doi: 10.1111/j.1751-7133.2010.00144.x

ORIGINAL PAPER

Uric Acid as Prognostic Marker in Advanced Nonischemic Dilated Cardiomyopathy: Comparison With N-Terminal Pro B-Type Natriuretic Peptide Level

Although uric acid (UA) level has been associated with an increased risk of cardiovascular events, it is unclear whether UA can provide greater prognostic information than N-terminal pro B-type natriuretic peptide (NT-proBNP) in advanced heart failure with nonischemic dilated cardiomyopathy (DCM). UA and NT-proBNP values were obtained from a total of 122 DCM patients. Development of clinical events during follow-up was defined as the composite of cardiac death and readmission for heart failure. During follow-up, there were 18 cardiac events. UA and NT-proBNP values were significantly higher in patients with events. The receiver operating characteristics curve showed the area under the curve for UA was greater than that for NT-proBNP. On multivariate analysis, UA remained the only independent predictor of prognosis. UA concentrations ≥8.7 mg/dL rather than NT-proBNP ≥3800 pg/mL were associated with significantly decreased event-free survival. The authors' findings demonstrated that UA value could be an informative predictor in nonischemic DCM. Congest Heart Fail. *2010;16:153–158.*

Hyungseop Kim, MD, PhD; Hong-Won Shin, MD; Jihyun Son, MD; Hyuck-Jun Yoon, MD; Hyoung-Seob Park, MD; Yun-Kyeong Cho, MD, PhD; Choon-Duk Han, MD; Chang-Wook Nam, MD, PhD; Seung-Ho Hur, MD, PhD; Yoon-Nyun Kim, MD, PhD; Kwon-Bae Kim, MD, PhD
From the Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea

Address for correspondence:
Hyungseop Kim, MD, PhD, 194 Dongsan-dong, Jung-gu, Keimyung University Dongsan Medical Center, Daegu 700-712, Republic of Korea
E-mail: khyungseop@dsmc.or.kr
Manuscript received June 8, 2009; revised November 4, 2009; accepted January 2, 2010

Congestive heart failure (CHF) is one of the most common diseases encountered in medical practice, and it has been associated with high mortality and morbidity rates despite advanced treatment methods, particularly in patients with dilated cardiomyopathy (DCM). The ability of serologic biomarkers to predict the prognosis is critical for appropriate treatment strategies. N-terminal pro B-type natriuretic peptide (NT-proBNP) level is regarded as an important predictor in cardiovascular diseases including CHF[1,2]; this may also be the case for uric acid (UA) level.[3–5] However, each of these 2 serologic markers characterizes different pathophysiologic mechanisms involved in CHF. NT-proBNP as a hemodynamic indicator and UA as a metabolic indicator could provide complementary information and help clinicians to stratify the cardiac risk more effectively among patients with CHF.[6,7] However, it is unclear whether UA is an independent risk factor in cardiovascular disease or only a single marker among the associated cardiovascular risk factors. In addition, the clinical implications and prognostic role of an elevated UA level in advanced nonischemic DCM remain poorly understood.

The aim of the present study is to carefully confirm the prognostic value of UA and to compare the predictive power of UA with that of NT-proBNP, which has been regarded as a useful marker for clinical cardiovascular adverse events.

Methods

This study is a retrospective single cardiovascular center study and gathered data from an institutional database search between January 2005 and December 2006. Patients with a clinical diagnosis of DCM were eligible for inclusion in the present study if they fulfilled the following criteria: symptoms or signs of CHF according to Framingham criteria; left ventricular (LV) ejection fraction (EF) <50% without regional wall motion abnormalities; LV end-diastolic dimension >55 mm as revealed by echocardiography; and absence of ischemic heart disease as detected by coronary angiography, stress electrocardiography, or radionuclide test. Patients were excluded if they had ischemic or valvular heart diseases and severe renal dysfunction (glomerular filtration rate <30 mL/min). Additionally, patients receiving pharmacologic therapy for hyperuricemia were also excluded.

Clinical data, echocardiographic data, and medical history were obtained from the electronic medical record (EMR). We obtained serologic data including UA and NT-proBNP levels at first visit to a cardiologic outpatient clinic or admission to cardiology department in all patients. In addition, the following conventional parameters were also recorded: serum creatinine, C-reactive protein, and hemoglobin. Glomerular filtration rate was estimated using

the simplified Modification of Diet in Renal Disease equation as follows[8]: $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if a woman})$; this has been developed and validated as an accurate estimate of glomerular filtration rate.

