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Original article

Relation between prognostic impact of hyperuricemia and sympathetic overactivation in patients with heart failure

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ABSTRACT

Background: Uric acid (UA), which could provide additional prognostic information in patients with heart failure (HF), can activate sympathetic nerve activity and vice versa, thus creating a vicious cycle in the cardiovascular system. However, it remains unclear whether hyperuricemia (UA > 7.0 mg/dl) can provide prognostic information independent of sympathetic nerve activity.

Methods: UA and potential prognostic variables including sympathetic nerve activity using microneurography (MSNA) were evaluated in 139 patients with HF (ejection fraction < 45%). Primary composite cardiovascular endpoints included cardiovascular death and hospitalization due to HF. Predictors for outcomes were analyzed using univariate, multivariable, and Kaplan–Meier analyses. To determine whether the negative impact of hyperuricemia on outcomes is homogenous, prognostic impacts of hyperuricemia were compared in subgroups of HF. Ejection fraction was followed for 9 months after MSNA measurement in 102 patients.

Results: During a follow-up period of 1636 days, 54 patients fulfilled the primary composite endpoint of cardiovascular death or HF hospitalization. Patients with hyperuricemia had a higher cardiovascular event rate than those with normouricemia ($p = 0.006$). On multivariable Cox proportional hazard analysis, hyperuricemia, higher MSNA, and β-blocker dose were independent predictors of cardiovascular events. In subgroup analyses, impact of hyperuricemia on outcome was similar in all subgroups except sympathetic nerve activity (interaction, $p = 0.033$). Hyperuricemia had negative impact on cardiovascular event rates (hazard ratio = 3.44) in group with higher MSNA ($p = 0.0002$), but not in those with lower MSNA. Additionally, the change in LVEF was also significantly lower in patients who had a higher MSNA burst incidence and hyperuricemia.

Conclusion: Hyperuricemia might have detrimental effect on prognosis and cardiac function in HF patients with sympathetic overactivation.

Introduction

Although guideline-directed medical therapy could reduce cardiovascular event rates in patients with heart failure (HF) and reduced ejection fraction, a part of the patients may have a development of cardiac remodeling and severe HF progressively and which is resulting in poor prognosis [1–3]. Mechanistically, the progression of HF might be associated with residual cardiac risk. Uric acid may be an important mediator of HF, and its overactivation has been linked to poor outcome [4–6].

In an experimental setting, it was shown that hyperuricemia (uric acid > 7.0 mg/dl) acts on vascular endothelial cells and vascular smooth muscle cells and contributes to the reduction of nitric oxide production and the proliferation of smooth muscle cells through activation of inflammation [7]. In an observational study, it was shown that an index of arteriosclerosis rises as the uric acid level increases [8]. Such findings suggest that hyperuricemia may be associated with arteriosclerosis over time [9]. Progression of arteriosclerosis indirectly affects the HF condition and may affect clinical outcome and prognosis. However, it remains unclear why uric acid itself has a negative effect on prognosis in patients with HF. If uric acid itself had an adverse effect, poor

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prognosis should be seen in patients with hyperuricemia regardless of the patient background. Notably, previous studies indicated that the impact of hyperuricemia on outcome in patients with HF was not homogenous [10,11].

Sympathetic nerve activity or norepinephrine activates serum uric acid and their precursors (hypoxanthine and xanthine) and vice versa, thus creating a vicious cycle with detrimental effects in the cardiovascular system [12–15]. Thus, the interplay between sympathetic nerve activity and uric acid is concerned; however, there is no study about the relation between them in the observational population study. Therefore, to determine homogeneity of associations of hyperuricemia with outcomes, we analyzed the impact of hyperuricemia on cardiovascular events in patients with HF. Additionally, we repeated our analysis in subgroups of patients including those with and without sympathetic overactivation, which is directly recorded from sympathetic neural activity using microneurography, so called muscle sympathetic nerve activity (MSNA).

