



Mediation of Arterial Stiffness for Hyperuricemia-Related Decline of Cardiac Systolic Function in Healthy Men

Hiroki Nakano, MD, PhD; Kazuki Shiina, MD, PhD; Takamichi Takahashi, MD; Kento Kumai, MD; Masatsune Fujii, MD; Yoichi Iwasaki, MD, PhD; Chisa Matsumoto, MD, PhD; Taishiro Chikamori, MD, PhD; Akira Yamashina, MD, PhD; Hirofumi Tomiyama, MD, PhD

Background: This prospective observational study examined whether hyperuricemia may be associated with impaired left ventricular (LV) systolic function and increased cardiac load resulting from increased arterial stiffness.

Methods and Results: In 1,880 middle-aged (mean [±SD] age 45±9 years) healthy men, serum uric acid (UA) levels, pre-ejection period/ejection time (PEP/ET) ratio, serum N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, and brachial-ankle pulse wave velocity (baPWV) were measured at the start and end of the 3-year study period. Linear regression analysis revealed that serum UA levels measured at baseline were significantly associated with the PEP/ET ratio, but not with serum NT-proBNP levels, measured at baseline ($\beta=0.73\times 10^{-1}$, $P<0.01$) and at the end of the study period ($\beta=0.68\times 10^{-1}$, $P<0.01$). The change in the PEP/ET ratio during the study period was significantly greater in the High-UA (UA >7 mg/dL in 2009 and 2012) than Low-UA (UA ≤7 mg/dL in 2009 and 2012) group. Mediation analysis demonstrated both direct and indirect (via increases in baPWV) associations between serum UA measured at baseline and the PEP/ET ratio measured at the end of the study period.

Conclusions: In healthy middle-aged Japanese men, hyperuricemia may be associated with an accelerated decline in ventricular systolic function, both directly and indirectly, via increases in arterial stiffness.

Key Words: Arterial stiffness; Cardiac systolic function; Heart failure; Uric acid

The prevalence of heart failure (HF) is increasing around the world, and it is becoming a major public health problem. Despite advances in treatments for HF, morbidity and mortality remain high.^{1,2} Thus, in current guidelines, HF is classified into Stages A–D based on severity, with an emphasis on the importance of early intervention in the Stage A population to prevent further progression to Stage B and beyond by managing HF risk factors.^{3–5} Therefore, confirming the risk factors for the development of HF and establishing risk management strategies are important issues.

Although a relationship between hyperuricemia and the risk of developing HF has been reported in a community-based population,^{6,7} it remains to be confirmed whether the serum uric acid (UA) concentration is, indeed, an independent risk factor for the development of HF. It has been noted that aging is associated with a decline in cardiac systolic and diastolic function in healthy subjects.⁸ In addition, regional cohort data suggest that hyperuricemia is associated with a decrease in left ventricular (LV) systolic function over time, but the underlying mechanisms have not been clarified.

Recent prospective studies have identified increased arterial stiffness as an independent risk factor for the development of HF,^{9,10} and arterioventricular coupling has been thought as being a key underlying mechanism.¹¹ Increased arterial stiffness is thought to directly affect cardiac function. Several previous studies have reported an association between hyperuricemia and increased arterial stiffness.^{12–14} Therefore, we hypothesized that hyperuricemia may influence the rate of progression of HF from an early stage by, at least in part, increasing arterial stiffness. The pre-ejection time to ejection time (PEP/ET) ratio has been reported as a useful and simple indicator for evaluating not only LV systolic function, but also arterioventricular coupling.^{15,16} Although the ejection fraction assessed by echocardiography is the standard method to assess cardiac systolic function, PEP/ET was used in the present study because of its simplicity and applicability to a large number of study subjects.

