Heart and Vessels (2019) 34:1–8
https://doi.org/10.1007/s00380-018-1207-4

ORIGINAL ARTICLE

Increased plasma xanthine oxidoreductase activity deteriorates coronary artery spasm

Ken Watanabe[1] · Tetsuro Shishido[1] · Yoichiro Otaki[1] · Tetsu Watanabe[1] · Takayuki Sugai[1] · Taku Toshima[1] · Tetsuya Takahashi[1] · Miyuki Yokoyama[1] · Daisuke Kinoshita[1] · Takayo Murase[2] · Takashi Nakamura[3] · Masahiro Wanezaki[1] · Harutoshi Tamura[1] · Satoshi Nishiyama[1] · Hiroki Takahashi[1] · Takanori Arimoto[1] · So Yamauchi[1] · Tamon Yamanaka[1] · Takuya Miyamoto[1] · Isao Kubota[1] · Masafumi Watanabe[1]

Received: 20 March 2018 / Accepted: 15 June 2018 / Published online: 23 June 2018
© Springer Japan KK, part of Springer Nature 2018

Abstract
Increased reactive oxygen species (ROS) contributes to the development of endothelial dysfunction, which is involved in coronary artery spasm (CAS). Xanthine oxidoreductase (XOR) plays a pivotal role in producing both uric acid and ROS. However, the association between plasma XOR activity and CAS has not been elucidated. The aim of this study was to investigate whether plasma XOR activity is associated with CAS. We measured XOR activity in 104 patients suspected for CAS, who presented without significant coronary artery stenosis and underwent intracoronary acetylcholine provocation tests. CAS was provoked in 44 patients and they had significantly higher XOR activity as compared with those without CAS. The patients were divided into three groups based on the XOR activity. The prevalence rate of CAS was increased with increasing XOR activity. A multivariate logistic regression analysis showed that the 3rd tertile group exhibited a higher incidence of CAS as compared with the 1st tertile group [odds ratio (OR) 6.9, $P=0.001$) and the 2nd tertile group (OR 3.2, $P=0.033$) after adjustment for conventional CAS risk factors, respectively. The C index was significantly improved by the addition of XOR activity to the baseline model based on CAS risk factors. Furthermore, the 3rd tertile group had the highest incidence of severe spasm defined as total obstruction, flow-limiting stenosis, diffuse spasm, multivessel spasm, and/or lethal arrhythmia. This is a first report to elucidate the association of plasma XOR activity with CAS. Increased plasma XOR activity is significantly associated with CAS.

Keywords Xanthine oxidoreductase · Coronary artery spasm · Reactive oxygen species · Uric acid

Introduction

Ischemic heart disease remains a major cause of morbidity and mortality [1]. Coronary artery spasm (CAS) is associated with the pathophysiological mechanism of ischemic heart disease, such as stable and unstable angina, acute myocardial infarction, and sudden cardiac death [2, 3]. Although the causes and mechanisms of CAS are multifactorial, endothelial dysfunction is considered to be one of the major underlying mechanisms [4, 5]. Reactive oxygen species (ROS) is thought to contribute to endothelial dysfunction [6]. It has been demonstrated that increased serum levels of uric acid (UA) cause endothelial dysfunction through the generation of ROS [7]. Xanthine oxidoreductase (XOR), a rate-limiting enzyme of purine metabolism, catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to UA, and also generates the ROS [8, 9]. Although it has been reported that serum UA was an independent risk factor for CAS [10], it remains to be determined whether plasma XOR activity is associated with the incidence of CAS. The aim of this study was to assess the relationship of plasma XOR activity with CAS.