Methods

Study protocol

The present study included 139 patients with stable HF [stage C, left ventricular ejection fraction (LVEF) < 45%]. All patients were receiving treatment in accordance with the current guidelines for at least one month. The etiology of HF was ischemic (n = 45) and non-ischemic (n = 94). Patients with primary valvular heart diseases, stroke, respiratory failure or pulmonary disease, severe anemia, and end-stage renal disease treated by hemodialysis were excluded. Because nerve disorders can affect recording of MSNA, patients who had symptoms of peripheral neuropathy including diabetic autonomic neuropathy were also excluded. The Institutional Ethics Board of Toyama University Hospital approved the study protocol, which complied with the Declaration of Helsinki. Written, informed consent was obtained from all patients before participation in the study.

Measurement of blood pressure, respiration, and muscle sympathetic nerve activity

MSNA is a sympathetic neural activity innervating muscle or cutaneous vascular beds and regulates systemic vascular resistance to contract arteriole directly. That is a gold standard method to evaluate sympathetic neural activity directly using microneurography [16]. Several studies showed that MSNA was correlated with norepinephrine level in patients with hypertension and HF [17,18]. Higher level of MSNA suggested similarly poor prognosis as reported with plasma norepinephrine level in patients with HF [19,20].

All parameters were obtained in resting patients who were awake and in a supine position, as previously described [20–22]. Briefly, blood pressure was serially recorded using noninvasive tonometry (Jentow 7700, Colin, Komaki, Japan). Multiunit recordings of efferent postganglionic sympathetic nerve activity to skeletal muscle regions were captured via a microelectrode inserted directly into the peroneal nerve posterior to the fibular head [20–22]. The nerve signal was amplified ×100,000, passed through a band-pass filter (500–5000 Hz), and integrated with a custom nerve-traffic analysis system (NeuropackΣ MEB-5504, Nihon Kohden, Tokyo, Japan). MSNA was expressed as the burst rate (bursts/min) and burst incidence (bursts/100 beats). Data were analyzed in a blinded manner by two of the investigators (SJ and RU). The range of burst incidence was 25 ± 8 bursts/100 beats in 7 healthy subjects (mean age = 26 years, unpublished data). Blood samples were withdrawn from the antecubital veins to measure B-type natriuretic peptide (BNP) levels.

Measures

The following demographic and clinical characteristics were collected from medical records: age; sex; body mass index; etiology of HF; heart rate; mean blood pressure; oxygen saturation; LVEF, which was calculated as the stroke volume (end-diastolic volume minus end-systolic volume) divided by the end-diastolic volume on echocardiography (Aplio SSA-770A, Toshiba, Tokyo, Japan) using the modified Simpson's method; LV end-diastolic/systolic diameter; left atrial dimension; hemoglobin level; blood urea nitrogen; serum creatinine; estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) study equation [23]; serum sodium; serum potassium; serum uric acid; plasma BNP; MSNA burst rate and burst incidence; medical therapy including the use of renin–angiotensin system inhibitors, dose of enalapril, β-blockers, β-blocker dose, digitalis, loop diuretics, dose of furosemide, mineralocorticoid receptor antagonists, and the doses of spironolactone and amiodarone. In the present study, uric acid level of >7.0 mg/dl was defined as hyperuricemia according to the Japanese guidelines [24]. Echocardiographic data from 6 to 12 months after the MSNA measurement were collected if possible. Echocardiography was performed by medical doctors who were blinded to patients' information. Intra-/inter-observer variability of LVEF were 2.7 ± 1.6%, 3.0 ± 2.6%, respectively. To evaluate the effects of different doses of β-blockers and loop diuretics, the doses were normalized to therapeutically equivalent doses of carvedilol and furosemide. Both bisoprolol 5 mg and metoprolol 80 mg were considered to be equivalent to carvedilol 20 mg [25,26]. Azosemide 30 mg was considered to be equivalent to furosemide 20 mg [27].

Outcome assessments

Follow-up began at the day of the MSNA measurements and ended in September 2016. The primary composite end-point was cardiovascular death, including pump failure death and sudden death, and hospitalization due to HF. Information about the time and cause of the cardiovascular death or hospitalization due to HF was directly obtained from medical records and family doctors. Individual follow-ups were censored by death or ventricular assist device implantation. No patients were lost to follow-up.