The present 3-year prospective observational study, conducted in healthy middle-aged Japanese men without a past history of cardiovascular disease (CVD), used the PEP/ET ratio to examine whether hyperuricemia may be associated with an increased rate of decline in LV systolic function and

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Department of Cardiology, Tokyo Medical University, Tokyo, Japan

Mailing address: Hirofumi Tomiyama, MD, PhD, Department of Cardiology and Division of Pre-emptive Medicine for Vascular Damage, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. E-mail: tomiyama@tokyo-med.ac.jp

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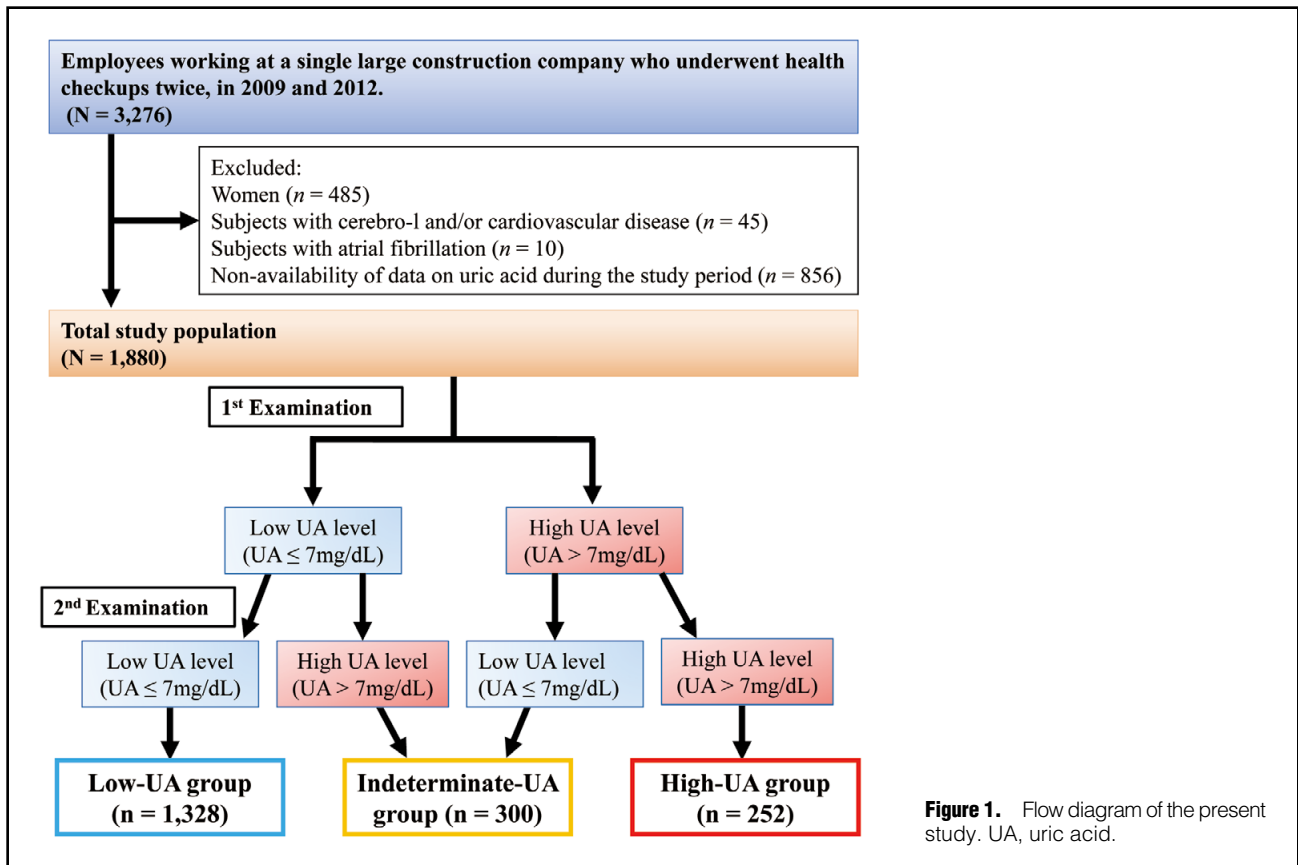


Figure 1. Flow diagram of the present study. UA, uric acid.

an increase in cardiac load via increased arterial stiffness.

Methods

Study Design

This study was a prospective observational study that used data from the same cohort as in our previously reported observational study.¹⁷ In summary, we used health checkup data of workers for a single large Japanese construction company. All subjects gave informed consent for the use of their data for this study.

This study was approved by the Ethics Committee of Tokyo Medical University (SH3450) and was conducted in compliance with the principles of the Declaration of Helsinki.