At study entry, a thorough medical history was reviewed for all patients; information was acquired from the EMR or directly from patients. The primary end point in this study was defined as cardiac death or readmission for CHF. Death or readmission was ascertained initially from the EMR, and the patients who did not have complete medical data were contacted by telephone. The institutional review board approved the study protocol. Informed consent was waived because of the retrospective nature of this study.

Statistical Analysis. Data analyses were performed with the Statistical Package for Social Science (SPSS for Windows 13.0; SPSS Inc., Chicago, IL). Baseline demographic and laboratory data were presented as mean ± standard deviation for continuous variables and frequencies for discrete variables. Student's *t*-test was performed to compare continuous variables, and chi-square test was used to compare categorical variables between groups. As the relationship between NT-proBNP level and the study outcome was not of a linear nature, NT-proBNP level was log-transformed to reduce the effect of extreme values and to perform analyses requiring normal distribution. Receiver operating characteristic (ROC) curves and the areas under the curves were performed to compare the predictive value of UA and NT-proBNP and to determine cutoffs for these 2 levels in terms of prediction of cardiac adverse events. Cox proportional hazard analyses were performed, and variables achieving $P<.10$ on univariate analyses were then tested in a multivariate Cox analysis to determine which ones were significantly associated with cardiac events. In addition, cardiac event-free survival was determined according to the Kaplan–Meier method, and the prognostic significance of UA and NT-proBNP levels was assessed using the overall Mantel–Cox log rank statistic. *P* values were 2-sided, and a *P* value $<.05$ was considered statistically significant.

Results

Clinical and Echocardiographic Characteristics. From a total of 140 patients with nonischemic DCM recruited for the study, 18 were excluded because laboratory values of UA and NT-proBNP were not available at baseline screening. Finally, 122 patients had complete data and formed the present study population. Their average age was 61±14 years, and LVEF was 27.3%±7.8%. Median follow-up duration was 24 months (interquartile range, 12–33 months). During this follow-up period, 18 cardiac events (15%) occurred: 5 deaths and 13 readmissions for CHF. Table I shows comparisons of clinical characteristics between patients with cardiac events and event-free patients. There were no significant differences in age, New York Heart Association class, body mass index, atrial fibrillation, past history of heart failure, and conventional risk factors between the 2 groups. However, patients in whom cardiac events developed had significantly lower systolic blood pressure, greater deterioration of anemia and renal function, and higher UA and NT-proBNP concentrations. In addition, as regards treatment with medication, there was a nonsignificant trend toward more patients receiving loop diuretics. However, at baseline, when the relations between dosage of thiazide or furosemide and UA were analyzed separately, no significant correlations related with dosage of diuretics were observed (data not shown). Furthermore, other medications were similar in both groups.

In terms of echocardiographic findings, as shown in Table II, patients with cardiac events had more enlarged LV cavity, larger LV mass, more reduced EF, and higher pulmonary arterial systolic pressure. Furthermore, mitral E velocity deceleration time (DT) was shorter and E flow velocity was higher. Consequently, mitral early inflow to annular tissue Doppler velocity ratio was higher in cardiac events patients.

Determination of UA. To determine which variables were significantly associated with elevated UA levels in DCM, the univariate and multivariate regression analysis were performed in the whole patient population (Table III). Increasing UA concentrations were found to be significantly associated with estimated glomerular filtration rate, DT, LV mass, NT-proBNP level, and EF. Furthermore, stepwise multivariate regression analysis revealed that estimated glomerular filtration rate, DT, and LV mass were independently associated with level of UA. In the present study, however, age, hypertension, diabetes, and medication history such as diuretics had no significant association with UA concentration (data not shown).

