ^{123}I-BMIPP cardiac scintigraphy and BNP levels when evaluating patients with HF.

METHODS

A total of 113 consecutive patients who were admitted with cardiac diseases associated with different grades of HF according to the New York Heart Association (NYHA) functional classification between January and December 2007 were enrolled in the study. Patients who presented with impaired renal function (serum creatinine > 2 mg/dL) and cardiogenic shock were excluded. Informed written consent was obtained from all patients prior to cardiac scintigraphy, and the protocol was approved by the institution's human research committee. All patients were clinically managed according to American College of Cardiology and American Heart Association guidelines.[1,6,7] Cardiac scintigraphy was performed on Day 7 ± 3 of admission. The serum BNP level was ascertained serially using the chemiluminescent enzyme immunoassay method on admission as well as on the day of cardiac scintigraphy (normal range 0.00–18.4 pg/mL).

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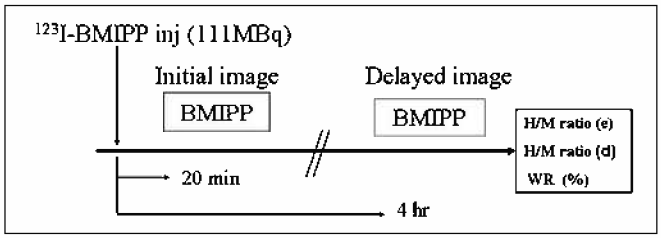

Fig. 1 Cardiac scintigraphy protocol.

On the day of cardiac scintigraphy, transthoracic echocardiography was performed by an experienced cardiologist to calculate the ejection fraction (EF) by the modified biplane Simpson's method using a Philips Sonos 5500 device (Philips, New York, NY, USA).

Cardiac scintigraphy was performed according to standard protocols using a dual-headed single-photon emission computed tomography (SPECT) gamma camera (ADAC, VERTEX plus EPIC, Houston, TX, USA). A low-energy and general purpose collimator was used, and the energy window for ^{123}I was centred at 160 keV ± 10%. Following an overnight fast and intravenous administration of 111 MBq of ^{123}I-BMIPP radiotracer (Cardiodine 111MBq/0.03–0.01 mg, Nihon Medi-Physics Co Ltd, Tokyo, Japan), early and delayed images were taken at 20 minutes and four hours after dosing, respectively (Fig. 1). Planar images were considered for calculating the heart-to-mediastinum (H/M) count ratio on early [H/M (e)] and delayed [H/M (d)] images. SPECT was acquired in a step-and shoot mode using two detectors (180° rotation) and a matrix size of 64 × 64. A series of contiguous transaxial images of 5.12 mm thickness were reconstructed using the Butterworth filtered back projection algorithm (order 5; cut-off 0.40 cycles pixel) without attenuation or scatter correction. Using the polar map presentation, the WR of ^{123}I-BMIPP was calculated between early and delayed acquisition.

For planar images, the LV ^{123}I-BMIPP activity was measured using a region of interest (ROI) that was placed over the heart and by placing a square ROI over the upper mediastinum. The H/M count ratio was calculated to quantify cardiac ^{123}I-BMIPP uptake as a fraction of the mean count/pixel in the heart with respect to uptake in the upper mediastinum. With the polar coordinate presentations of the early and late images, the over all WR (%) between 20 minutes and four hours after intravenous injection of ^{123}I-BMIPP was calculated using the following equation:

$$\text{WR (\%)} = \frac{\text{Count at 20 min} - \text{Count at 4 hrs}}{\text{Count at 20 min}} \times 100$$

Statistical analysis was performed using the Statistical Package for the Social Sciences version 12 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. The Student's unpaired *t*-test was used to determine significant intergroup differences and the paired *t*-test applied for detecting significant differences among variables in a certain group. Correlations between continuous variables were assessed using linear regression analysis. The analysis of variance (ANOVA) test was used to evaluate significant predictors of overt HF. A p-value < 0.05 was considered to be statistically significant.

Table I. Patient characteristics (n = 113).