Study Population

We extracted 3,276 datasets from the annual health checkup records of subjects for the years 2009 and 2012. Among these subjects, women (n=485), patients with cerebrovascular disease and/or CVD (n=45), patients with atrial fibrillation (n=10), and those for whom complete data for serum UA concentrations during the study period were not available (n=856) were excluded. This left data for 1,880 subjects for use in the present study. Cross-sectional and longitudinal analyses were performed using the data recorded in 2009 as baseline data and data recorded in 2012 as the data for the end of the study period (Figure 1).

Measurements

In the subject cohort included in this study, health checkups were conducted in the morning hours after the participants

had fasted overnight and consisted of a medical interview, physical examination, blood examinations, blood pressure measurement (twice), measurement of brachial-ankle pulse wave velocity (baPWV), and determination of the PEP/ET ratio. Serum UA was measured using an enzymatic method, and serum N-terminal pro B-type natriuretic peptide (NT-proBNP) was determined by chemiluminescence immunoassay (Roche Diagnostic, Mannheim, Germany). The baPWV was measured using a volume plethysmograph (Form/ABI; Colin, Komaki, Japan), as described previously.¹⁸ The ET was automatically measured from the pulse-volume waveform, from the foot to the dicrotic notch (equivalent to the incisura on the downstroke of the aortic pressure waveform produced by the closure of the aortic valves). The total electromechanical systolic interval (QS2) was measured from the onset of the QRS complex on the electrocardiogram to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram. PEP was automatically calculated by subtracting ET from QS2.^{19,20}

Statistical Analysis

Continuous variables are presented as the mean±SD and categorical variables are presented as numbers with percentages. The significance of differences in variables between the first and second examinations was assessed using paired t-tests or the McNemar test. Multivariate linear regression analyses was used to assess the associations of the serum UA concentrations with the PEP/ET ratio, log-transformed serum NT-proBNP concentrations (the distribution of NT-proBNP concentrations was skewed, so values were log-

Parameter	Baseline	End of the study period	P value
Age (years)	45±9	48±9	<0.01
BMI (kg/m ²)	24.0±3.0	24.2±3.1	<0.01
Current smoking	543 (29)	456 (24)	<0.01
SBP (mmHg)	123±14	121±14	<0.01
Heart rate (beats/min)	69±10	68±10	<0.01
Uric acid (mg/dL)	6.2±1.2	6.1±1.2	<0.01
Hemoglobin (g/L)	14.9±1.0	14.6±0.9	<0.01
LDL-C (mg/dL)	129±31	128±32	0.63
HDL-C (mg/dL)	63±16	65±16	<0.01
TG (mg/dL)	130±118	125±90	0.02
Serum creatinine (mg/dL)	0.88±0.48	0.85±0.39	<0.01
HbA1c (%)	5.2±0.5	5.1±0.6	<0.01
Serum NT-proBNP (pg/mL)	18 [8–31]	24 [14–38]	<0.01
baPWV (cm/s)	1,291±187	1,317±203	<0.01
Ankle brachial index	1.14±0.73	1.15±0.71	0.01
PEP/ET ratio	0.35 [0.32–0.38]	0.36 [0.32–0.39]	<0.01
Medication history			
Hypertension	172 (9)	261 (14)	<0.01
Dyslipidemia	67 (4)	115 (6)	<0.01
Diabetes	51 (3)	73 (4)	<0.01
Hyperuricemia	68 (4)	81 (4)	<0.01

Continuous variables are presented as the mean ± SD if normally distributed and as the median [interquartile range] if not; categorical variables are presented as n (%). baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro B-type natriuretic peptide; PEP/ET, pre-ejection period/ejection time; SBP, systolic blood pressure; TG, triglyceride.