✉ Tetsuro Shishido
tshishid@med.id.yamagata-u.ac.jp

1 Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

2 Radioisotope and Chemical Analysis Center, Sanwa Kagaku Kenkyusho Co., Ltd, Mie, Japan

3 Pharmacological Study Group, Pharmaceutical Research Laboratories, Sanwa Kagaku Kenkyusho Co., Ltd, Mie, Japan

Materials and methods

Study subjects

The present study enrolled 107 consecutive patients suspected for CAS, who presented with resting chest pain at midnight or early in the morning, who had no significant coronary artery stenosis and underwent coronary angiography with acetylcholine (Ach)-provocation test between June 2008 and October 2016. We defined significant coronary artery stenosis as ≥ 50% diameter narrowing by coronary angiography. We excluded 3 patients who had been administered with XOR inhibitors. A total of 104 eligible patients were included for analysis. The major coronary risk factors, including hypertension, dyslipidemia, diabetes mellitus, body mass index (BMI), and smoking were assessed. Smoking included both current and past smokers. Medications, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), calcium-channel blockers (CCBs), statins, antiplatelet drugs, nitrates, and nicorandils were investigated before diagnosis of CAS by Ach-provocation test. Baseline data were obtained on the basis of medical records or history of medical therapy. The study protocol was approved by the Yamagata University Ethics Committee and all patients provided their written informed consent.

Induction of coronary spasm

Coronary angiography with Ach-provocation test was performed according to the CAS guideline by the Japanese Circulation Society [11]. The administration of CCBs, nitrates, nicorandils, and other vasoactive drugs was withdrawn for at least three days before performing the Ach-provocation test. Provoked CAS was defined as a reduction of at least 90 percent of luminal diameter narrowing with accompanying symptoms of chest pain and/or ischemic ST-segment changes on the electrocardiogram as compared with that following administration of intracoronary nitrates. Furthermore, we classified the patients with CAS into moderate spasm and severe spasm. Severe spasm was defined as total obstruction, flow-limiting stenosis, diffuse spasm, multivessel spasm, and/or onset of lethal arrhythmia, such as ventricular fibrillation and complete atrioventricular block.

XOR activity assay

Blood samples were collected in the early morning before coronary angiography with Ach-provocation test. XOR activity assay was performed using stable isotope-labeled substrate and liquid chromatography–triple quadrupole mass spectrometry (Sanwa Kagaku Kenkyusho Co., Ltd, Japan) [12]. We divided the patients into tertiles according to XOR activity: low XOR group (26.3 pmol/h/mL, interquartile range (IQR) 15.6–28.7, n = 34), middle XOR group (43.4 pmol/h/mL, IQR 37.2–51.0, n = 35), high XOR group (123.0 pmol/h/mL, IQR 72.2–158.0, n = 35). We compared the presentation of coronary risk factors, cardiac function, the serum markers, and medications among the three groups.

Statistical analysis

The results are expressed as the mean ± standard deviation for continuous variables and percentages for categorical variables. Skewed values are presented as the median and IQR. Correlation between XOR activity and UA was analyzed by single linear regression analysis. We used t tests and Chi-square tests to compare continuous and categorical variables, respectively. If the data were not normally distributed, the Mann–Whitney U-test was employed. Differences among groups were analyzed by analysis of variance. Comparison of plasma XOR activity among the three groups was performed by the Kruskal–Wallis test. Conventional CAS risk factors, including age, smoking, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), UA, and high-sensitivity C-reactive protein (hs-CRP), were entered into a multivariate logistic model to identify independent CAS risk factors [5, 10, 13]. We calculated the C index, net reclassification index (NRI), and integrated discrimination index (IDI) to measure the quality of improvement for correct reclassification following the addition of XOR activity to the conventional risk model. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed with a standard software package (JMP version 12; SAS Institute, Cary, NC, USA).

Results

Comparison of clinical characteristics among the XOR groups

Table 1 shows baseline characteristics according to the XOR groups. The high XOR group had the highest plasma levels of triglycerides and UA among the three groups. The high XOR group was younger with often more males as compared with the other groups. There were no significant differences in the prevalence rates of hypertension, dyslipidemia, diabetes mellitus and cigarette smoking, left ventricular end-diastolic diameter, and left ventricular ejection fraction among the three groups. There were positive correlations between the plasma XOR activity and the levels of UA (r = 0.212, P = 0.031) and triglycerides (r = 0.217, P = 0.028), and negative correlation between the XOR activity and age

Table 1 Comparison of clinical characteristics among the three groups based on XOR activity