Characteristic	Mean ± SD; range
Age (yrs)	67 ± 12; 16–90
Gender (ratio male:female)	78:35
BMI (kg/m²)	24.26 ± 3.50
HbA1C (%)	5.75 ± 0.89
Diabetes mellitus [No. (%)]	29 (32.77)
BNP* (pg/mL)	282 ± 432; 2.3–3,080
Cardiac scintigraphy†	
H/M (e)	2.29 ± 0.29
H/M (d)	1.93 ± 0.28
WR (%)	25.86 ± 9.62
Ejection fraction* (%)	47 ± 13

* On the same day as cardiac scintigraphy. † On Day 7 ± 3 of admission.
SD: standard deviation; BMI: body mass index; BNP: B-type natriuretic peptide; H/M: heart-to-mediastinum count ratio; (e): early image; (d): delayed image; WR: washout rate of ^{123}I-BMIPP

RESULTS

In a group of 113 patients with HF, 78 were men and the mean age of the group was 67 ± 12 (range 16–90) years. 68 patients presented with different forms of IHD, including acute coronary syndrome, acute and/or old myocardial infarction, ischaemic cardiomyopathy and unstable angina pectoris, and 45 presented with different forms of cardiomyopathies, sarcoidosis, arrhythmias and left ventricular hypertrophy. 22 patients presented with overt HF (NYHA class III), while 61 patients presented with NYHA class II disease and the remaining 30 patients presented with NYHA class I disease.

All patients had stable clinical parameters on the day of cardiac scintigraphy, with proper management. Table I presents the characteristics of the patients. The mean BNP level was 282 ± 432 (range 2.3–3,080) pg/mL and the BNP levels were higher in patients with NYHA class III HF (343.45 ± 260.68 pg/mL) than in those without (267.55 ± 464.04 pg/mL), although the difference was not statistically significant. There was a significant negative correlation between BNP levels and EF ($r = -0.42$, $p < 0.00001$) (Fig. 2). The mean BNP level was higher in patients with HF due to NIHD than in those with HF due to IHD (328.47 ± 454.090 pg/mL vs. 255.1 ± 418.06 pg/mL). However, the difference was also not statistically significant.

The myocardial ^{123}I-BMIPP uptake was relatively low, and the mean H/M (e) and H/M (d) ratios were 2.29 ± 0.29 and 1.93 ± 0.28, respectively. The H/M (e) ratio was lower in patients with overt HF than in others (2.22 ± 0.29 vs. 2.32 ± 0.29), and similar results were noted for H/M (d) ratio as well (1.91 ± 0.26 vs. 1.93 ± 0.29). However, the differences were not statistically significant for both H/M (e) and H/M (d). The mean EF was 47% ± 13%, and a significant positive correlation was found between H/M ratios (for both early and delayed images) and EF ($r = 0.31$, $p = 0.0006$) (Figs. 3a & b). EF was significantly higher in patients with IHD than in those with NIHD (49% ± 11% vs. 44% ± 14%;

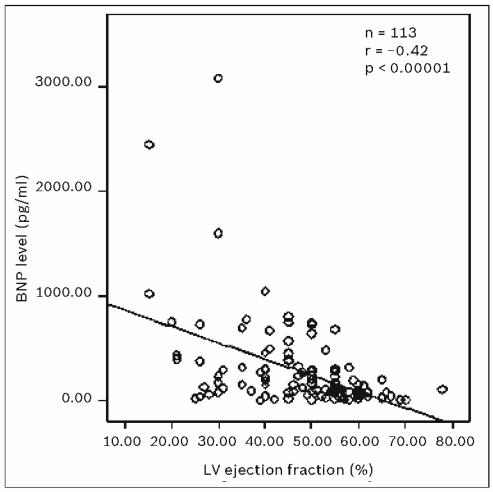

Fig. 2 Linear regression analysis plot shows a strong negative correlation between serum B-type natriuretic peptide levels and ejection fraction.

p = 0.03, 95% confidence interval [CI] 0.249–9.746). There was a significant negative correlation between H/M (e) ratio and serum BNP level (r = −0.24, p < 0.008) (Fig. 3c). However, the difference between the ratios of H/M (e) and H/M (d) of patients with IHD and NIHD was not significant [H/M (e) 2.30 ± 0.27 vs. 2.29 ± 0.33; H/M (d) 1.94 ± 0.27 vs. 1.90 ± 0.04]. The mean WR of ^{123}I-BMIPP was 25.86% ± 9.62%, and the WR in patients with overt HF was significantly higher than in others (29.45% ± 9.57% vs. 25.00% ± 9.48%; p < 0.001, 95% CI −15.83 to −4.48). WR was significantly correlated with EF (r = −0.36, p < 0.0001) (Fig. 4) and serum BNP level (r = 0.33, p = 0.003) (Fig. 5). The results of ANOVA revealed that the presence or absence of ischaemia and WR of ^{123}I-BMIPP were significant predictors of overt HF (Table II). The planar images of ^{123}I-BMIPP imaging of a representative patient are presented in Fig. 6.