Outcome variable	Crude				Adjusted ^A			
	Total R ² (×10 ⁻¹)	Standardized coefficient (×10 ⁻¹)	Non-standardized coefficient (×10 ⁻¹ ; 95% CI)	P value	Total R ² (×10 ⁻¹)	Standardized coefficient (×10 ⁻¹)	Non-standardized coefficient (×10 ⁻¹ ; 95% CI)	P value
PEP/ET ratio								
At baseline	0.04	0.69	0.03 (0.01, 0.04)	<0.01	1.4	0.73	0.03 (0.01, 0.05)	<0.01
At the end of the study	0.08	0.93	0.04 (0.02, 0.06)	<0.01	1.0	0.60	0.02 (0.01, 0.04)	0.01
Log [NT-proBNP]								
At baseline	0.04	-0.62	-0.43 (-0.69, 0.17)	<0.01	1.7	-0.48	-0.33 (-0.63, 0.03)	0.03
At the end of the study	-0.05	-0.08	-0.05 (-0.33, 0.23)	0.72	0.14	-	-	0.53
baPWV								
At baseline	0.05	0.76	1.2 (0.6, 1.8)	<0.01	4.9	0.71	1.1 (0.56, 1.6)	<0.01
At the end of the study	0.1	1.0	1.7 (1.0, 2.5)	<0.01	3.8	0.81	1.3 (0.72, 2.0)	<0.01

^AAdjusted for age, BMI, SBP, heart rate, HbA1c, serum LDL-C, current smoking, amount of drinking, and past medical history of hyperuricemia at baseline. CI, confidence interval; [NT-proBNP], serum NT-proBNP concentration. Other abbreviations as in Table 1.

transformed prior to analysis), and baPWV measured at baseline. In addition, stepwise multivariate linear regression analyses were used to assess the associations of serum UA concentrations measured at baseline with the PEP/ET ratio, log-transformed serum NT-proBNP concentrations, and baPWV measured at the end of the study period.

The subjects were divided into 3 groups based on serum UA concentrations at the start and end of the study period: High-UA, serum UA >7 mg/dL in both 2009 and 2012; Low-UA, serum UA ≤7 mg/dL in both 2009 and 2012; and

Indeterminate-UA, serum UA ≤7 mg/dL in 1 examination (2009 or 2012) and >7 mg/dL in the other examination (2009 or 2012). Changes in each of the measured variables were compared among the 3 groups using the least significant difference method. Mediation analysis was used to further investigate the mechanism underlying the association between serum UA concentrations and the rate of decline in cardiac function. Adjustments were made for the covariates of age, body mass index, systolic blood pressure (SBP), heart rate (HR), blood HbA1c, serum low-density

Table 3. Results of Univariate and Multivariate Linear Regression Analyses Assessing Associations Between the baPWV Measured at Baseline and the PEP/ET Ratio and NT-proBNP Concentrations Measured at Baseline and at the End of the Study Period

Outcome variable	Crude				Adjusted ^A			
	Total R ² (×10 ⁻¹)	Standardized coefficient (×10 ⁻¹)	Non-standardized coefficient (×10 ⁻¹ ; 95% CI)	P value	Total R ² (×10 ⁻¹)	Standardized coefficient (×10 ⁻¹)	Non-standardized coefficient (×10 ⁻¹ ; 95% CI)	P value
PEP/ET ratio								
At baseline	1.0	3.0	0.08 (0.07–0.1)	<0.01	1.7	2.9	0.8 (0.6–0.9)	<0.01
At the end of the study	0.3	1.8	0.05 (0.04–0.06)	<0.01	1.0	1.1	0.03 (0.02–0.04)	<0.01
Log [NT-proBNP]								
At baseline	0.2	0.1	0.6 (0.4–0.8)	<0.01	1.7	–	–	0.51
At the end of the study	0.3	1.8	0.7 (0.5–0.9)	<0.01	0.1	–	–	0.53

^AAdjusted for age, BMI, SBP, heart rate, HbA1c, serum LDL-C, current smoking, amount of drinking, and past medical history of hyperuricemia at baseline. Abbreviations as in Tables 1,2.

