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Impact of short-acting loop diuretic doses and cardiac sympathetic nerve abnormalities on outcomes of patients with reduced left ventricular function

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Abstract

Recent studies reported that high doses of short-acting loop diuretics are associated with poor outcomes in patients with heart failure (HF). Short-acting loop diuretics have been shown to activate the renin-angiotensin system (RAS) and have no favorable effects on cardiac sympathetic nervous system (SNS) activity. The goal of this study is to investigate the relationship between daily doses of furosemide and the outcomes of patients with left ventricular dysfunction (LVD) from the viewpoint of cardiac SNS abnormalities using iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy.

We enrolled 137 hospitalized patients (62.5 ± 14.2 years old, 103 men) with LVEF < 45% who underwent ^{123}I-MIBG myocardial scintigraphy. A delayed heart-to-mediastinum ratio (delayed HMR) was assessed using ^{123}I-MIBG scintigraphy. Cardiac events were defined as cardiac death or re-hospitalization due to the deterioration of HF. Cox proportional hazard analysis was used to identify predictors of cardiac events.

Cardiac events occurred in 57 patients in a follow-up period of 33.1 ± 30 months. In a multivariate Cox proportional hazard analysis, delayed HMR and furosemide doses were identified as independent predictors of cardiac events ($P = .0042$, $P = .033$, respectively). Inverse probability of treatment weighting Cox modeling showed that the use of furosemide (≥40 mg /day) was associated with cardiac events with a hazard ratio of 1.96 ($P = .003$). In the Kaplan-Mayer analysis, the cardiac event-free survival rate was significantly lower in patients treated with high doses of furosemide (≥60 mg/day vs 40–60 mg/day vs <40 mg/day, the Log-rank test $P < .0001$). In a receiver-operating characteristic (ROC) analysis, the cut-off value for cardiac events was 40 mg/day of furosemide. The cardiac event-free rate was significantly lower in patients with delayed HMR <1.8 (median value) and receiving furosemide ≥40 mg/day than in other patients (the Log-rank test $P < .0001$). Significant differences in cardiac event rates according to furosemide doses among patients with delayed HMR <1.8 were observed among patients without β-blocker therapy ($P = .001$), but not among those with β-blocker therapy ($P = .127$).

The present results indicate that a relationship exists between higher doses of furosemide and poor outcomes. The prognosis of HF patients with severe cardiac SNS abnormalities receiving high-dose short-acting loop diuretics is poor.

Abbreviations: ^{123}I-MIBG = iodine-123-labeled metaiodobenzylguanidine, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = plasma B-type natriuretic peptide, BUN = blood urea nitrogen, CCB = calcium channel blocker, CMR = cardiac magnetic resonance, eGFR = Estimated glomerular filtration rate, Hb = hemoglobin, HF = heart failure, HMR = heart-to-mediastinum activity ratio, ICM = ischemic cardiomyopathy, IPTW = inverse probability of treatment weighting, IVSTd = intraventricular septum thickness at diastole, LVD = left ventricular dysfunction, LVDd = left ventricular diastolic dimension, LVDs = left ventricular systolic dimension, LVEF = left ventricular ejection fraction, LVM= left ventricular mass, LVMI = left ventricular mass index, LVPWTd = left ventricular posterior wall thickness at diastole, NYHA = New York Heart Association, RAS = renin-angiotensin system, ROC = receiver-operating characteristic, SCD = sudden cardiac death, SNS = sympathetic nervous system.

Keywords: cardiac sympathetic nerve activity, heart failure, outcome, short-acting loop diuretics

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The authors have no conflicts of interest to disclose.

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1. Introduction

Loop diuretics are widely used as basic therapy to improve volume overload in patients with heart failure (HF). However, the long-term influence of short-acting loop diuretics on the prognosis of patients with HF has not yet been established. Previous studies showed that furosemide, a short-acting loop diuretic, activated the renin-angiotensin system (RAS) and did not have any favorable effects on cardiac sympathetic nervous system (SNS) activity over long-acting loop diuretics.[1,2] An independent, dose-dependent relationship has been reported between short-acting loop diuretic use and an impaired prognosis in patients with advanced HF.[3–6] Eshaghian et al previously showed that the highest diuretic doses (>160 mg per day) had a more negative impact on outcomes than the lowest loop diuretic doses (0–40 mg per day).[3]

Iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy is now an established modality for evaluating cardiac SNS activity.[7–9]^{123}I-MIBG imaging is widely used for risk stratification and predicting the outcomes of patients with HF.[10–13] The aim of the present study is to evaluate the relationship between furosemide doses and patient prognoses from the viewpoint of cardiac SNS activity using ^{123}I-MIBG imaging.