Variables	Low XOR $n=34$	Middle XOR $n=35$	High XOR $n=35$	*P* value
Age (years old)	67 ± 11	64 ± 10	60 ± 14	0.046
Men/women	8/26	20/15	28/7	< 0.001
BMI (kg/m^2)	23.0 ± 3.5	24.1 ± 3.5	24.2 ± 3.8	0.373
Hypertension, *n* (%)	18 (53)	21 (60)	20 (57)	0.838
Dyslipidemia, *n* (%)	16 (47)	10 (29)	14 (20)	0.275
Diabetes mellitus, *n* (%)	3 (9)	2 (6)	4 (11)	0.689
Smoking, *n* (%)	12 (35)	20 (57)	15 (43)	0.178
Echocardiographic data				
LVEDD (mm)	47 ± 6	48 ± 5	49 ± 6	0.271
LVEF (%)	68 ± 10	68 ± 6	65 ± 11	0.479
Blood examination				
Triglycerides (mg/dL)	102.5 (77.5–111.0)	111.5 (74.8–172.3)	150.0 (93.0–205.0)	0.005
LDL-C (mg/dL)	109.7 ± 26.3	102.5 ± 25.5	112.7 ± 29.2	0.283
HDL-C (mg/dL)	61.2 ± 19.3	55.5 ± 12.3	53.4 ± 11.9	0.081
HbA1c (%)	5.5 ± 0.4	5.7 ± 0.9	5.6 ± 0.6	0.480
eGFR (mL/min/1.73 m^2)	75.4 ± 16.1	80.0 ± 18.6	78.7 ± 21.7	0.597
UA (mg/dL)	4.7 ± 1.3	5.5 ± 1.1	5.8 ± 1.4	0.001
hs-CRP (mg/dL)	0.035 (0.019–0.093)	0.040 (0.018–0.125)	0.060 (0.027–0.131)	0.854
Log BNP (pg/mL)	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	0.546
Urinalysis				
UACR (mg/g)	7.8 (5.4–12.6)	9.7 (5.6–19.6)	5.0 (4.3–9.7)	0.144
Proteinuria (%)	5 (15)	6 (17)	2 (6)	0.277
NAG (U/g)	5.7 (4.5-7.5)	5.1 (4.1-8.7)	5.3 (4.0-7.4)	0.858
Urine pH	6.3 ± 0.7	6.0 ± 0.5	6.3 ± 0.8	0.207
Medications				
ACEIs and/or ARBs, *n* (%)	9 (26)	8 (23)	10 (29)	0.858
CCBs, *n* (%)	8 (24)	20 (57)	18 (51)	0.009
Statins, *n* (%)	9 (26)	8 (23)	8 (23)	0.922
Antiplatelet drugs, *n* (%)	14 (41)	10 (29)	9 (26)	0.348
Nitrates, *n* (%)	2 (6)	9 (26)	6 (17)	0.065
Nicorandils, *n* (%)	3 (9)	8 (23)	6 (18)	0.264

Data are expressed as mean ± SD, number (percentage), or median (interquartile range)

ACEIs angiotensin-converting enzyme inhibitors, ARBs, angiotensin II receptor blockers, *BMI* body mass index, *BNP* B-type natriuretic peptide, *CCBs* calcium-channel blockers, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *LDL-C* low-density lipoprotein cholesterol, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *NAG* *N*-acetyl-beta-D-glucosamidase, *UA* uric acid, *UACR* urine albumin/creatinine ratio, *XOR* xanthine oxidoreductase

($r = -0.197$, $P = 0.045$), respectively (Fig. 1). The use rate of CCBs was the lowest in the low XOR group.

Association between the XOR activity and coronary artery spasm

CAS was provoked in 44 patients and they had significantly higher XOR activity as compared with those without CAS (Fig. 2). Univariate and multivariate logistic regression analyses were performed to assess factors predicting the incidence of CAS (Table 2). In the univariate analysis, only the plasma XOR activity was associated with the incidence of CAS. Conventional CAS risk factors, such as smoking, UA, and hs-CRP, were not associated with the incidence of CAS. Male gender and low HDL-C tended to be associated with CAS, but the difference did not reach statistical significance. Multivariate analysis revealed that XOR activity was associated with CAS after adjustment for conventional CAS risk factors. The high XOR group was associated with the highest risk of CAS after adjustment for conventional CAS risk factors (Fig. 3).