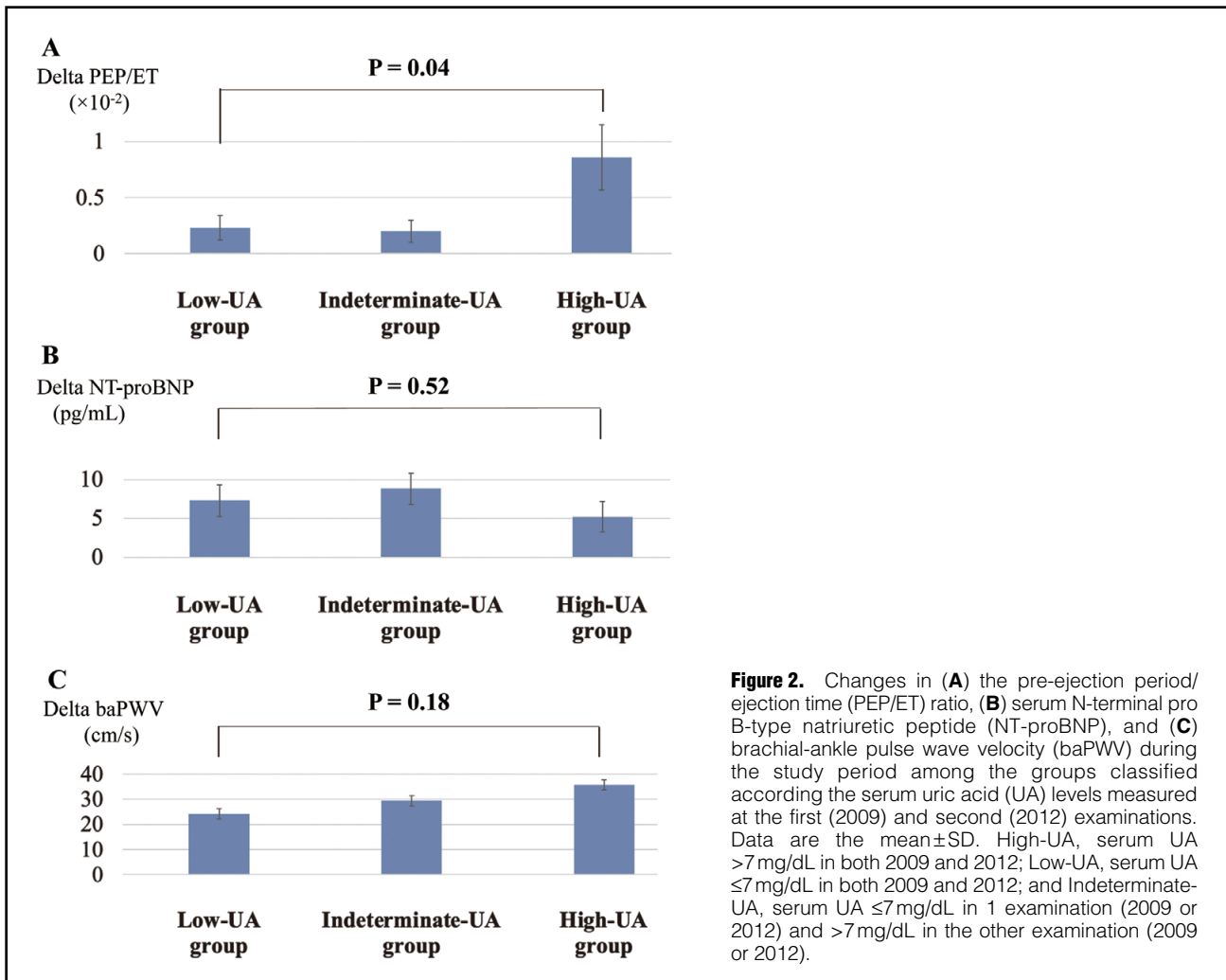


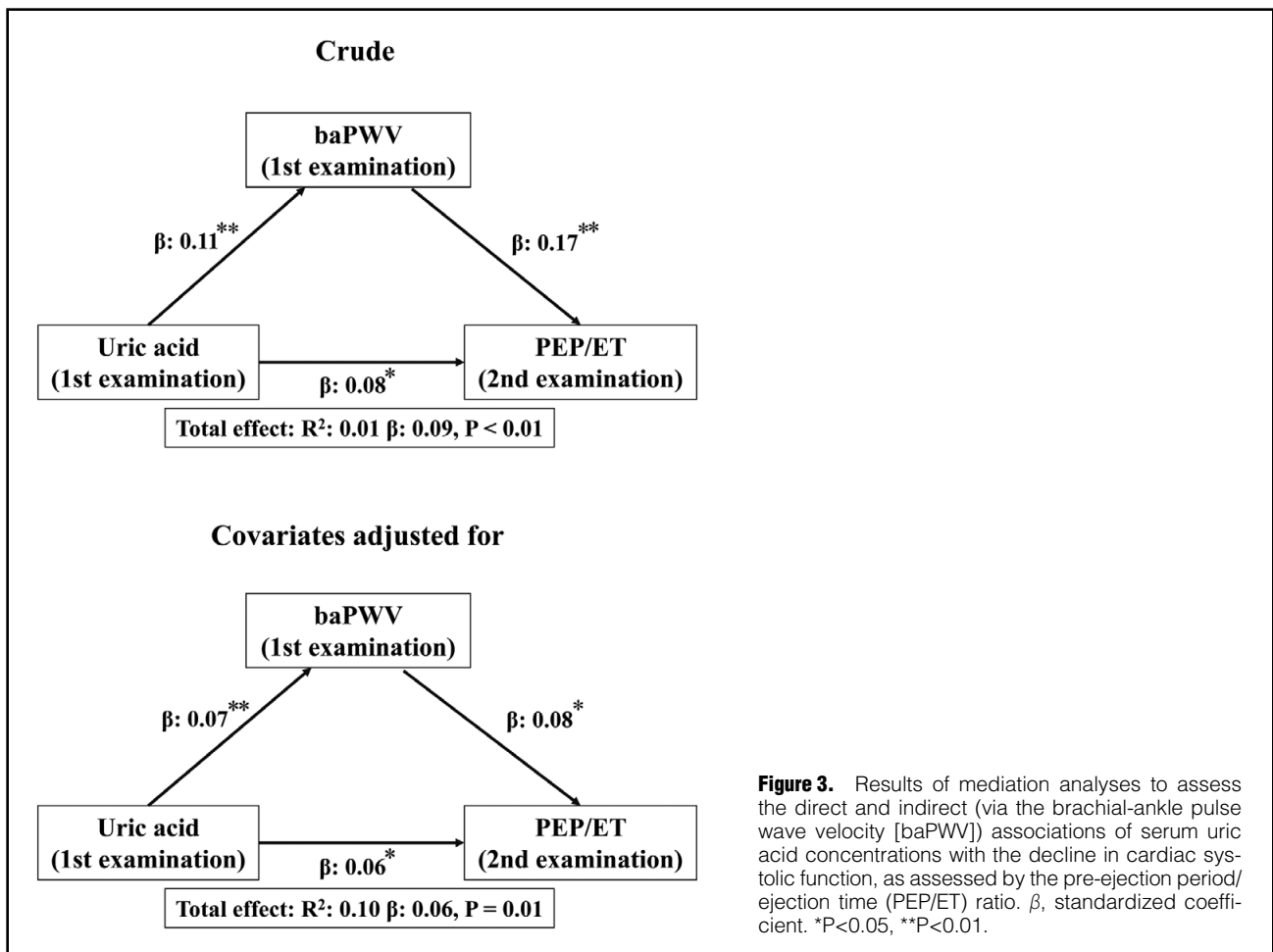
Figure 2. Changes in (A) the pre-ejection period/ejection time (PEP/ET) ratio, (B) serum N-terminal pro B-type natriuretic peptide (NT-proBNP), and (C) brachial-ankle pulse wave velocity (baPWV) during the study period among the groups classified according the serum uric acid (UA) levels measured at the first (2009) and second (2012) examinations. Data are the mean±SD. High-UA, serum UA >7 mg/dL in both 2009 and 2012; Low-UA, serum UA ≤7 mg/dL in both 2009 and 2012; and Indeterminate-UA, serum UA ≤7 mg/dL in 1 examination (2009 or 2012) and >7 mg/dL in the other examination (2009 or 2012).

lipoprotein cholesterol (LDL-C), serum creatinine, current smoking, amount of drinking, and a past medical history of hyperuricemia at the start of the study period as factors that could potentially affect the risk of developing HF.

All statistical tests were 2-tailed, and $P < 0.05$ was considered significant. All analyses were conducted using IBM/SPSS version 25.0 (IBM/SPSS, Chicago, IL, USA).