Statistical analysis

Data are expressed as means ± standard deviation. Analyses were performed using statistical software (JMP (R) 13, SAS Institute Inc., Cary, NC, USA). Variables were compared between groups using the unpaired t-test or χ^2 test, as appropriate. Kaplan–Meier survival curves determined the time-dependent cumulative cardiac event-free rates in patients stratified into the two groups (hyperuricemic and normouricemic) on the basis of MSNA. These curves were analyzed by a log-rank test. Significant relationships between baseline explanatory variables and cardiovascular events were identified using univariate and multivariable Cox proportional hazard models. Explanatory variables selected from the clinical variables had p-values less than 0.05 for the univariate analysis. To determine homogeneity of associations of hyperuricemia with outcomes, we repeated our analysis in subgroups of patients including those with and without sympathetic overactivation. The level of significance was set at $p < 0.05$.

Results

Fig. 1 shows the distribution of serum uric acid and MSNA in 139 patients. Median value of serum uric acid and MSNA in the study subjects were 6.5 mg/dL and 63 bursts/100 beats, respec-

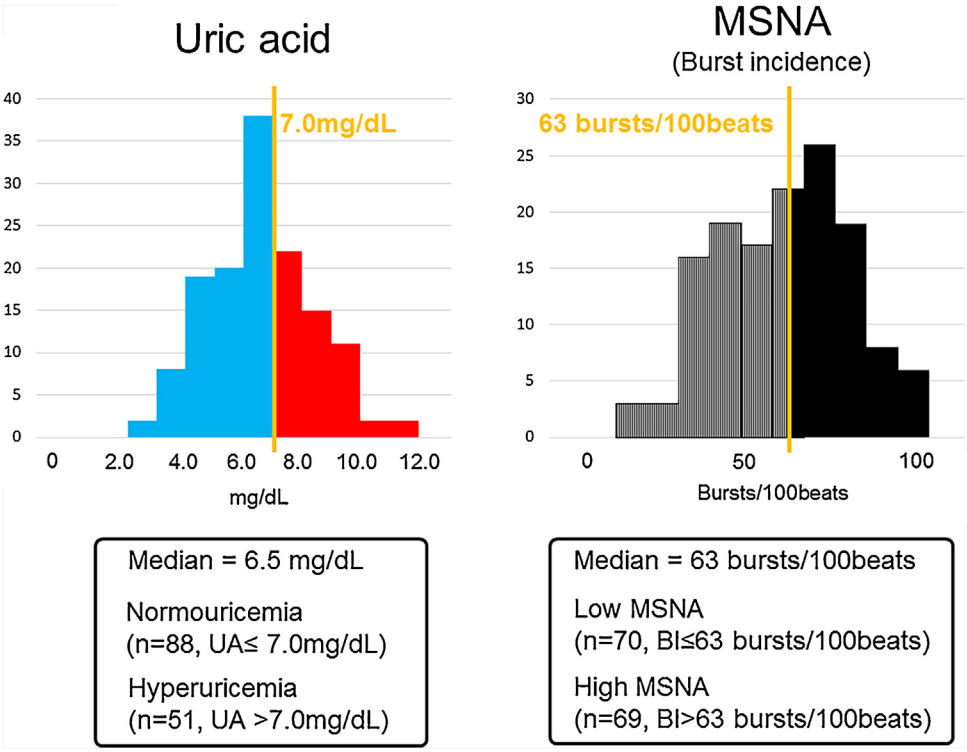

Fig. 1. Distribution of serum uric acid and muscle sympathetic nerve activity in 139 patients with heart failure. *Abbreviations*: BI, burst incidence; MSNA, muscle sympathetic nerve activity; UA, uric acid.

tively. Fifty-one (37%) patients had hyperuricemia defined as serum uric acid >7.0 mg/dL. Table 1 summarizes the demographic and clinical characteristics of all patients, groups with hyperuricemia and normouricemia. Approximately 90% of the patients were treated with renin–angiotensin-system inhibitors. Of the 94 patients (71%) being treated with β-blockers, the majority were taking carvedilol (48%) or bisoprolol (41%), with the others administered metoprolol (11%). Of the 34 patients (24%) being treated with antiuricemic agents, allopurinol was used in 19 patients (56%), febuxostat in 12 patients (35%), and benzbromarone in 3 patients (9%).