2. Materials and methods

2.1. Study population

A total of 203 patients admitted to Miyazaki University Hospital between January 2005 and December 2010 had left ventricular dysfunction (LVD) with a left ventricular ejection fraction (LVEF) less than 45% on echocardiography, including hospitalization due to acute HF. All patients were hospitalized to treat HF or evaluate its causes. A flow diagram was shown in Figure 1. Patients on hemodialysis, with inflammatory disease, malignant disease, hemorrhagic disease, acute coronary syndrome, psychiatric disease, or autonomic failure related to neurological diseases, such as Parkinson's disease, were excluded. Patients with ischemic heart disease scheduled for revascularization and with severe valvular diseases scheduled for valve replacement were also excluded. No medications that directly affected the uptake or secretion of MIBG had been administered to any patient. We examined 137 patients. All patients were in New York Heart Association (NYHA) functional classes I–III at entry and underwent cardiac ^{123}I-MIBG imaging. This study was approved by the Human Investigation Review Committee of the University of Miyazaki (No. 826) and confirmed to the principles outlined in the *Declaration of Helsinki*. Informed consent was obtained from all patients.

2.2. Data collection and study design

Baseline demographic data, including age, sex, height, weight, history of acute HF at admission, the NYHA functional class, furosemide dose, other medications (e.g., angiotensin-converting enzyme inhibitor: ACE-I, angiotensin receptor blockers: ARB, β-blockers, calcium channel blockers: CCB, spironolactone, statins), comorbid diseases (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation), underlying diseases (ischemic cardiomyopathy: ICM or non-ICM), heart rate on resting ECG, plasma B-type natriuretic peptide (BNP), blood urea nitrogen (BUN), serum creatinine, total bilirubin, serum uric acid, hemoglobin (Hb), echocardiography data, and parameters of

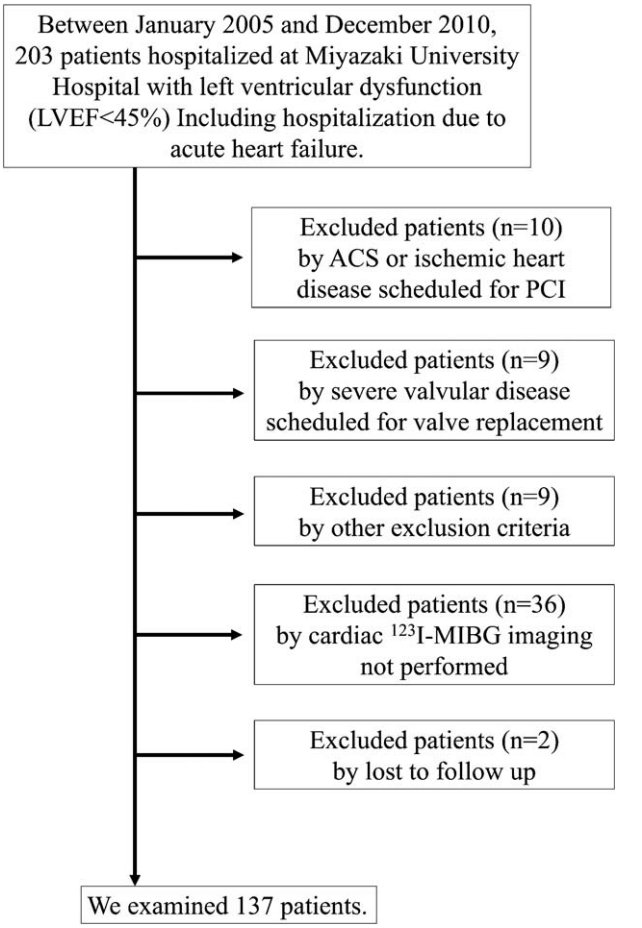

Figure 1. Flow diagram of participants in the present study. ACS = acute coronary syndrome, PCI = percutaneous coronary intervention, LVEF = left ventricular ejection fraction, ^{123}I-MIBG = iodine-123-labeled metaiodobenzylguanidine.

^{123}I-MIBG imaging, were retrospectively collected from medical records. Estimated GFR (eGFR) was calculated using the Japanese GFR estimated equation [14]: eGFR (in ml/min/1.73 m^2) = $194 \times (\text{serum creatinine in mg/dl})^{-1.094} \times (\text{age})^{-0.287} \times$ (0.739 if female). The echocardiographic study, including blood sampling, and MIBG imaging study were performed within 2 weeks of the participants becoming clinically stable. Blood samples were collected to assess plasma human BNP after resting in the supine position for at least 1 week in the morning of the day of the MIBG imaging study. In patients with acute HF at admission, data collection was performed in a stable state after intensive care.