UA and NT-proBNP Levels as Predictors of Adverse Cardiac Events. To determine prognostic factors for cardiac events, univariate and multivariate Cox proportional hazard regression analyses were performed (Table IV). As detailed, in univariate analysis, UA and NT-proBNP values were significant prognostic factors besides confounders such as blood pressure value, EF, hemoglobin level, renal function, and pulmonary arterial systolic pressure; however, UA concentration still remained the only independent predictor for cardiac events in multivariate Cox analysis (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.18–1.86; *P*=.001). As shown in Figure 1, the ROC curve analysis revealed cutoffs of UA and NT-proBNP concentrations to predict cardiac events. The area under the ROC curve for UA was greater (HR, 0.83; 95% CI, 0.741–0.925) than that for NT-proBNP (HR, 0.74; 95% CI, 0.633–0.844). When a UA level of 8.7 mg/dL was used as the cutoff, sensitivity and specificity were 70.6% and 82.8%, respectively. For an NT-proBNP level of 3800 pg/mL, sensitivity and specificity were 82.4% and 59.1%, respectively. Figure 2 shows Kaplan–Meier cardiac event-free survival curves corresponding to the 122 patients who were stratified into 2 groups according to the above determined cutoffs for UA and NT-proBNP. A UA

Table I. Baseline Clinical Characteristics of Study Patients With Nonischemic Advanced Dilated Cardiomyopathy

	Patients Without Cardiac Events (N=104)	Patients With Cardiac Events (N=18)	*P* Value
Age, y	61±14	60±13	.867
Male, No. (%)	65 (62.5)	11 (61.1)	1.000
NYHA class II/III/IV, No. (%)	62 (59.7)/38 (36.5)/4(3.8)	7 (38.8)/10 (55.6)/1(5.6)	.261
Body mass index, kg/m^2	23.7±4.1	22.3±2.9	.188
Systolic blood pressure, mm Hg	121.3±19.4	111.0±19.2	.040
Diastolic blood pressure, mm Hg	73.6±12.2	68.1±12.9	.085
Atrial fibrillation, No. (%)	19 (18.3)	5 (27.8)	.347
Past history of heart failure, No. (%)	34 (32.7)	5 (22.8)	.789
Risk factors			
Hypertension, No. (%)	36 (34.6)	7 (38.9)	.792
Diabetes, No. (%)	24 (23.1)	4 (22.2)	1.000
Stroke, No. (%)	5 (4.8)	3 (16.7)	.094
Log NT-proBNP	7.5±0.6	8.9±0.8	.001
CRP, mg/L	8.3±1.9	5.8±0.7	.587
Uric acid, mg/dL	6.7±2.2	9.7±2.1	<.001
Hemoglobin, g/dL	13.8±2.1	12.2±2.2	.007
BUN, mg/dL	20.3±9.3	24.7±7.2	.057
Creatinine, mg/dL	1.2±0.4	1.3±0.5	.040
eGFR, mL/min/1.73 m^2	68.2±19.9	58.0±25.1	.057
Medications			
Aspirin, No. (%)	58 (55.8)	8 (44.4)	.446
ACEI, No. (%)	40 (38.5)	5 (27.8)	.440
ARB, No. (%)	38 (36.5)	6 (33.3)	1.000
β-Blockers, No. (%)	78 (75.0)	13 (72.2)	.776
Thiazide diuretics, No. (%)	27 (26.0)	4 (22.2)	1.000
Loop diuretics, No. (%)	63 (60.6)	15 (83.3)	.069
Spironolactone, No. (%)	36 (34.6)	5 (27.8)	.788

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Table II. Echocardiographic Findings of Study Patients With Nonischemic Advanced Dilated Cardiomyopathy

	Patients Without Cardiac Events (N=104)	Patients With Cardiac Events (N=18)	*P* Value
Conventional parameters			
LVEDD, cm	6.4±0.8	6.9±1.0	.033
LVESD, cm	5.5±0.8	5.9±1.1	.042
IVSd, cm	0.9±0.2	0.9±0.2	.513
PWd, cm	1.0±0.2	0.9±0.2	.394
Ejection fraction, %	28.3±7.7	21.8±6.4	.001
LA dimension, cm	4.8±1.5	5.0±1.7	.468
LV mass, g	256.4±79.9	271.2±76.0	.044
PASP, mm Hg	23.3±13.9	35.5±15.8	.001
Mitral inflow			
Deceleration time, ms	188.4±64.6	152.8±58.1	.042
Isovolumic relaxation time, ms	119.0±35.1	121.1±51.5	.824
Mitral E velocity, cm/s	73.4±29.5	94.7±32.1	.006
Tissue Doppler imaging			
Septal TDI-Sm, cm/s	4.2±1.2	3.8±0.9	.152
Septal TDI-Em, cm/s	4.3±1.7	4.2±1.5	.763
E/Em ratio	19.0±10.0	24.3±9.3	.038

Abbreviations: E/Em, mitral early inflow to annular tissue Doppler velocity; IVSd, diastolic intraventricular septal thickness; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PASP, pulmonary artery systolic pressure; PWd, diastolic posterior wall thickness; TDI-Em, tissue Doppler image of early diastolic mitral annular velocity; TDI-Sm, tissue Doppler image of systolic mitral annular velocity.

concentration ≥8.7 mg/dL relative to an NT-proBNP level ≥3800 pg/mL had a significantly decreased cardiac event-free survival (log rank χ^2=30.7; *P*<.001, log rank χ^2=7.6; *P*=.006, respectively).