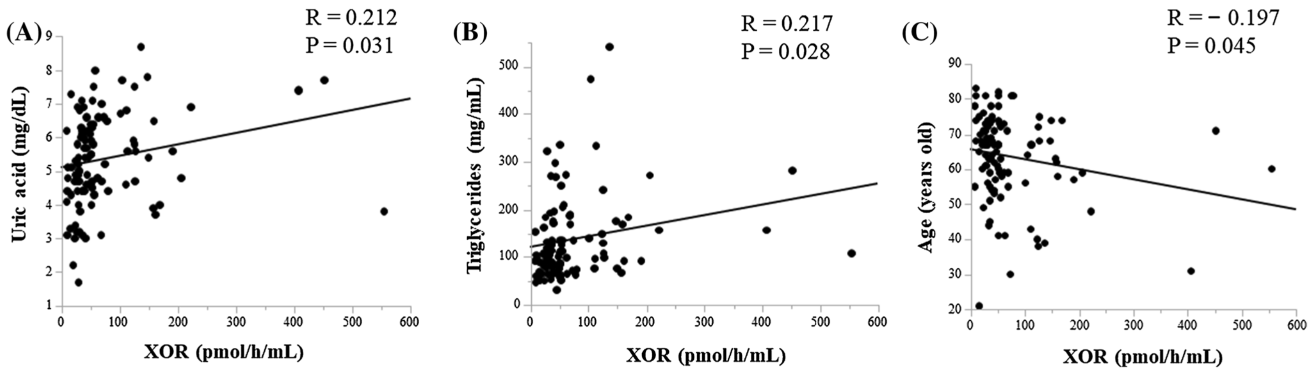

Fig. 1 The correlation between plasma XOR activity, age, triglycerides and serum UA. The correlation between plasma XOR activity and age (**a**), triglycerides (**b**) and serum UA (**c**). *XOR* xanthine oxidoreductase, *UA* uric acid

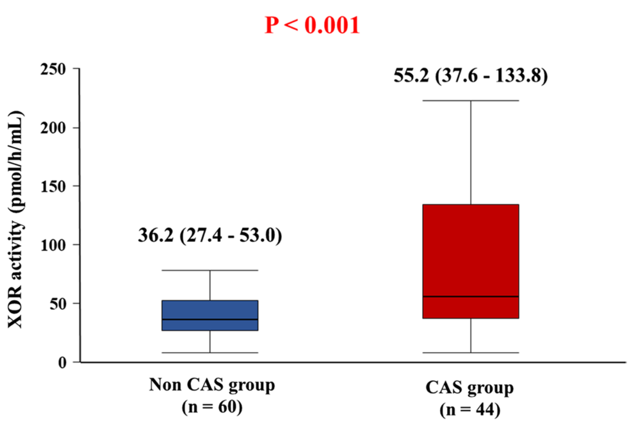

Fig. 2 The comparison of plasma XOR activity between the patients with CAS and those without. *XOR* xanthine oxidoreductase, *CAS* coronary artery spasm

Increase in severity of CAS in accordance with an increase in XOR activity

There were 27 (26%) patients who were provoked for severe spasm. The plasma XOR activity was increased with a severity of CAS. The severe spasm patients had the highest plasma XOR activity among the three severity groups: non-spasm (36.2 pmol/h/mL, IQR 27.4–53.0), moderate spasm (51.8 pmol/h/mL, IQR 33.7–95.0), severe spasm (101.0 pmol/h/mL, IQR 37.2–147.0), respectively ($P < 0.001$). The proportion of the high XOR group was increased in parallel to an increase in severity of CAS, while the proportion of the low XOR group was decreased (Fig. 4). Representative cases documenting CAS, including the moderate spasm and the severe spasm, by Ach-provocation test are shown in Fig. 5.