2.3. Echocardiography

Echocardiography was performed using the Sonos 5500 or ATL Philips IE33 Ultrasound machine (Garnerville, NY) with the measurement of standard and Doppler parameters. Echocardiographic data were obtained in the stable phase during hospitalization in patients with acute HF. The left ventricular diastolic dimension (LVDd), left ventricular systolic dimension (LVDs), intraventricular septal diastolic wall thickness (IVSTd), and posterior diastolic wall thickness (LVPWTd) were assessed from the two-dimensional parasternal long-axis view. LVEF was calculated using the modified Simpson method in apical 4-

chamber and 2-chamber views. Left ventricular mass (LVM) was estimated by the left ventricular cavity dimension and wall thickness at end-diastole, according to the formulae of a previous study.[15] The left ventricular mass index (LVMI) was then calculated as the ratio of LVM to body surface area.

2.4. ^{123}I-MIBG imaging

All patients underwent resting ^{123}I-MIBG scintigraphy under pain-free conditions after fasting for more than 3 hours. Each dose of 111 MBq of ^{123}l-MIBG (FUJIFILM RI Pharma, Co., Ltd., Tokyo, Japan) was injected intravenously with patients seated. At 30 minutes and 4 hours after the injection, static data were acquired in the anterior view with a double-head commercially available gamma camera (E.CAM; SIEMENS, Wittelsbacherplatz, Munich, Germany) with a low-energy, general purpose collimator. A region of interest (ROI) was selected to encompass the whole heart, and a square ROI was selected to include the upper mediastinum on early and delayed anterior planner projection images for a quantitative analysis of the myocardial accumulation of ^{123}l-MIBG. Counts per pixel were measured for each ROI, and the heart-to-mediastinum (H/M) activity ratio was calculated. The activity of ^{123}l-MIBG was corrected by the time interval and background, and the myocardial washout rate of ^{123}l-MIBG was assessed as the percentage of the change in activity from the early image (early HMR) to delayed image (delayed HMR). The clearance rate from the myocardium (washout rate; WR) was calculated as follows: [early myocardial ^{123}I-MIBG uptake - delayed myocardial ^{123}I-MIBG uptake] / [initial ^{123}I-MIBG uptake] $\times$ 100. The normal ranges of delayed HMR and WR in our institution were 2.8 ± 0.43 (SD) and 20.9 ± 7.39 (%) (SD), respectively.

2.5. Outcomes

Cardiac events were defined as death from HF, lethal arrhythmia and sudden cardiac death (SCD), the need for cardiac transplantation, and unexpected hospitalization due to the deterioration of HF. SCD was defined as witnessed cardiac arrest and death within 1 hour after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 hours. Information on cardiac events was collected from medical records or contact with cardiologists. All patients were followed up until October 2013 unless a major end-point terminated the follow-up.

2.6. Statistical analyses

Values are expressed as the mean $\pm$ standard deviation. Mean values for continuous variables were compared using the Wilcoxon rank-sum test and the frequencies of categorical variables were compared using the chi-squared test or χ^2 test. Variables that predicted outcomes in univariate analyses ($P < .05$) were entered into multivariate analyses, and their significance as independent predictors of cardiac events was assessed using Cox proportional hazards regression model. In addition, to reduce the impact of treatment selection bias and potential confounders in an observational study, we performed weighted Cox proportional hazards regression models using an inverse probability of treatment weighting (IPTW). Kaplan-Meier survival curves were compared using the Log-rank test. A receiver-operating characteristic (ROC) analysis was performed to obtain cut-off values for parameters predicting cardiac events. Significance was defined as $P < .05$. All data were statistically analyzed using JMP version 9.1 (SAS Institute Inc.) and software R version 3.5.0 (http://www.r-project.org/).

The datasets analyzed during the present study are available from the corresponding author on reasonable request.

3. Results

3.1. Clinical characteristics of patients with and without cardiac events

The baseline characteristics of patients in this study are shown in Table 1. The median age of patients was 64 years (27–89 years) and there were 103 males (75.2%). The number of patients with acute HF at admission was 36 (26.3%). Ninety-three patients (67.9%) had NYHA functional class $\geq$II. The number of patients with ischemic cardiomyopathy, chronic atrial fibrillation, hypertension, and diabetes mellitus were 34 (24.8%), 44 (32.1%), 43 (31.4%), and 46 (33.6%), respectively. The number of patients receiving furosemide, spironolactone, ACE-I, or ARB and β-blockers were 113 (82.5%), 69 (50.4%), 108 (78.8%), and 65 (47.4%), respectively. The median values of LVEF, eGFR, Hb, and BNP were 32% (10–44%), 51.3 ml/min/1.73 m^2 (10.8–158.1), 13.9 g/dl (6.5–20.5), and 355.8 pg/ml (14.8–3480), respectively. The median dose of furosemide administered was 20 mg/day (0–160). Cardiac death occurred in 36 patients (26.3%), while 21 patients (15.3%) had unexpected hospitalization in the follow-up period of 33.1 ± 30 months. 26 patients died of HF and 10 patients had arrhythmic death or SCD. No significant differences were observed in gender, uric acid, total bilirubin, LVEF, LVDd, LVMI, or the prevalence of atrial fibrillation. Patients with cardiac events were significantly older ($P = .0003$) and had a higher proportion of acute HF at admission ($P = .0057$) and a higher prevalence of ICM ($P = .019$). The NYHA class was significantly worse in patients with cardiac events ($P < .0001$). The dose of furosemide administered was significantly higher in patients with cardiac events ($P < .0001$). No significant differences were observed in the administration of other medications such as ACE-I or ARB, aldosterone blockers, and β-blockers between patients with and without cardiac events. Serum sodium ($P = .0044$), eGFR ($P < .0001$), and Hb ($P = .0009$) were significantly lower, while BUN ($P < .0001$) and plasma BNP ($P = .0001$) were significantly higher in patients with cardiac events. In parameters of ^{123}I-MIBG scintigraphy, delayed HMR was significantly lower ($P < .0001$) and WR was significantly higher ($P = .005$) in patients with cardiac events (Table 1). The percentage of patients treated with β-blocker therapy was low at baseline (47.4%), but increased at discharge (73.7%). The ratio of patients treated with β-blocker therapy was not significantly different between patients with and without cardiac events at discharge (66.7% vs 78.8%).