Discussion

While UA is the final result of purine metabolism and its levels are usually increased in chronic heart failure, the prognostic value of UA, particularly in DCM, is still unknown. The increased UA level was caused by the acute insult to a failing heart, leading to aggravating tissue hypoperfusion and hypoxia, which induce xanthine oxidase (XO) activation and oxidative stress production.[9–11] Moreover, XO is activated by immune activation as reflected by up-regulated expression of tumor necrosis factor alpha or free oxygen radicals in heart failure.[7,12–14] Thus, UA would provide a

Table III. Univariate and Multivariate Regression Analyses for Uric Acid Level

	Univariate		Multivariate	
Independent Variables	β Coefficients (95% CI)	*P* Value	β Coefficients (95% CI)	*P* Value
Creatinine	2.160 (1.220 to 3.100)	<.001	1.794 (0.821 to 2.766)	<.001
Deceleration time	−0.014 (−0.021 to −0.007)	<.001	−0.014 (−0.020 to −0.007)	<.001
LV mass	0.008 (0.003 to 0.014)	.002	0.007 (0.002 to 0.012)	.007
Age	−0.033 (−0.065 to −0.001)	.047	–	
Log NT-proBNP	0.409 (0.130 to 0.688)	.004	–	
Ejection fraction	−0.068 (−0.125 to −0.012)	.017	–	
PASP	−0.051 (0.021 to 0.080)	.001	–	

Abbreviations: CI, confidence interval; LV, left ventricle; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure.

Table IV. Cox Regression Analysis of Predictors of Adverse Cardiac Events

	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Uric acid	1.590 (1.242–2.037)	<.001	1.483 (1.181–1.862)	.001
Log NT-proBNP	2.412 (1.262–4.609)	.008	1.402 (0.717–2.743)	.323
Systolic BP	0.963 (0.930–0.997)	.032	0.964 (0.928–1.002)	.066
Ejection fraction	0.887 (0.811–0.970)	.009	0.961 (0.870–1.062)	.435
Hemoglobin	0.772 (0.596–1.000)	.050	0.870 (0.642–1.177)	.366
eGFR	0.975 (0.953–0.997)	.028	0.990 (0.957–1.024)	.558
PASP	1.056 (1.020–1.092)	.002	1.030 (0.991–1.071)	.128
Age	1.012 (0.971–1.054)	.576	–	
Hypertension	1.572 (0.528–4.683)	.416	–	
Diabetes	0.645 (0.143–2.908)	.568	–	
NYHA class	1.960 (0.845–4.548)	.117	–	
BUN	1.030 (0.983–1.079)	.218	–	
E/Em ratio	1.035 (0.991–1.080)	.118	–	

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; E/Em, mitral early inflow to annular tissue Doppler velocity; eGFR, calculated glomerular filtration; HR, hazard ratio; NT-ProBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure.

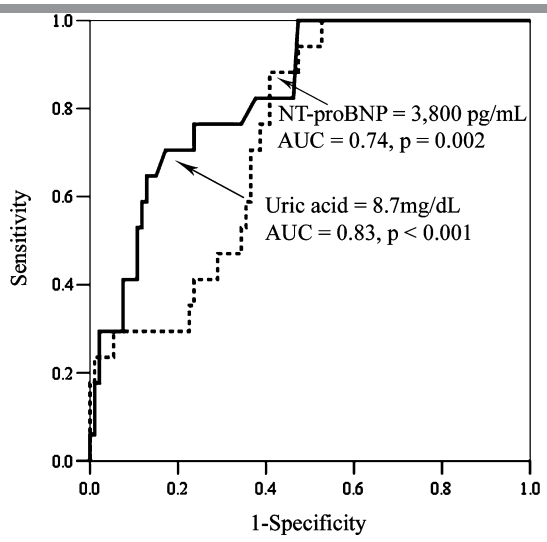

Figure 1. Receiver operating characteristic curve for ability of N-terminal pro B-type natriuretic peptide (NT-proBNP) and uric acid levels to predict cardiac events. AUC indicates area under the receiver operating characteristic curve.

useful marker for the decompensation trigger in chronic heart failure.