Improvement of reclassification by adding XOR activity

We evaluated the improvement of C index, NRI, and IDI to examine whether model fit and discrimination are improved by adding the XOR activity to the basic predictors, such as age, smoking, HDL-C, LDL-C, UA, and hs-CRP. As shown in Fig. 6, the C index was significantly improved by the addition of XOR activity to the basic predictors. Both NRI and IDI were also significantly improved by the addition of XOR activity to the basic predictors (NRI 0.612; 95% confidence interval, 0.237–0.986; $P = 0.001$ and IDI, 0.098; 95% confidence interval, 0.040–0.156; $P = 0.001$, respectively).

Discussion

Main findings

The main findings of this study were as follows: (1) high XOR activity was an independent risk for CAS after adjustment for conventional risk factors; (2) high XOR activity was associated with severity of CAS; (3) the prediction model including XOR activity had an improved C index, NRI and IDI.

The impact of XOR activity on coronary artery spasm

In the present study, a significant association between conventional CAS risk factors, including UA, and the incidence of CAS was not observed; however, the plasma XOR activity was an independent risk factor for the incidence of CAS. Furthermore, the present study showed that higher XOR activity was related to spasm severity.

It has been reported that elevated serum UA was related to metabolic syndrome, hypertension, diabetes mellitus, dyslipidemia, and renal dysfunction [14]. In addition to this,

Table 2 Univariate and multivariate logistic regression analyses for predicting the incidence of CAS

Variables	*Univariate analysis*			*Multivariate analysis*		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age[a]	1.016	0.984–1.052	0.342	1.052	1.007–1.104	0.021
Male gender	2.000	0.909–4.500	0.085			
BMI[b]	0.937	0.622–1.405	0.752			
Hypertension	1.006	0.459–2.218	0.988			
Dyslipidemia	1.667	0.750–3.737	0.210			
Diabetes mellitus	0.361	0.052–1.584	0.186			
Smoking	1.643	0.751–3.632	0.214	1.697	0.677–4.335	0.259
LVEDD[b]	0.689	0.398–1.136	0.147			
LVEF[b]	0.969	0.593–1.601	0.900			
Triglycerides[b]	1.310	0.882–2.016	0.181			
LDL-C[b]	1.181	0.796–1.769	0.409	1.191	0.740–1.916	0.468
HDL-C[b]	0.676	0.424–1.026	0.066	0.668	0.373–1.127	0.134
HbA1c[b]	0.962	0.628–1.429	0.849			
eGFR[b]	0.868	0.569–1.290	0.488			
UA[b]	1.354	0.911–2.053	0.135	1.106	0.655–1.906	0.707
XOR[b]	3.630	1.741–8.904	<0.001	4.341	1.860–12.768	<0.001
hs-CRP[b]	1.367	0.914–2.182	0.130	1.380	0.863–2.252	0.176
Log BNP[b]	0.723	0.472–1.080	0.115			

BMI body mass index, *BNP* B-type natriuretic peptide, *CAS* coronary artery spasm, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *LDL-C* low-density lipoprotein cholesterol, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *UA* uric acid, *XOR* xanthine oxidoreductase

[a]Per 1-year increase

[b]Per 1-SD increase

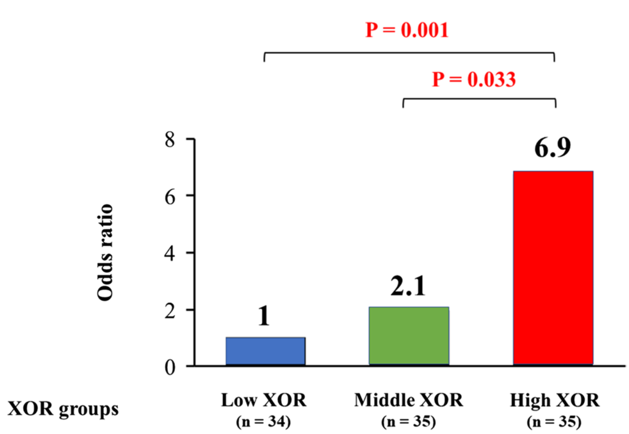

Fig. 3 Association between the plasma XOR activity and the incidence of CAS. Odds ratios relative to the first tertile are shown. *XOR* xanthine oxidoreductase, *CAS* coronary artery spasm

many previous studies have shown that hyperuricemia can contribute to impaired endothelial function and to increased risk of cardiovascular disease [15, 16]. Although it was reported that hyperuricemia was associated with CAS [10], there was no significant association between serum UA and CAS in this study. Since UA can provide an antioxidative effect and be protective against oxidative stress, the role of UA in cardiovascular disease is still controversial [17].