3.2. Evaluation of factors predicting outcomes

Table 2 shows the determinants of cardiac events identified in univariate and multivariate Cox hazard regression analyses. Hypertension (HR: 0.435, $P = .026$), ICM (HR: 2.51, $P = .008$), the dose of furosemide (HR: 1.016, $P = .0042$), and delayed HMR (HR: 0.212, $P = .033$) were identified as independent predictors of cardiac events. In the ROC analysis, the cut-off value for the dose of furosemide to predict cardiac events was 40 mg per day. IPTW Cox regression hazard analyses revealed that the use of high-dose furosemide ($\geq$40 mg per day) correlated with a poor prognosis (adjusted HR, 3.531; 95% CI: 1.522–8.196, $P = .003$, Table 3).

Table 1

Clinical characteristics of with events and without events groups.

	Variables	All patients (n = 137)	Events (−) (n = 80)	Events (+) (n = 57)	*P* value Event (−) vs Event (+)
Demographics	Age (years)	62.5 ± 14.2	58.9 ± 14.2	67.6 ± 12.6	.0003
	Sex (male)	103 (75.2%)	62 (77.5%)	41 (88%)	NS
	BMI	23.4 ± 4.5	24.2 ± 4.8	22.4 ± 3.7	.029
	Acute HF at admission	36 (26.3%)	14 (38.9%)	22 (61.1%)	.0057
	NYHA ≥II (n)	93 (67.9%)	43 (53.8%)	50 (87.7%)	<.0001
	Ischemic cardiomyopathy (n)	34 (24.8%)	13 (16.3%)	19 (33.3%)	.019
	Hypertension (n)	43 (31.4%)	34 (42.5%)	9 (15.8%)	.0009
	Diabetes mellitus (n)	46 (33.6%)	23 (28.8%)	23 (40.4%)	NS
Medications	Furosemide (n)	113 (82.5%)	59 (73.8%)	54 (94.7%)	.009
	Dose of furosemide (mg/day)	32.6 ± 27.8	22.9 ± 19.9	46.1 ± 31.6	<.0001
	Spironolactone (n)	69 (50.4%)	37 (46.3%)	32 (56.1%)	NS
	ACE-I or ARB (n)	108 (78.8%)	63 (78.8%)	45 (78.9%)	NS
	β-blocker (n)	65 (47.4%)	38 (47.5%)	27 (47.4%)	NS
Electrocardiogram	Heart rate (bpm)	75.8 ± 18.8	75.5 ± 18.6	76 ± 19.1	NS
	Atrial fibrillation (n)	44 (32.1%)	25 (31.3%)	19 (33.3%)	NS
Echocardiography	LVEF (%)	31.6 ± 8.6	32.4 ± 8.7	30.5 ± 8.3	NS
	LVDd (cm)	5.9 ± 1.0	5.8 ± 0.9	6.1 ± 1.1	NS
	LVMI (g/m^2)	172.2 ± 52.7	165.2 ± 47.6	182 ± 58.1	NS
Laboratory tests	BUN (mg/dl)	24.5 ± 13.1	19.9 ± 6.9	30.9 ± 16.6	<.0001
	eGFR (ml/min/1.73 m^2)	52.9 ± 21.4	58.4 ± 18.9	45.3 ± 22.4	<.0001
	Na (mEq/l)	138.5 ± 4.6	139.6 ± 3.1	136.8 ± 5.8	.0044
	Hemoglobin (g/dl)	13.6 ± 2.4	14.2 ± 2.0	12.8 ± 2.7	.0009
	BNP (pg/dl)	567.3 ± 610.5	411.4 ± 492.4	786.1 ± 692.7	.0001
	Uric acid (mg/dl)	7.2 ± 1.9	7.2 ± 1.85	7.1 ± 2.1	NS
	Total bilirubin (mg/dl)	0.94 ± 0.7	0.95 ± 0.79	0.94 ± 0.5	NS
^{123}I-MIBG data	Delayed HMR	1.80 ± 0.35	1.91 ± 0.35	1.66 ± 0.3	<.0001
	WR (%)	42.3 ± 14.6	39.8 ± 15.6	45.7 ± 12.3	.005

Values are means ± SD or numbers.