Generally, agents such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or potassium-sparing diuretics might have a great impact on survival in CHF. In addition, angiotensin receptor blockers and diuretics also have been shown to be associated with an increased UA concentration.[15,16] However, our study was not sufficiently powered to comment on the association and role of the medication with prognosis. As expected in the advanced DCM patients in this study, only half of patients were taking these drugs, because of lower EF or cardiac output. Thus, adjusted for medications and other risk factors, we could not have statistical significance of the therapeutic effect in the present study. Alternatively, the explanation will of course lie in the advanced severity of heart failure and the exclusion of ischemic heart failure.

Implications for the Prognostic Power of UA Level as a Nonhemodynamic Marker. Generally, hyperuricemia seems to be related to a variety of diseases such as renal impairment, diabetes, hypertension, and gout, all of which appear to contribute to the progression of the failing heart.[17] CHF is linked to the consequence of interrelated hemodynamic, neurohormonal, immunologic, or endocrine mechanisms, and thus, advanced CHF such as DCM has multifactorial metabolic features leading to cardiac cachexia, which carries a very poor prognosis.[6] Moreover, CHF is a state of impaired oxidative metabolism, and serum UA concentrations reflect

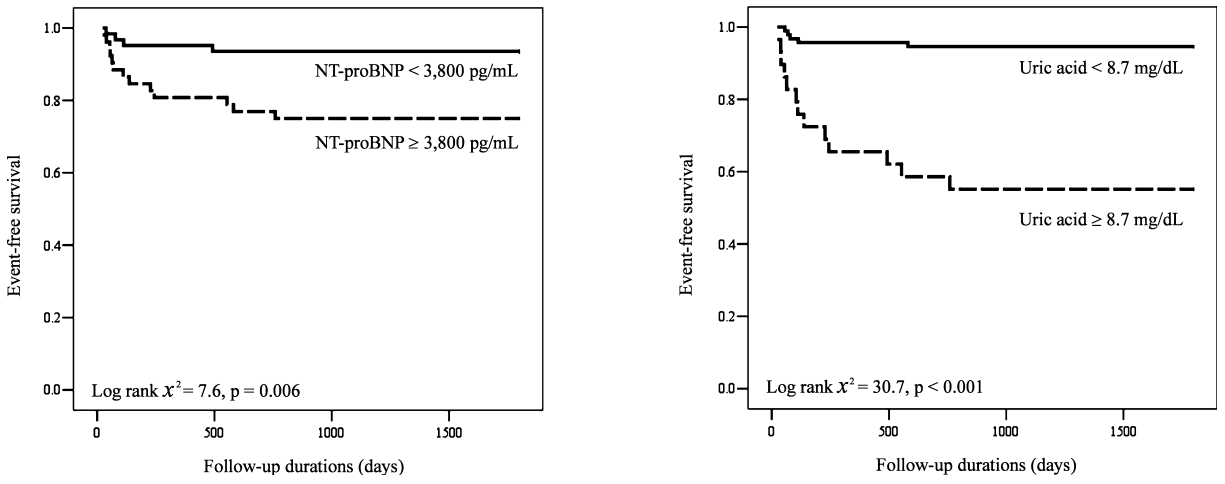

Figure 2. Kaplan–Meier cardiac event-free survival curves of N-terminal pro B-type natriuretic peptide (NT-proBNP) and uric acid concentration.

functional capacity, disease severity, and an impairment of oxidative metabolism.[9] Therefore, severely advanced DCM usually has the tendency toward a proinflammatory environment and increased oxidative stress. Additionally, LV myocardium also becomes one of the etiologies causing an elevated UA level. The larger LV mass or hypertrophy has the important potential to increase UA level,[18] because hyperuricemia is an independent risk factor for vascular constriction and hypertension,[19,20] which were primarily associated with cardiac hypertrophy. Accordingly, with the evidence of a link between LV hypertrophy and UA level, our findings provide a potential concept to support the increased risk of cardiac events in DCM patients with increased LV mass, although the significant power of LV mass in this group of patients is less impressive than in the patients with the general demographics of CHF. Indeed, UA could be regarded as a more encompassing marker or potential surrogate by reflecting general condition as well as a status of LV mass or hypertrophy.