DISCUSSION

Approximately 60%–80% of the adenosine triphosphate for myocardial energy is derived from fatty acid oxidation.[2] It is also well known that in patients with myocardial infarction, those with LV dysfunction have a distinctly worse prognosis than those with preserved ventricular function.[8,9] For such patients, studies have reported that ^{123}I-BMIPP is useful not only for the evaluation of LV regional and global systolic functional recovery but also for approximating prognosis.[10,11] In addition, metabolic imaging can potentially differentiate between ischaemic cardiomyopathy and primary dilated cardiomyopathy (DCM) – diseases that share similar features.[2] The present study therefore aimed to ascertain the usefulness of H/M ratios from planar images and the WR of ^{123}I-BMIPP from polar maps when evaluating patients with HF. As patients with HF due to various aetiologies (both IHD and NIHD) were enrolled in the present study, the WR of ^{123}I-BMIPP imaging was deemed to be a relatively easier parameter to choose for evaluating the severity of HF when compared to an interpretation of SPECT images.

We found that H/M ratios and WR values from ^{123}I-BMIPP imaging, along with an assessment of serum BNP levels, could

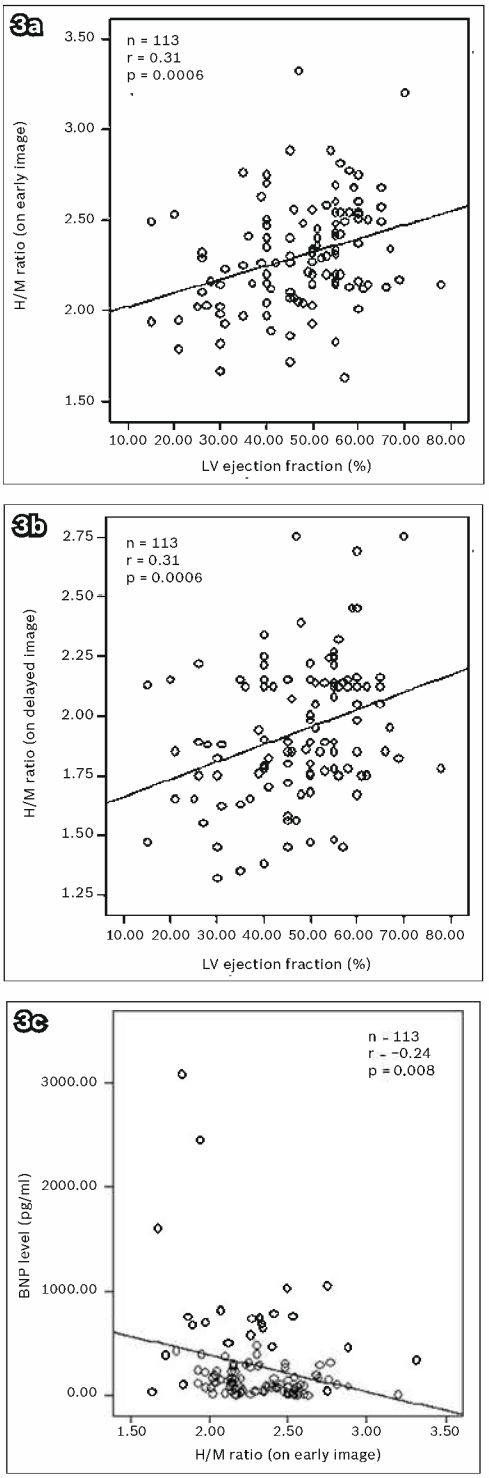

Fig. 3 Linear regression analyses plots show (a) a strong positive correlation between H/M (e) and ejection fraction; (b) a strong positive correlation between H/M (d) and ejection fraction; and (c) a strong negative correlation between H/M (e) and B-type natriuretic peptide level.

be invaluable for evaluating the severity of HF due to IHD and NIHD. Key findings were that the LV EF was significantly correlated with serum BNP level, H/M ratios and the WR of ^{123}I-BMIPP imaging. The serum BNP level was also associated with H/M ratios and the WR of ^{123}I-BMIPP imaging. The EF was significantly higher in patients with IHD than in those with NIHD. The WR of ^{123}I-BMIPP was significantly higher in patients with overt HF than in those with asymptomatic HF. This suggests

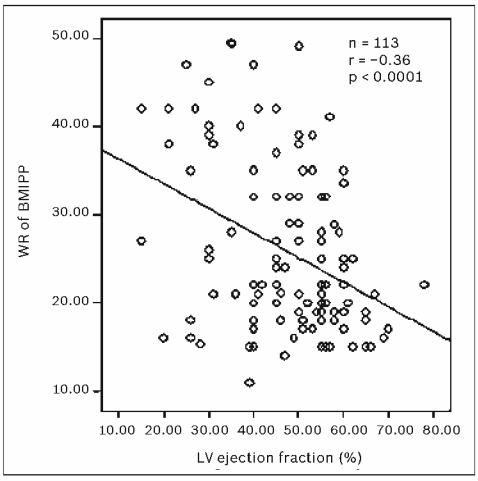

Fig. 4 Linear regression analysis plot shows a strong negative correlation between the washout rate of ^{123}I-BMIPP and ejection fraction.