^{123}I-MIBG = iodine-123-labeled metaiodobenzylguanidine, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, HF = heart failure, HMR = heart-to-mediastinum ratio, LVDd = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, NYHA = New York Heart Association, WR = washout rate.

3.3. Relationship between furosemide doses and cardiac events

In the Kaplan-Mayer analysis, the cardiac event-free survival rate was significantly lower in patients treated with high doses of furosemide (≥60 mg per day vs 40–60 mg per day vs <40 mg per day, the Log-rank test $P < .0001$, Fig. 2).

3.4. Relationship between clinical parameters and furosemide doses

The relationships between the dose of furosemide and clinical parameters were shown in Table 4. The proportion of acute HF at admission was significantly higher ($P = .0007$) and the NYHA functional class was significantly worse in patients receiving

Table 2

Univariate and multivariate Cox hazard regression analysis of characteristics for cardiac events.

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.034	1.013–1.056	.0009			
Acute HF at admission	2.054	1.187–3.482	.011			
NYHA Classification ≥II	3.887	1.885–9.402	<.0001			
Hypertension	0.366	0.167–0.711	.002	0.435	0.188–0.91	.026
Ischemic cardiomyopathy	2.457	1.372–4.274	.0031	2.51	1.277–4.861	.008
BMI	0.93	0.873–0.987	.0153			
Dose of furosemide	1.024	1.016–1.032	<.0001	1.016	1.005–1.027	.0042
Hemoglobin	0.784	0.699–0.88	<.0001			
Na	0.873	0.828–0.926	<.0001			
eGFR	0.97	0.955–0.985	<.0001			
BUN	1.046	1.03–1.061	<.0001			
Log BNP	1.685	1.322–2.172	<.0001			
Delayed HMR	0.129	0.056–0.289	<.0001	0.212	0.05–0.884	.033
WR	1.023	1.005–1.039	.01			

BMI = body mass index, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CI = confidence interval, eGFR = estimated glomerular filtration rate, HF = heart failure, HMR = heart-to-mediastinum ratio, HR = hazard ratio, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, WR = washout rate.

Table 3

IPTW Cox hazard multivariate regression analysis of characteristics for cardiac events.

Variables	HR	95% CI	*P* value
Use of furosemide	3.968	0.854–18.44	.079
Use of furosemide ≥40 mg per day	3.531	1.522–8.196	.003

CI = confidence interval, HR = hazard ratio, IPTW = inverse probability of treatment weighting.

furosemide ≥40 mg per day ($P = .0003$). Serum sodium ($P < .0001$) and eGFR ($P = .011$) were also significantly lower. Furthermore, plasma BNP ($P = .0016$), BUN ($P < .0001$), and uric acid ($P = .0059$) were significantly higher than in patients treated with furosemide <40 mg per day. Regarding scintigraphic parameters, delayed HMR was significantly lower ($P < .0001$) and WR was significantly higher ($P < .0001$) in patients receiving furosemide ≥40 mg per day than in those receiving <40 mg per day.

3.5. Impact of the combination of cardiac SNS abnormalities and furosemide doses on outcomes

When stratified into a higher delayed HMR group (≥1.8) and lower delayed HMR group (<1.8) according to the median value for delayed HMR, the cardiac event-free survival curve was significantly lower in patients with delayed HMR (<1.8) and receiving furosemide ≥40 mg per day than in other patients in the Kaplan-Mayer analysis (the Log-rank test $P < .0001$, Fig. 3). Furthermore, among patients with delayed HMR <1.8, an increase in the cardiac event rate according to the dose of furosemide was observed in patients without β-blocker therapy ($P = .0011$), but not in those with β-blocker therapy (Fig. 4).

Table 4

Relationships between furosemide doses and clinical parameters.