During a follow-up period of 1636 days (median), 27 patients died (sudden death 11, progressive HF 15, stroke 1), 45 patients were admitted to the hospital for HF, and 54 patients fulfilled the primary composite endpoint of cardiovascular death or HF hospitalization. The Kaplan–Meier survival curves demonstrated that patients with hyperuricemia had a higher cardiovascular event rate than those with normouricemia (log-rank test, $p = 0.006$) (Fig. 2A). Although the impact of hyperuricemia seemed smaller when the definition of hyperuricemia was extended to include patients who were on antiuricemic agents, they still had a significantly higher cardiovascular event rate ($p = 0.039$) (Fig. 2B). On multivariable Cox proportional hazard analysis, hyperuricemia ($p = 0.003$, hazard ratio 2.44), higher MSNA (MSNA >63 bursts/100 beats, $p = 0.004$, hazard ratio 2.56), and β-blocker dose ($p = 0.030$) were independent predictors of cardiovascular events (Table 2).

The impact of hyperuricemia on outcomes was similar in subgroups of patients except sympathetic nerve activity (Fig. 3). Notably, the impact of hyperuricemia on the outcomes was evident only in patients with sympathetic overactivation, but not in those without sympathetic overactivation.

To clarify the influence of sympathetic activity on the prognostic impact of hyperuricemia in patients with HF, the patients were stratified into four groups based on the median MSNA burst incidence (63 bursts/100 beats) and hyperuricemia or normouricemia. Kaplan–Meier analysis showed that there was a significantly higher cardiovascular event rate in patients who had a higher MSNA burst incidence and hyperuricemia (Fig. 4B) compared to patients with a higher MSNA burst incidence and normouricemia ($p < 0.0001$). In contrast, Kaplan–Meier analysis showed similar curves in patients who had a lower MSNA burst incidence and hyperuricemia compared to patients with lower MSNA burst incidence and normouricemia ($p = 0.97$, Fig. 4A). In fact, hyperuricemia remained an independent predictor in higher MSNA patients (hazard ratio 3.05, $p = 0.002$); however, hyperuricemia was not a significant predictor in lower MSNA patients on univariate analysis (Table 2).

Echocardiographic data at follow-up were confirmed in 102 of 139 patients (73%). The change in LVEF was also significantly lower in patients who had a higher MSNA burst incidence and hyperuricemia, as compared to patients with a lower MSNA and hyperuricemia or those with higher MSNA and normouricemia (Fig. 5).

Discussion

The interplay between sympathetic nerve activity and uric acid is of concern; however, there has been no study about the relation between them in an observational population study. The major findings of the present study were as follows. First, multivariable analysis showed that the MSNA burst incidence, β-blocker dose, and hyperuricemia were independent predictors of cardiovascular events. In fact, patients with hyperuricemia had a higher cardiovascular event rate than those with normouricemia (log-rank test, $p = 0.006$). Second, the impact of hyperuricemia on outcomes was similar in subgroups of patients except sympathetic nerve activity. Third, hyperuricemia remained an independent predictor of outcome in patients with higher MSNA groups (hazard ratio 3.05, $p = 0.002$); however, hyperuricemia was not a significant

Table 1
Demographic and clinical characteristics of the patients.