Although NT-proBNP levels were also significantly elevated and correlated with heart failure severity, pathophysiologic pathways such as those associated with a nonhemodynamic mechanism in the current study would be able to elevate UA rather than NT-proBNP levels. In fact, the elevation of NT-proBNP may be mediated mainly by hemodynamic changes in cardiac or pulmonary circulation; meanwhile, elevated UA level was demonstrated as a metabolic marker independent of LV hemodynamics or function. Moreover, the lack of significance of NT-proBNP in the present study could be the result of advanced DCM itself, as was supported by the findings of an exhaustion of the ability of cardiomyocytes to synthesize and secrete a sufficient amount of NT-proBNP, particularly in end-stage heart failure.[21] In addition, the paradoxically low NT-proBNP level in chronic and advanced heart failure would be an adverse prognostic marker.[22] Consequently, the predictive values of NT-proBNP for severe advanced DCM seemed to be markedly weaker than those of UA upon ROC analysis.

Implications for the Prognostic Power of UA Level as a Hemodynamic Marker. With respect to hemodynamic insult, UA, contributed by increased XO, reflects an imbalance between myocardial performance and energy consumption; in contrast, XO inhibition by allopurinol enhances the contractile responses of the myocardium to inotropic agents or to exercise.[7] XO is believed to be the key enzyme related to UA synthesis, and it may also contribute to oxidative injury to myocytes.[14] Therefore, UA would have a key role as an endogenous critical agent when released from damaged myocardium. When these characteristics of UA on prognosis of CHF are considered, UA itself would be both player and bystander in CHF, and it would have a more powerful impact than NT-proBNP, which is only a bystander in CHF pathophysiology[23]; however, the mechanisms through which UA would have greater prognostic value than NT-proBNP in CHF are uncertain. In patients with CHF, in which XO activity is usually up-regulated,[14] hyperuricemia is caused by increased production with or without decreased renal excretion. These findings would be charged with hemodynamic and renal functional deterioration or worsening, as suggested by the DT and serum creatinine level determining UA concentration in the present study. In fact, UA had a good, positive correlation with serum creatinine level and DT, which suggests that UA levels are increased in patients with renal dysfunction and restrictive mitral filling pattern. These findings agree with the results of an inverse relationship between UA and echocardiographic parameters of diastolic function.[24] During hemodynamic insult, the ensuing renal hypoperfusion would result in transient decreased renal function and glomerular filtration rate, which would contribute to the increased UA level. Therefore, hyperuricemia could be a marker for not only an impaired metabolism but also the detrimental process of the failing heart. Indeed, by demonstrating a close

association between UA and deteriorating hemodynamic parameters, the present study would add to this evidence. However, despite the significance of renal perfusion, unfortunately, we found no additional significance in prediction for cardiac events. In this study, the patients with advanced renal failure were excluded in order to assess not the passive UA elevation secondary to renal failure but the active involvement of UA pathogenesis associated with CHF. Thus, the multivariate analysis would reveal the lack of independent significance of the renal dysfunction in the present study, although the result obtained in this study could not be applied to some patients in advanced stages of renal disease.

Limitations. This study has several limitations. It was a retrospective study of patients' treatment; thus, the current findings might not be representative of all clinical CHF. Furthermore, we also have to acknowledge that it was a single-center study performed in a relatively small sample size with a very low event rate. In addition, with respect to the relation of blood urea nitrogen to prognosis, we could not obtain similar results for cardiac events, whereas several studies previously have shown that increased blood urea nitrogen was associated with adverse cardiac outcomes.[25–28] In our population, the number of patients with New York Heart Association class IV heart failure was relatively small, and it is possible that the effects of acute vasoconstriction of afferent arteriole on blood urea nitrogen concentration could not be observed in the current study.

Conclusions

The present study provides practical evidence on the prognostic value of UA level in nonischemic DCM. UA is a marker of metabolic status and also would be actively involved in the hemodynamic process, both of which are important to CHF pathophysiology. Thus, high UA level would be an informative link as a global marker for general conditions associated with CHF, as compared to the more established NT-proBNP level. In addition to NT-proBNP, UA level seems therefore to emerge as a useful predictor of progression or exacerbation of CHF, with stronger prognostic power than that of NT-proBNP, particularly in patients with nonischemic DCM.