Variables	Furosemide >40 mg (n = 62)	Furosemide <40 mg (n = 75)	*P* value
Age (years)	64.5 ± 12.8	61.0 ± 12.8	NS
Sex (male)	50 (80.7%)	53 (70.7%)	NS
Acute HF at admission	25 (40.3%)	11 (14.7%)	.0007
NYHA classification ≥II (n)	52 (83.9%)	41 (54.7%)	.0003
BMI	22.6 ± 3.5	24.1 ± 5.1	NS
Diabetes mellitus (n)	28 (45.2%)	52 (83.9%)	.009
Hypertension (n)	15 (24.2%)	28 (37.3%)	NS
Ischemic cardiomyopathy (n)	13 (21%)	19 (25.3%)	.9707
Use of ACE-I or ARB (n)	52 (83.9%)	56 (74.7%)	NS
Use of β-blockers (n)	34 (54.8%)	31 (41.3%)	NS
Use of digitalis (n)	23 (37.1%)	18 (24%)	.0458
Use of spironolactone (n)	46 (74.2%)	23 (30.7%)	<.0001
Atrial fibrillation (n)	24 (38.7%)	20 (26.7%)	NS
Hemoglobin (g/dl)	13.3 ± 2.8	13.9 ± 0.32	NS
Uric acid (mg/dl)	7.6 ± 2.2	6.8 ± 1.7	.0059
Total bilirubin (mg/dl)	0.96 ± 0.54	0.93 ± 0.79	NS
BUN (mg/dl)	29 ± 14.7	20.8 ± 10.2	<.0001
BNP (pg/dl)	414.2 ± 445.9	752.5 ± 725.4	.0016
Na (mEq/l)	136 ± 5.3	140.1 ± 3.2	<.0001
eGFR (ml/min/1.73m^2)	47.1 ± 15.4	57.8 ± 24.4	.011
Heart rate (bpm)	76.1 ± 19.7	75.4 ± 18.1	NS
LVEF (%)	30.2 ± 9.3	32.7 ± 7.8	NS
LVDd (mm)	6.1 ± 1.1	5.8 ± 0.9	NS
LVMI (g/m^2)	179.5 ± 58.9	166.1 ± 46.5	NS
Delayed HMR	1.66 ± 0.32	1.92 ± 0.33	<.0001
WR	47.1 ± 14.5	38.2 ± 13.4	<.0001

Values are means ± SD or numbers.

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, HF = heart failure, HMR = heart-to-mediastinum ratio, LVDd = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, NYHA = New York Heart Association, WR = washout rate.

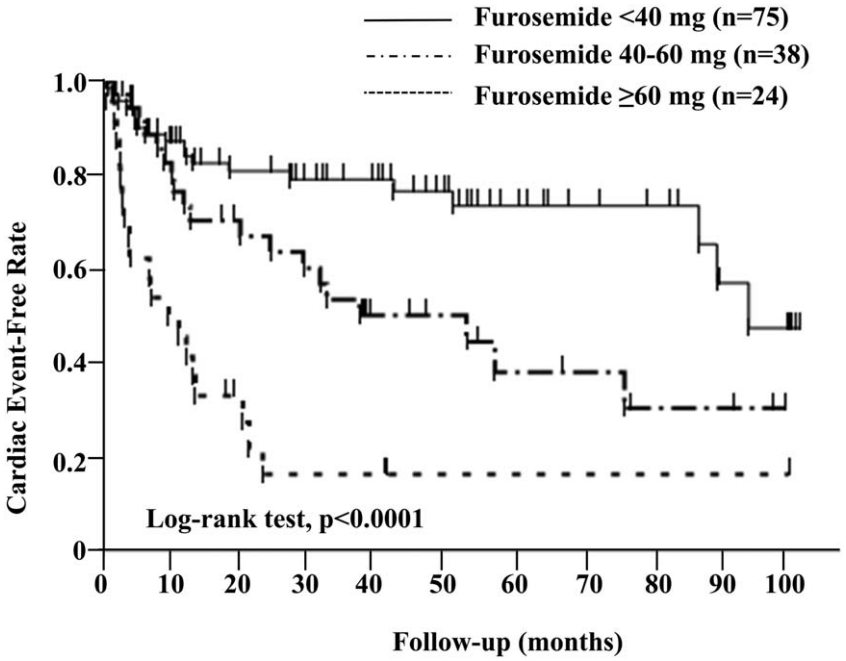

Figure 2. Kaplan-Meier event-free curves according to furosemide doses for cardiac events.