	All patients (n = 139)	Normouricemia (n = 88)	Hyperuricemia (n = 51)	p-Value
Age (y)	65 ± 13	64 ± 13	65 ± 14	0.74
Men (%)	76	70	86	0.03
Body mass index (kg/m^2)	22.2 ± 4.0	21.8 ± 3.8	22.8 ± 4.4	0.19
Ischemic etiology (%)	32	30	37	0.35
CRT (%)	5	7	2	0.21
ICD (%)	11	10	12	0.78
Atrial fibrillation (%)	26	24	29	0.48
Heart rate (beats/min)	67 ± 11	67 ± 11	67 ± 12	0.98
Mean blood pressure (mmHg)	79 ± 13	77 ± 12	81 ± 13	0.06
Oxygen saturation (%)	97 ± 2	97 ± 2	97 ± 2	0.51
Ejection fraction (%)	32 ± 7	32 ± 8	30 ± 7	0.14
Hemoglobin (g/dL)	13.3 ± 2.2	13.2 ± 2.0	13.3 ± 2.5	0.89
BUN (mg/dL)	24 ± 13	21 ± 11	28 ± 14	<0.01
Serum creatinine (mg/dL)	1.1 ± 0.4	1.0 ± 0.3	1.2 ± 0.6	<0.01
Estimated GFR (mL/min/1.73 m^2)	57 ± 20	59 ± 20	53 ± 21	0.07
Uric acid (mg/dL)	6.6 ± 1.8	5.5 ± 1.1	8.4 ± 1.1	<0.001
Na (mEq/L)	138 ± 4	138 ± 4	137 ± 4	0.59
K (mEq/L)	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	0.66
BNP (pg/mL)	231 ± 210	231 ± 212	231 ± 210	1.00
MSNA				
Burst rate (bursts/min)	42 ± 15	42 ± 14	41 ± 17	0.64
Burst incidence (bursts/100 beats)	63 ± 21	63 ± 19	62 ± 25	0.71
Medications				
RAS inhibitors (%)	90	89	92	0.51
β-Blockers (%)	72	75	67	0.30
Digitalis (%)	19	20	18	0.69
Loop diuretics (%)	65	56	80	<0.01
Mineralocorticoid receptor antagonists (%)	64	59	73	0.11
Amiodarone (%)	27	28	24	0.53
Antiuretic agents (%)	24	24	25	0.83

Values are means ± SD or percentages of patients.
BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; MSNA, muscle sympathetic nerve activity; RAS, renin–angiotensin system.

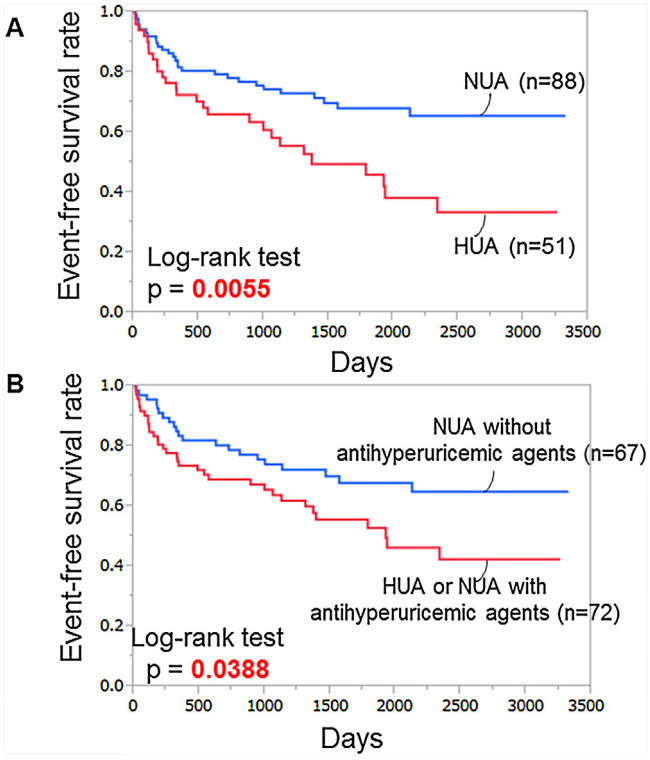

Fig. 2. Kaplan–Meier analysis for cardiovascular death and heart failure admission comparing normouricemia and hyperuricemia in patients with heart failure (A). The patients are also divided into 2 groups, extending the definition of hyperuricemia to include patients on antiuricemic agents (B). *Abbreviations*: HUA, hyperuricemia; NUA, normouricemia.

predictor in the lower MSNA group using the univariate analysis. Thus, hyperuricemia might have a detrimental effect on prognosis in HF patients with sympathetic overactivation.