Interestingly, there were significant gender differences in relation to XOR activity. Among the patients without CAS, male patients had significantly higher XOR activity [51.7 (IQR 38.2–68.8) pmol/h/mL vs. 29.2 (IQR 22.4–36.9) pmol/h/mL, $P=0.001$], while there were no significant gender differences in the patients with CAS [66.0 (IQR 39.2–126.8) pmol/h/mL vs. 52.6 (IQR 24.7–155.8) pmol/h/mL, $P=0.574$]. When considering this, the association between XOR activity and CAS might be stronger in female patients than in male patients.

Pathophysiological role of XOR in the vascular function

XOR pathways are one of the major ROS-generating systems in the vascular vessels. XOR is present in two interconvertible forms, namely, xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XDH uses nicotinamide adenine dinucleotide as an electron acceptor; however, XO uses molecular oxygen, which is accompanied with the

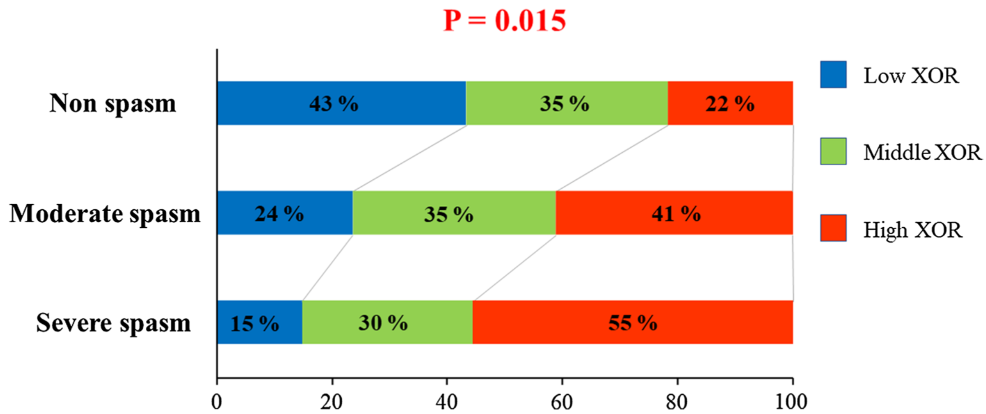

Fig. 4 Association between XOR activity and severity of CAS. *XOR* xanthine oxidoreductase, *CAS* coronary artery spasm