Results

The mean age of the patients at study baseline was 45 years. Significant increases in the PEP/ET ratio, serum NT-proBNP concentrations, baPWV, and serum high-density lipoprotein cholesterol, and significant decreases in SBP, HR, serum UA, serum LDL-C, serum triglyceride, serum



creatinine, and blood HbA1c were observed during the 3-year study period (based on differences in values measured at baseline in 2009 and at the end of the study period in 2012; **Table 1**).

Linear regression analyses revealed significant associations between serum UA concentrations at baseline and both the PEP/ET ratio and baPWV measured at baseline and at the end of the study period, even after adjusting for the aforementioned covariates (**Table 2**; for details, see **Supplementary Tables 1 and 2**). Conversely, no significant association was noted between the serum UA concentrations and the log-transformed serum NT-proBNP concentrations (**Table 2**). Linear regression analysis also revealed a significant association between baPWV measured at baseline and the PEP/ET ratio, but not log-transformed serum NT-proBNP concentrations, measured at baseline and at the end of the study period (**Table 3**).

Subjects were divided into 3 groups based on serum UA concentrations measured at the start and end of the study period: High-UA (serum UA >7 mg/dL in 2009 and 2012), Low-UA group (serum UA ≤ 7 mg/dL in 2009 and 2012), and Indeterminate-UA (serum UA ≤ 7 mg/dL in 1 examination and >7 mg/dL in the other; **Figure 1**). Although changes in the PEP/ET ratio (Δ PEP/ET; i.e., the value at the end of the study minus the baseline value) during study the period were significantly higher in the High-UA than Low-UA group, there were no significant differences among the 3 groups in

changes in serum NT-proBNP and baPWV (**Figure 2**). These results remained unchanged when only the High-UA and Low-UA groups were compared (**Supplementary Figure**). The mediation analyses showed that serum UA measured at baseline had both a direct and indirect effect, mediated by baPWV, on the PEP/ET ratio measured at the end of the study period, even after adjusting for the covariates mentioned above (**Figure 3**).

Discussion

The novel findings of this study were that: (1) elevated serum UA concentrations were significantly associated with impaired cardiac systolic function, as estimated by the PEP/ET ratio; and (2) serum UA concentrations showed a significant longitudinal association with the rate of decline in cardiac systolic function in healthy middle-aged men in the Japanese general population. The latter association was direct, as well as indirect, mediated by increased arterial stiffness.

Serum UA and Impaired LV Systolic Function

Serum UA has been reported as a marker for predicting the prognosis in patients with HF;^{21–23} furthermore, some reports suggest that hyperuricemia is associated with an increased risk of developing HF. Based on the results of a meta-analysis, Huang et al reported that hyperuricemia is a risk factor

for the development of HF.²⁴ Significantly, Krishnan showed that hyperuricemia was an independent risk factor for the development of HF in the general population.⁷ Furthermore, animal studies have shown that hyperuricemia could be associated with impaired cardiac contraction, LV fibrosis, and LV remodelling.²⁵ According to one cross-sectional study of subjects in the general population, hyperuricemia was correlated with LV strain, which is an index of LV contraction and decreased LV function.²⁶ The present study is the first to demonstrate a longitudinal association between serum UA concentrations and a decline in LV systolic function in apparently healthy subjects.

Mechanism Underlying the Association of Serum UA With Impaired LV Function

The results of the present study suggest that hyperuricemia may impair cardiac systolic function via both a direct and an indirect pathway, mediated via arterial stiffness. As a plausible direct pathway, UA is the final product of the purine metabolic pathway and, during this metabolic process, xanthine oxidase generates reactive oxygen species (ROS). Moreover, it has been reported that when UA is taken up by cells via urate transporter 1 (URAT-1), it causes cell damage as a pro-oxidant that induces the generation of ROS. ROS play an important role in the pathophysiology of HF and have been reported to cause myocardial fibrosis, LV remodeling, and, finally, reduced myocardial contractility.^{27,28} As a plausible indirect pathway, via its effect on arterial stiffness, UA taken up into cells by URAT-1, where it: (1) activates extracellular signal-regulated kinase 1/2 and p38 via a redox reaction, causing arterial sclerosis by increasing the production of cyclooxygenase 2 through activation of nuclear transcription factors such as nuclear factor (NF)- κ B, and activator protein 1; (2) promotes inflammation through activation of monocyte chemoattractant protein-1; and (3) promotes cell proliferation through activation of platelet-derived growth factor (PDGF) and PDGF receptors. In fact, addition of UA to human vascular endothelial cells in culture has been reported to induce inflammation.²⁹ The aforementioned mechanisms could be involved in the increase in arterial stiffness associated with elevated serum UA concentrations, which is known to affect LV remodeling, myocardial fibrosis, and contractile dysfunction via arterioventricular coupling.¹¹