Effect of the interaction between hyperuricemia and sympathetic nerve activity on the outcome

Although hyperuricemia is an ominous sign in HF, the association between hyperuricemia and outcomes were not always homogeneous as reported previously [10,11]. Here, we mentioned first the impact of the specific interaction between sympathetic nerve activity and hyperuricemia on cardiovascular events in patients with HF. Additionally, the change in LVEF was significantly lower in patients who had higher MSNA and hyperuricemia. Sympathetic nerve activity or norepinephrine activates serum uric acid and their precursors (hypoxanthine and xanthine) and vice versa, thus creating a vicious cycle with detrimental effects in the cardiovascular system [12–15]. These findings might be associated with detrimental effect of hyperuricemia on prognosis in HF patients with sympathetic overactivation.

Relationship between increased level of oxidative stress and sympathetic overactivation in the heart

Our findings also suggest that hyperuricemia might be a bystander and not directly responsible for the poor prognosis because the association between hyperuricemia and outcomes were generally not homogeneous across subgroups of patients. Our perspective was supported by a recent randomized study in which allopurinol was not effective on cardiovascular mortality rate in patients with HF in spite of reduction of uric acid level by the drug

Table 2
Predictors of cardiovascular events.

Subjects	All patients ($n=139$)				Higher MSNA group ($n=69$)				Lower MSNA group ($n=70$)			
	Univariate analysis		Multivariable analysis*		Univariate analysis		Multivariable analysis*		Univariate analysis		Multivariable analysis*	
Variable	*p*-Value	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value	HR
Age	0.120	–			0.420	–			0.806	–		
Gender	0.076	–			0.974	–			0.060	–		
Body mass index	0.035	0.927	0.28	–	0.652	–			0.050	–		
Ischemic etiology	0.036	1.809	0.066	–	0.548	–			0.010	3.76	0.006	4.35
Atrial fibrillation	0.122	–			0.718	–			0.457	–		
Heart rate	0.393	–			0.424	–			0.138	–		
Mean blood pressure	0.097	–			0.277	–			0.876	–		
Oxygen saturation	0.522	–			0.988	–			0.571	–		
Ejection fraction	0.001	0.002	0.203	–	0.01	0.005	0.223	–	0.191	–		
Hemoglobin	0.008	0.847	0.965	–	0.820	–			0.005	0.721	0.002	0.701
Estimated GFR	0.032	0.985	0.605	–	0.057	–			0.997	–		
Na	0.004	0.915	0.462	–	0.056	–			0.188	–		
BNP	<0.0001	1.002	0.092	–	0.003	1.002	0.107	–	0.220	–		
Burst incidence	<0.0001	1.036			0.066	–			0.025	–		
Group of MSNA (vs low: burst incidence <65 bursts/100 beats)	<0.0001	3.127	0.004	2.558								
Dose of ACEIs	0.668	–			0.687	–			0.268	–		
Dose of β-blockers	0.009	0.934	0.03	0.939	0.029	0.932	0.035	0.934	0.203	–		
Dose of MRA	0.001	1.019	0.066		0.001	1.02	0.114	–	0.398	–		
Dose of furosemide	0.001	1.012	0.703		0.061	–			0.035	1.02	0.053	–
Hyperuricemia	0.007	2.1	0.003	2.435	0.0002	3.441	0.002	3.045	0.973	–		

ACEIs, angiotensin-converting enzyme inhibitors; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; MSNA, muscle sympathetic nerve activity.
* Multivariable analysis was performed using factors with *p* values less than 0.05, provided the univariate analysis of the "Hyperuricemia" was also significant.