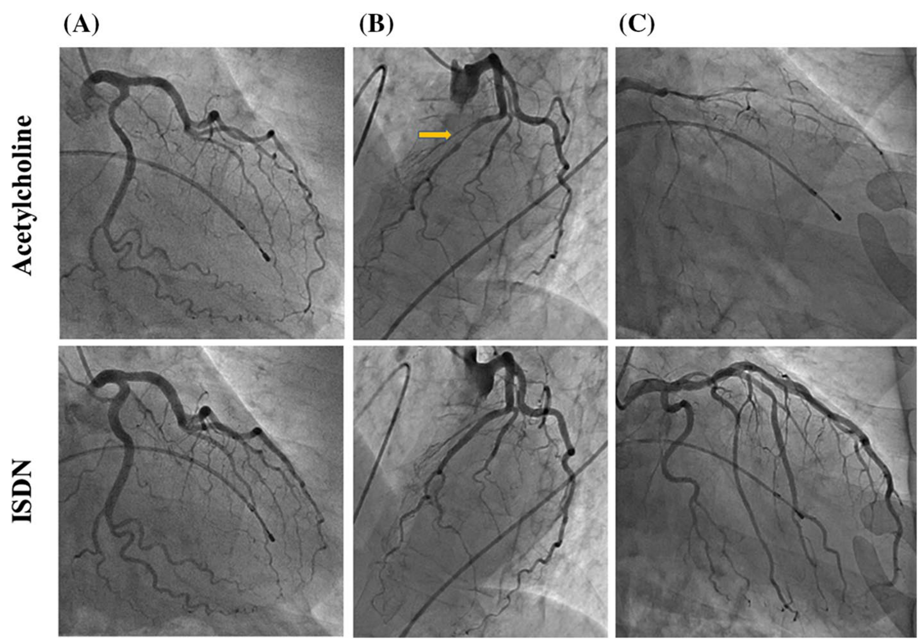

Fig. 5 Representative cases documenting CAS by acetylcholine provocation test. **a** non-spasm, **b** moderate spasm, **c** severe spasm. *CAS* coronary artery spasm, *ISDN* isosorbide dinitrate

generation of superoxide anion (O_2^-) [18]. In physiological conditions, XOR exists in its XDH form in the vascular endothelial cells [19, 20]. XDH can be converted to XO by reversible sulfhydryl oxidation or by irreversible proteolytic modification [21].

In coronary arteries, endothelial nitric oxide (NO) plays a pivotal role in maintaining a basal tone [22]. O_2^- is one of the major species of ROS and is thought to contribute to impaired endothelium-dependent vasodilation in coronary artery [23]. Besides inactivating endothelial NO, O_2^- can convert NO into peroxynitrate ($ONOO^-$), which is more cytotoxic and damages vascular endothelium [6]. Furthermore, O_2^- can contribute to uncoupling of endothelial NO synthase (eNOS), which produces O_2^- at the expense of NO [21]. $ONOO^-$ is a highly reactive species and generates a strong oxidant capable of oxidizing sulfhydryl groups [24]. $ONOO^-$ facilitates converting endothelial XDH into XO, increasing ROS generation in the endothelial cells, which causes endothelial dysfunction. Conversely, XOR inhibition was reported to improve endothelial function [25]. Therefore, it is plausible that XOR-derived ROS can contribute to the incidence of CAS via endothelial dysfunction.

It has been reported that the CAS risk factor is distinct from that of coronary atherosclerotic stenosis, and the predilection sites are different in CAS and coronary atherosclerosis [26, 27]. On the other hand, it was reported that focal CAS is likely to occur at the sites of early stages of atherosclerosis [28]. Furthermore, the study using intravascular ultrasound showed that atherosclerosis is present at the site of focal CAS, even in the absence of angiographically organic stenosis [29].

It has been demonstrated that XOR activity is correlated with hypertension, hypercholesterolemia, diabetes mellitus, obesity, and cigarette smoking [30]. The present study showed the positive correlation between plasma XOR activity and triglycerides. Considering the high XOR expression

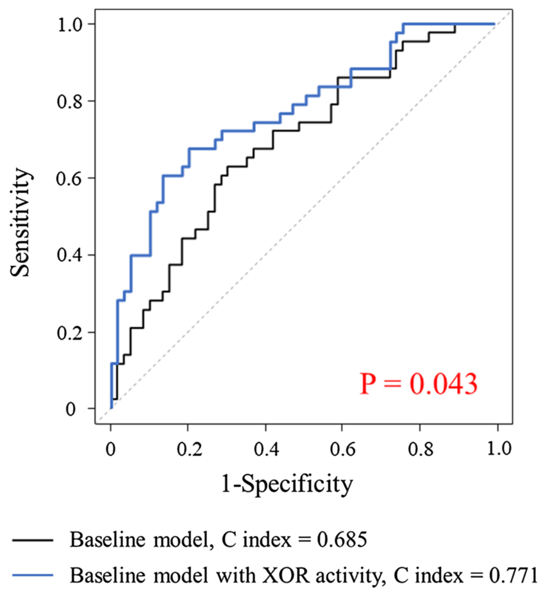

Fig. 6 Receiver operating characteristic curve of the baseline model and those including XOR activity to predict the incidence of CAS. *XOR* xanthine oxidoreductase, *CAS* coronary artery spasm

and activity in obese adipose tissues [31], the mechanism of focal CAS at the site of organic stenosis might be involved in XOR activity. In addition to this, it was reported that XOR activity and quantity of UA increased in the endothelial and smooth muscle cells in atherosclerotic plaque [32]. Accordingly, an increase of XOR activity in atherosclerotic lesions can cause endothelial dysfunction through decreasing endothelial NO production, which might lead to incidence of focal CAS at the site of the atherosclerosis lesion.