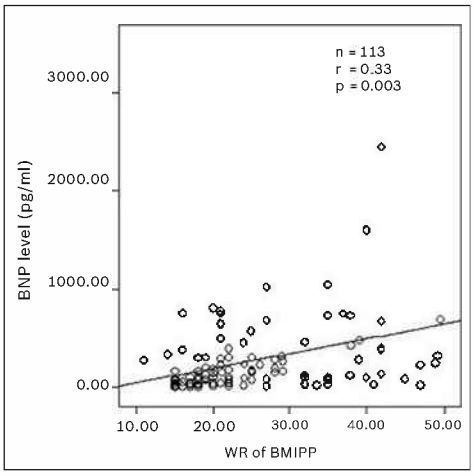

Fig. 5 Linear regression analysis plot shows a strong positive correlation between the washout rate of ^{123}I-BMIPP and serum B-type natriuretic peptide levels.

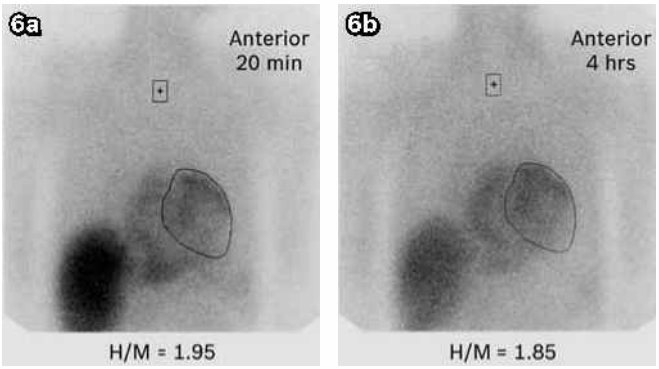

Fig. 6 Planar images of ^{123}I-BMIPP imaging of a patient who presented with severe heart failure from ischaemic cardiomyopathy. The regions of interest placed over the heart and mediastinum show decreased H/M ratios on (a) early; and (b) delayed images. Decreased tracer concentrations are seen in the inferolateral and apical regions.

Table II. Results of univariate regression analysis for predicting overt heart failure (NYHA class III).

Variable	RR (95% CI)	p-value
Age	1.86 (64.87–76.03)	0.175
Gender	6.74 (1.31–1.17)	0.011†
IHD/NIHD	13.61 (1.52–1.92)	0.0001†
BNP level*	0.54 (227.87–459.03)	0.462
H/M (e)	1.62 (2.09–2.35)	0.205
H/M (d)	0.08 (1.79–2.03)	0.771
WR	3.90 (25.20–33.70)	0.05†
HbA1C	0.04 (5.28–6.17)	0.836
EF (%)	12.60 (34.63–43.63)	0.001†

* On the same day as cardiac scintigraphy. † p-value was statistically significant. RR: risk ratio; CI: confidence interval; IHD: ischaemic heart disease; NIHD: non-ischaemic heart disease; BNP: B-type natriuretic peptide; H/M: heart-to-mediastinum count ratio; (e): early image; (d): delayed image; WR: washout rate of ^{123}I-BMIPP; Hb: haemoglobin; EF: ejection fraction.

that EF and WR may be important diagnostic parameters for evaluating the status of patients and also their clinical management irrespective of the aetiology of HF.