[28]. What is involved in the poor prognosis among the background of hyperuricemia and hyperadrenergic state? Hyperuricemia is a potent surrogate marker of an increased level of xanthine oxidase. Xanthine oxidase and xanthine dehydrogenase levels were significantly increased in myocardium obtained from HF patients with dilated cardiomyopathy [29]. Xanthine oxidase could provide a source of reactive oxygen species sufficient to activate cardiac afferents during ischemia [30], and its inhibition significantly reduced the responses of cardiac sympathetic afferents during ischemia [31]. Thus, xanthine oxidase itself might be closely linked to sympathetic nerve activity and have a detrimental effect on cardiac function and HF prognosis. On the other hand, increased production of reactive oxygen species via sympathetic overactivation might be also related to a detrimental effect on the failing heart [32]. Both xanthine oxidase and sympathetic overactivation could produce reactive oxygen species

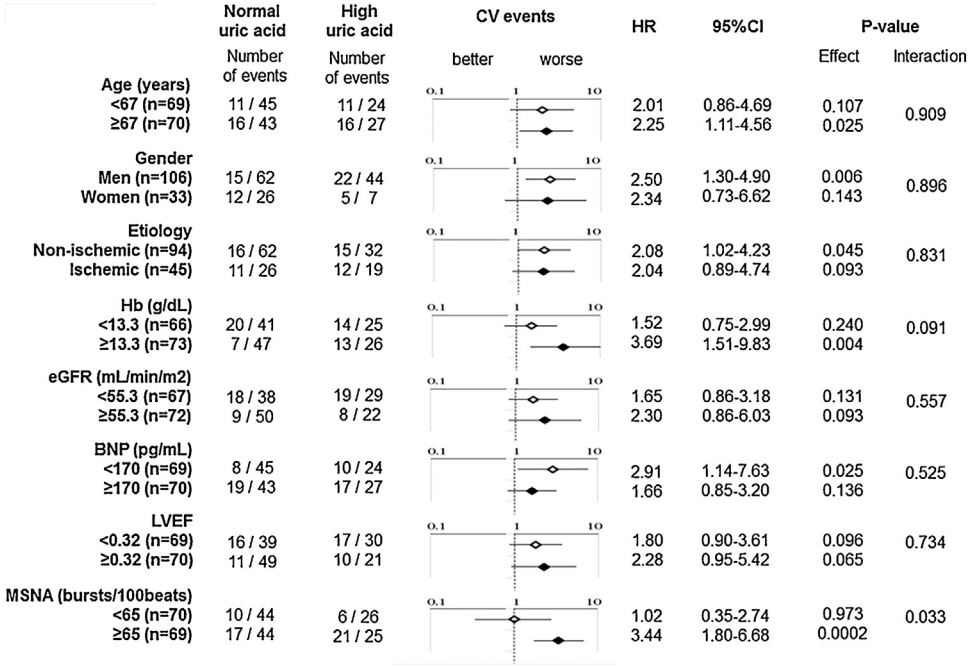

Fig. 3. Association of hyperuricemia and cardiovascular events in subgroups of matched patients. *Abbreviations*: BNP, b-type natriuretic peptide; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction, MSNA, muscle sympathetic nerve activity.