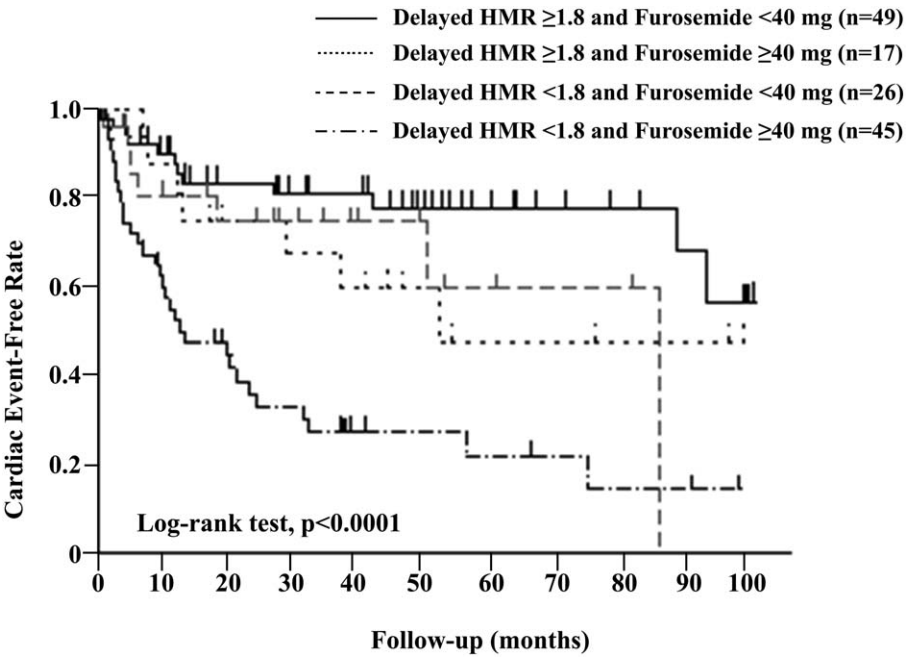

Figure 3. Kaplan-Meier event-free curves according to the combination of furosemide doses and delayed HMR for cardiac events. HMR = heart-to-mediastinum ratio.

4. Discussion

In the present study, the dose of furosemide was identified as an independent predictor of cardiac death or unexpected hospitalization due to the deterioration of CHF in patients with LVD. The cut-off value for the furosemide dose to predict cardiac events was 40 mg per day. Background-adjusted IPTW analyses identified the use of high-dose furosemide (≥40 mg per day) as a significant determinant for a poor prognosis. Furthermore, cardiac SNS activity was more abnormal in patients treated with high doses of furosemide. In addition, the prognosis of patients with cardiac SNS abnormalities and receiving high doses of furosemide was poor.

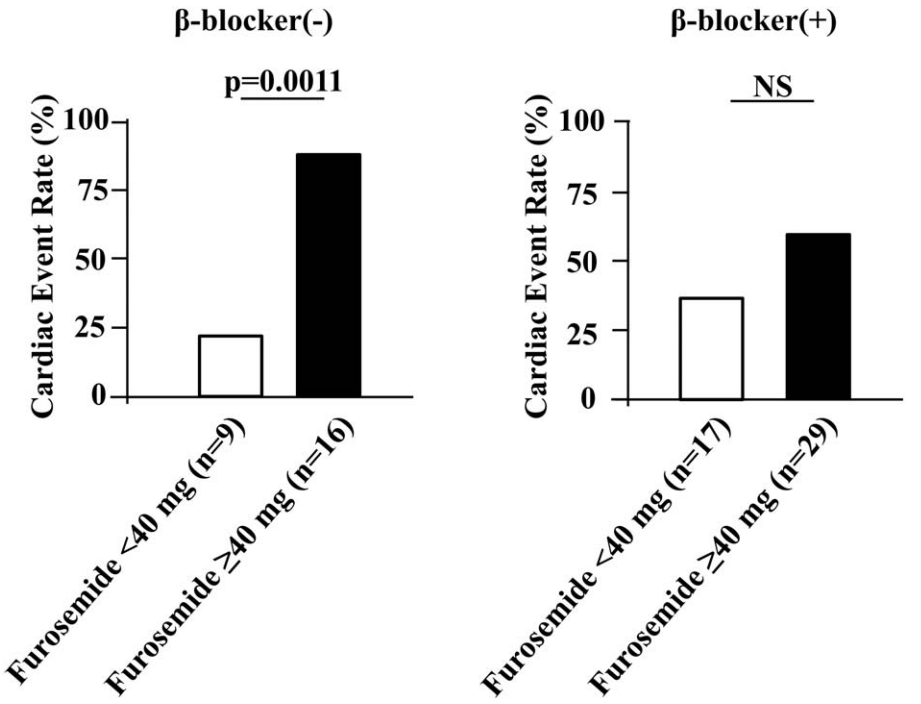

Figure 4. Cardiac event rate according to furosemide doses with and without β-blocker treatments among patients with delayed HMR <1.8. HMR = heart-to-mediastinum ratio.

Diuretic therapy improves clinical symptoms in patients with HF. However, the adverse effects of short-acting loop diuretics need to be considered. Bayliss et al previously reported that furosemide activated plasma renin activity.[31] Recent studies revealed that long-acting loop diuretics had a number of advantages over short-acting loop diuretics. Kasama et al showed that torasemide improved cardiac SNS activity and LV remodeling in patients with CHF, whereas furosemide had no favorable effects.[1] Furthermore, Matsuo et al demonstrated that azosemide produced more favorable changes on ^{123}I-MIBG scintigraphy than furosemide in patients with CHF.[32] Masuyama et al reported that azosemide reduced the risk of cardiovascular death or re-hospitalization due to the deterioration of CHF more than furosemide.[33] They speculated an impact on cardiac SNS activity as a reason for the prognostic difference between azosemide and furosemide, but were unable to provide an explanation from the viewpoint of plasma epinephrine levels.