Despite previous reports of a significant association between arterial stiffness and serum NT-proBNP concentrations,³⁰ no significant association was observed between serum UA and NT-proBNP concentrations in the present study. One plausible explanation for this is that the association between increased arterial stiffness and hyperuricemia is not sufficiently strong as to be reflected in elevated serum NT-proBNP concentrations.

Clinical Implications and Perspectives

It is now thought that management of hyperuricemia is essential to prevent the development of CVD. In addition, the findings of the present study suggest that management of hyperuricemia is an effective measure to prevent the development of HF. This study demonstrated that hyperuricemia-related impairment of cardiac systolic function may also be mediated, at least in part, by increased arterial stiffness. Hypertension and diabetes are well-known risk factors for the development of HF, and lifestyle modifications in patients with hypertension and diabetes have been reported to lead to improvements in arterial stiffness.³¹ Therefore,

further large-scale prospective studies are needed to clarify whether lifestyle modifications in patients with hypertension, diabetes, or hyperuricemia are beneficial in preventing the development of HF via arterial de-stiffening.

Study Limitations

This study has several possible limitations that need to be acknowledged. First, this study was a single-center study, which may inevitably have introduced selection bias. Therefore, a larger-scale multicenter study is warranted to confirm our findings. Second, because the present study was conducted in healthy subjects, the amount of change in each of the variables examined over the 3-year study period was small. This may be one of the reasons for the absence of any significant correlation between serum UA and NT-proBNP concentrations. Furthermore, because the number of items that could be used was limited because the study was based on medical examination data, it is possible that confounding factors may not have been completely eliminated. In addition, we adjusted for alcohol consumption levels and obesity,^{32,33} which are known to affect the serum UA concentrations, but not for other factors, including medication data (e.g., a history of treatment with antihypertensive drugs and hypolipidemic drugs). Third, this study was conducted only in men because of the small number of women registered in the corporate health checkup database. Fourth, although the PEP/ET ratio has been reported to show a good correlation with LV ejection fraction,^{15,16,34} which is an index of LV contractility, no data on the markers of LV systolic function other than the PEP/ET ratio, including echocardiographic data, were available for the present study. Furthermore, because the amount of change in the PEP/ET ratio corresponding to the LV ejection fraction (LVEF) is small ($LVEF = 1.125 - 1.25 \times PEP/ET$),³⁴ the amount of change in the PEP/ET ratio during the study period was also small. Although the study population for this study was large, technical errors in the PEP/ET measurements could have affected the results. It has been reported that arterioventricular coupling affects LV diastolic function, but LV diastolic function could not be examined in the present study. In addition, baPWV reflects the stiffness of large- to intermediate-sized arteries. Therefore, further studies are needed to examine the association of serum UA concentrations with LV systolic function as assessed by markers other than the PEP/ET ratio, with LV diastolic function, and with the stiffness of the large arteries as assessed by the carotid-femoral pulse wave velocity in other ethnicities and in women.

Conclusions

In healthy middle-aged Japanese men, hyperuricemia may be associated with an accelerated rate of decline in LV systolic function, both directly and indirectly, via increases in arterial stiffness.

Sources of Funding

This study was supported by Omron Health Care Company (Kyoto, Japan), Asahi Calpis Wellness Company (Tokyo, Japan), and Teijin Pharma Company (Tokyo, Japan), all of which awarded funds to H.T.

Disclosures

H.T. reports that the sponsor (Omron Health Care Company) assisted with data formatting (i.e., transferring brachial-ankle pulse wave velocity data stored by the measurement equipment to Excel files). The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of Tokyo Medical University (SH3450) and was conducted in compliance with the principles of the Declaration of Helsinki.

Data Availability

The anonymized participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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