Acknowledgement: *This study was supported by the Regional Technology Innovation Program (RTI04-01-01) of the Ministry of Commerce, Industry and Energy (MOCIE).*

References

1 Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol.* 2001;37:386–391.

2 Maeda K, Tsutamoto T, Wada A, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. *J Am Coll Cardiol.* 2000;36:1587–1593.

3 Iwashima Y, Horio T, Kamide K, et al. Uric acid, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. *Hypertension.* 2006;47:195–202.

4 Alderman MH. Uric acid and cardiovascular risk. *Curr Opin Pharmacol.* 2002;2:126–130.

5 Niizeki T, Takeishi Y, Arimoto T, et al. Hyperuricemia associated with high cardiac event rates in the elderly with chronic heart failure. *J Cardiol.* 2006;47:219–228.

6 Anker SD, Rauchhaus M. Heart failure as a metabolic problem. *Eur J Heart Fail.* 1999;1:127–131.

7 Cappola TP, Kass DA, Nelson GS, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation.* 2001;104:2407–2411.

8 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461–470.

9 Leyva F, Anker S, Swan JW, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *Eur Heart J.* 1997;18:858–865.

10 Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation.* 2003;107:1951–1953.

11 Pascual-Figal DA, Hurtado-Martinez JA, Redondo B, et al. Hyperuricaemia and long-term outcome after hospital discharge in acute heart failure patients. *Eur J Heart Fail.* 2007;9:518–524.

12 Johnson RJ, Rodriguez-Iturbe B, Kang DH, et al. A unifying pathway for essential hypertension. *Am J Hypertens.* 2005;18:431–440.

13 Ruggiero C, Cherubini A, Ble A, et al. Uric acid and inflammatory markers. *Eur Heart J.* 2006;27:1174–1181.

14 de Jong JW, Schoemaker RG, de Jonge R, et al. Enhanced expression and activity of xanthine oxidoreductase in the failing heart. *J Mol Cell Cardiol.* 2000;32:2083–2089.

15 Hamada T, Ichida K, Hosoyamada M, et al. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. *Am J Hypertens.* 2008;21:1157–1162.

16 Reyes AJ, Leary WP. Hypertension, diuretics, and uric acid. *Am J Hypertens.* 2006;19:1093–1094.

17 Steele TH. Control of uric acid excretion. *N Engl J Med.* 1971;284:1193–1196.

18 Kurata A, Shigematsu Y, Higaki J. Sex-related differences in relations of uric acid to left ventricular hypertrophy and remodeling in Japanese hypertensive patients. *Hypertens Res.* 2005;28:133–139.

19 Selby JV, Friedman GD, Quesenberry CP Jr. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol.* 1990;131:1017–1027.

20 Jossa F, Farinaro E, Panico S, et al. Serum uric acid and hypertension: the Olivetti heart study. *J Hum Hypertens.* 1994;8:677–681.

21 Packer M. Should B-type natriuretic peptide be measured routinely to guide the diagnosis and management of chronic heart failure? *Circulation.* 2003;108:2950–2953.

22 Sun T, Wang L, Zhang Y. Prognostic value of B-type natriuretic peptide in patients with chronic and advanced heart failure. *Intern Med J.* 2007;37:168–171.

23 Duan X, Ling F. Is uric acid itself a player or a bystander in the pathophysiology of chronic heart failure? *Med Hypotheses.* 2008;70:578–581.

24 Cicoira M, Zanolla L, Rossi A, et al. Elevated serum uric acid levels are associated with diastolic dysfunction in patients with dilated cardiomyopathy. *Am Heart J.* 2002;143:1107–1111.

25 Giamouzis G, Kalogeropoulos AP, Georgiopoulou VV, et al. Incremental value of renal function in risk prediction with the Seattle Heart Failure Model. *Am Heart J.* 2009;157:299–305.

26 Cauthen CA, Lipinski MJ, Abbate A, et al. Relation of blood urea nitrogen to long-term mortality in patients with heart failure. *Am J Cardiol.* 2008;101:1643–1647.

27 Filippatos G, Rossi J, Lloyd-Jones DM, et al. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Theraputic Impact of a Vasopressin Antagonist in Chronic Heart Faiure (ACTIV in CHF) study. *J Card Fail.* 2007;13:360–364.

28 Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52:1527–1539.