Kataoka et al reported that a significant reduction in ^{123}I-BMIPP uptake was associated with a reduction of cardiac output and EF.[12] It was also observed that H/M ratios (on both early and delayed images) were well correlated with EF, and that the correlation of serum BNP levels with EF was significant. These findings suggest that LV systolic dysfunction can be effectively assessed using both BNP as a cardiac biomarker and fatty acid metabolism imaging. We found that EF was higher in patients with IHD than in patients with NIHD. A possible explanation for this finding may be that contractile function is regained more quickly in patients with IHD (e.g. acute myocardial infarction [AMI] or unstable angina) than in those with NIHD (e.g. DCM or cardiac sarcoidosis). Another important feature of metabolic imaging is that it provides physicians with a treatment strategy for patients with chronic HF, as decreased uptake of ^{123}I-BMIPP in patients with DCM may indicate that these patients are poor responders to treatment with β-blockers, and conversely, those with relatively preserved ^{123}I-BMIPP uptakes may respond well to such a treatment regimen.[13]

Nakae et al observed that both H/M (e) and H/M (d) were significantly lower in patients with HF than in controls (H/M (e) 1.96 ± 0.18 vs. 2.30 ± 0.29, $p < 0.01$; HM (d) 1.72 ± 0.15 vs. 1.97 ± 0.21, $p < 0.01$), but that WR was higher in patients with HF than in controls (WR 23.70% ± 5.70% vs. 18.20% ± 6.00%, $p < 0.01$).[14] Both H/M (e) and H/M (d) correlated positively with EF ($p < 0.05$). Furthermore, WR correlated positively with the plasma BNP level. They also showed an earlier HF progression for patients with a lower H/M (e). The results of ^{123}I-BMIPP cardiac scintigraphy in the present study also revealed that mean WR was higher than normal (25.86% ± 9.62% vs. 18.20% ± 6.00%),[14] and that WR was significantly higher in patients with overt HF than in asymptomatic patients (29.45% ± 9.57% vs. 25.00% ± 9.48%).

Another recent study showed that delayed H/M ratios and myocardial WR of ^{123}I-BMIPP enhance the assessment of myocardial fatty acid metabolism disorders in patients with heart diseases with or without full-blown clinical pictures.[15] The delayed H/M ratio was much lower in patients with HF than in those with angina pectoris (AP) (1.93 ± 0.37 vs. 2.21 ± 0.38) and controls (2.47 ± 0.38). The WR in patients with HF and

AP was higher than that in the controls (HF 39.80% ± 12.70%; AP 38.70% ± 11.10%; controls 27.90% ± 10.20%). EF was well correlated with delayed H/M ratio while BNP levels were correlated with WR and delayed H/M ratio.[15] We found similar results in our study.

BNP is synthesised as an inactive prohormone, pro BNP, before it splits into the active hormone and an inactive N-terminal fragment (NT-pro BNP). It has been shown that NT-pro BNP is a strong predictor of mortality in AMI irrespective of sampling time, even up to four weeks after the index event.[16] Studies have also suggested that appropriate treatment and monitoring strategies should be considered for this group of patients, as an elevated BNP level 48 hours following AMI strongly predicts HF or death within the next year.[17,18] Although mortality can be predicted using several clinical and biochemical parameters, BNP (or NT-pro BNP) emerges as the most suitable biomarker for the prediction of fatal complications associated with heart disease. Much like ^{123}I-BMIPP, BNP is also a useful measure for the diagnosis and prognosis of patients with HF as well as for the prognostication of patients with AMI.[19]

A normal serum BNP level has a high negative predictive value (~95%) for the diagnosis of HF.[20] Patients with BNP values of 100–500 pg/mL require management in the emergency room. Therefore, the serum BNP assay may have important roles to play in hospital discharge, in guiding successful treatment and helping to determine prognosis. A high serum BNP level at discharge (> 500 pg/mL) may indicate that the patient would likely be hospitalised again in the near future with decompensated HF.[21] The mean BNP level in our study was 282 ± 432 pg/mL, with relatively higher BNP levels recorded in patients presenting with overt HF and NIHD. However, the H/M ratios of patients with IHD and NIHD showed nearly comparable results. This may indicate that acute ischaemic episodes and other cardiac diseases that lead to long-standing LV pressure overload may impair fatty acid metabolism as a result of impaired myocardial perfusion. However, in our study, the WR varied significantly depending on the degree of HF, and this may be due to the recording of delayed images during ^{123}I-BMIPP imaging.

The findings of our study support the incorporation of nuclear techniques for the evaluation of various cardiac diseases leading to HF. Serum BNP levels, which can be measured easily and repeatedly to assess the severity of HF, may help to determine the appropriate clinical management and prognostication of patients with HF. Similarly, ^{123}I-BMIPP imaging to obtain H/M ratios and the WR of ^{123}I-BMIPP could serve as important adjuncts to SPECT images when evaluating patients with HF, as any myocardial metabolic abnormality demonstrated on such planar images could predict the severity of HF. The various parameters of ^{123}I-BMIPP cardiac scintigraphy were found to significantly correlate with serum BNP levels in our patients.

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