Experimental studies have suggested neurohumoral and sympathetic activation by short-acting loop diuretics. McCurley et al demonstrated that the acceleration of LVD by furosemide was associated with an increase in plasma aldosterone levels in a tachycardia-induced HF model.[34] Yoshida et al suggested sympathetic activation as a reason for the lack of improvements in mortality for HF treated with furosemide despite reductions in the preload and afterload.[35]

Sympathetic nerve hyperactivity plays an important role in the pathophysiology of HF. SNS hyperactivation also maintains cardiac contractility by releasing norepinephrine (NE) from sympathetic nerve dendrites.[16] In HF patients, the spillover of NE into plasma increases exponentially due to sympathetic nerve hyperactivity.[17]

Furthermore, the cardiac content of NE is markedly reduced.[18] The impaired reuptake of NE by presynaptic neurons may also contribute to decreasing the cardiac content of NE in human HF.[19] In addition, β adrenergic receptors (βARs) are down-regulated in HF. Decreased βAR responsiveness, increased circulating catecholamines, and overall hyposensitivity to adrenergic stress have been observed in patients with failing hearts. Decreased βAR responsiveness is related to changes in G-protein and kinase activities.[16]

SNS activation adversely affects cardiac energy metabolism.[16,20] SNS hyperactivity increases plasma free fatty acid (FFA) levels and modulates the insulin secretion of Langerhans' pancreatic islets.[16] In an animal model, increased FFA was associated with LVD.[21] Djoussé et al showed that higher plasma FFA was associated with an increased risk of HF.[22] Elevated plasma FFA may increase myocardial FFA uptake. Changes in myocardial fatty acid metabolism reduced glucose utilization. [20] Moreover, a chronic βAR stimulation induced insulin resistance.[23] Cardiac insulin resistance contributes to the development of LVD by reducing cardiac efficiency through a metabolic shift toward fatty acid use.[24] Furthermore, sympathetic overactivation may trigger interstitial matrix remodeling and fibrosis through the induction of matrix metalloproteinase/tissue inhibitor of metalloproteinase activity.[25]

Hence, increased cardiac SNS activity is strongly associated with the deterioration of LV function, the development of lethal ventricular tachyarrhythmia, and a poor prognosis.[26,27]

^{123}I-MIBG is an analog of noradrenaline that reflects cardiac SNS activity.[6,7] Myocardial imaging with MIBG was previously reported to be useful for evaluating disease severity, prognosis, and treatment responses in patients with HF. Delayed HMR and WR are generally used as predictors of the severity and prognosis of HF.[28–30] In the present study, delayed HMR was identified as an independent predictor of cardiac events, which is consistent with previous findings.

Furthermore, the prognosis of patients with cardiac SNS abnormalities (delayed HMR <1.8) and receiving high doses of furosemide ($\geq$40 mg per day) was poor. A difference in cardiac event rates according to the furosemide dose among patients with cardiac SNS abnormalities was noted among patients without β-blocker therapy, but not among those with β-blocker therapy. β-blocker therapy is an established treatment for HF.[36,37] Therefore, patients receiving high doses of short-acting loop diuretics with cardiac SNS abnormalities or without β-blocker therapy need to be carefully monitored.

There were several notable limitations in the present study. This study was small in size and retrospective. Since we selected patients who underwent ^{123}I-MIBG scintigraphy, we cannot deny that the background of this population was biased. In the present study, high doses of furosemide were associated with the severity of HF (Table 4). Patients with more severe HF generally receive larger doses of loop diuretics to improve volume overload. The use of higher doses of furosemide may be employed to identify patients at high risk of mortality regardless of diuretic therapy. In the present study, IPTW Cox regression hazard analysis showed that the use of furosemide was not associated with outcomes; only high doses of furosemide correlated with a poor prognosis. These results indicate that high doses of furosemide are detrimental to the prognosis of patients with HF. Despite the use of IPTW Cox hazard multivariate regression analysis, we cannot completely exclude the selection bias and other unmeasurable confounders. Recently, the evaluation of left ventricular remodeling and myocardial fibrosis using cardiac magnetic resonance (CMR) imaging is considered to be important in predicting the prognosis of patients with HF.[38,39] But we did not focus on left ventricular remodeling in this study. Therefore we entrust the investigation from viewpoint of CMR imaging to a future research.

5. Conclusion

The results of the present study indicate that a relationship exists between higher doses of furosemide and poor outcomes. The prognosis of HF patients with severe cardiac SNS abnormalities receiving high-dose short-acting loop diuretics is poor. ^{123}I-MIBG scintigraphy may be useful for predicting the outcomes of high-risk patients treated with higher doses of short-acting loop diuretics. The present results indicate that patients receiving high doses of furosemide with the overactivation of cardiac SNS activity need to be carefully monitored.

Author contributions

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