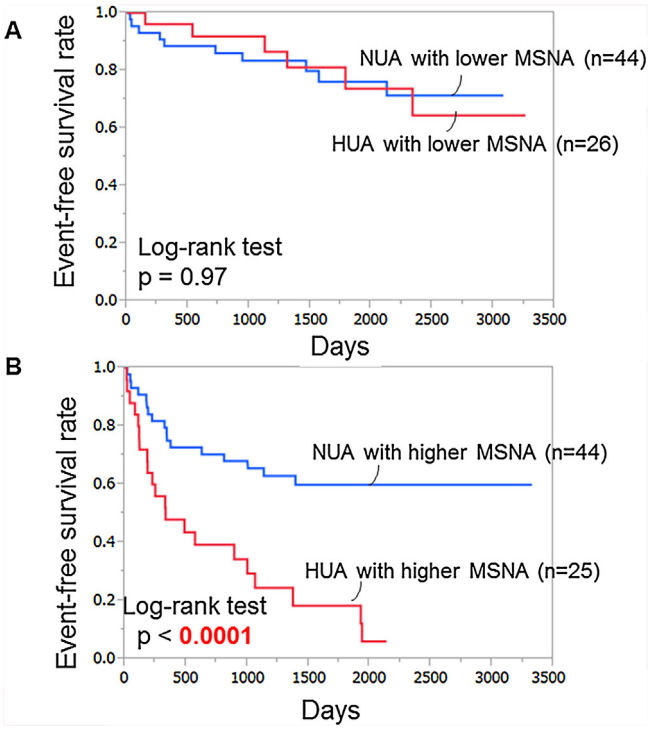

Fig. 4. Kaplan–Meier analysis for cardiovascular death and heart failure admission comparing normouricemia and hyperuricemia in patients with lower muscle sympathetic nerve activity (A) and higher muscle sympathetic nerve activity (B). *Abbreviations*: HUA, hyperuricemia; MSNA, muscle sympathetic nerve activity, NUA, normouricemia.

[33,34], which might be closely related to the pathophysiology of HF. Because β-blockers could protect the myocardium from β-adrenergic receptor-induced myocyte apoptosis, administration of β-blockers is indispensable for the treatment of HF.

Limitations

The present study had several limitations. First, we did not measure xanthine oxidase activity. The measurement might help us to understand the impact of xanthine oxidase on prognosis.

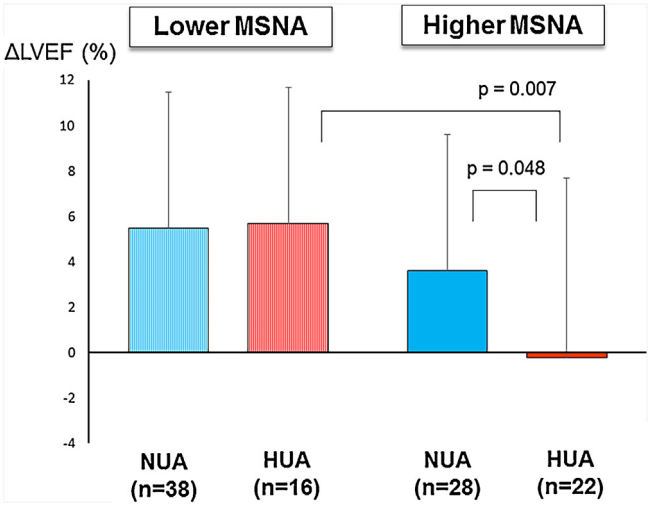

Fig. 5. Changes in left ventricular ejection fraction among the four groups based on the median level of the MSNA burst incidence (64 bursts/100 beats) and the presence of hyperuricemia. *Abbreviations*: HUA, hyperuricemia; ΔLVEF, change in left ventricular ejection fraction; MSNA, muscle sympathetic nerve activity; NUA, normouricemia.

Secondly, we did not examine the effect of antiuricemic drugs on prognosis in patients with HF. Further study might be needed to find the true target behind the hyperuricemia and re-evaluate the effectiveness of possible treatment in patients with HF. Thirdly, change in LVEF may bias due to (1) lack of data on patients who died before follow-up echocardiography and (2) variation of time interval between MSNA measurement and medical treatment in accordance with the guidelines. However, the death of patients was frequent in the hyperuricemia patient group with sympathetic overactivation and the cardiac function of the dead patients was likely to be declining. Therefore, the change in cardiac function of the group should be more markedly deteriorated if the data were not lost due to patients' deaths. Lastly, the number of analyzed patients was small, thus it is difficult to draw definitive conclusions only from the present study. Further study may be needed to confirm the point.

Conclusions

Although limited for these reasons, the present findings suggest that hyperuricemia might be an ominous predictor, especially in a hyperadrenergic state, in patients with HF. The present data support the hypothesis that measurement of xanthine oxidase levels might be helpful in understanding the exact mechanisms of the present findings in HF.

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Conflict of interest

None declared.

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