In addition, CAS can be induced by smooth muscle cell hypercontractility [5]. It has been reported that Rho/Rho kinase pathway plays an important role in vascular smooth muscle cell contraction and a Rho-kinase inhibitor is effective for the treatment for CAS [33]. Previous studies have shown that XOR-derived ROS can induce arterial smooth muscle cell proliferation and migration, and can trigger vasoconstriction by the up-regulation of the renin-angiotensin system [30].

Clinical implications

In spite of several medical treatments for CAS, including CCBs, nitrates, and nicorandils, it is noted that drug-refractory CAS exists in approximately 20% of patients with CAS, which can trigger various critical cardiac events, such as acute myocardial infarction, fatal arrhythmia and sudden death [34].

Allopurinol, a xanthine oxidase inhibitor, has been reported to improve not only hyperuricemia but also the impaired endothelial NO production by reducing vascular oxidative stress [25, 35]. Taking our results into consideration, XOR inhibitors could have beneficial effects in suppressing CAS.

To the best of our knowledge, this is the first report that elucidates the association of plasma XOR activity with the incidence of CAS. The results of the present study suggest that XOR plays an important role in the mechanism of CAS. There is the possibility that XOR could be a biomarker for predicting high-risk CAS. Further studies are needed to elucidate whether XOR inhibitors are effective or not for the treatment of CAS.

Study limitations

The present study had several limitations. First, as this was an observational study, we could not evaluate the cause-effect relationship between plasma XOR activity and CAS. Second, since we did not assess coronary artery endothelial function, we could not determine the association between endothelial dysfunction and CAS. Third, there was racial bias that the prevalence of CAS is higher in Japanese than in Caucasians. Finally, the study subjects were relatively small in the present investigation.

Conclusions

The present study demonstrated that increased plasma XOR activity is significantly associated with the incidence of CAS.

Acknowledgements This work was in part supported by the consigned research fund from Sanwa Kagaku Kenkyusho Co., Ltd and by Japan Society for Promotion of Science KAKENHI (Grant No. 17K15984, 18K08025, 18K08059, and 18K15838). We also would like to thank Editage (https://www.editage.jp) for the English language review.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Finegold JA, Asaria P, Francis DP (2013) Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. Int J Cardiol 168:934–945
2. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y (2008) Coronary artery spasm–clinical features, diagnosis, pathogenesis, and treatment. J Cardiol 51:2–17
3. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, Cianflone D, Sanna T, Sasayama S, Maseri A (2000) Major racial differences in coronary constrictor response

between japanese and caucasians with recent myocardial infarction. Circulation 101:1102–1108
4. Lanza GA, Careri G, Crea F (2011) Mechanisms of coronary artery spasm. Circulation 124:1774–1782
5. Hung MJ, Hu P, Hung MY (2014) Coronary artery spasm: review and update. Int J Med Sci 11:1161–1171
6. Munzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC (2017) Impact of oxidative stress on the heart and vasculature: Part 2 of a 3-Part series. J Am Coll Cardiol 70:212–229
7. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ (2005) Hyperuricemia induces endothelial dysfunction. Kidney Int 67:1739–1742
8. Battelli MG, Bolognesi A, Polito L (2014) Pathophysiology of circulating xanthine oxidoreductase: new emerging roles for a multi-tasking enzyme. Biochim Biophys Acta 1842:1502–1517
9. Otaki Y, Watanabe T, Kinoshita D, Yokoyama M, Takahashi T, Toshima T, Sugai T, Murase T, Nakamura T, Nishiyama S, Takahashi H, Arimoto T, Shishido T, Miyamoto T, Kubota I (2017) Association of plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure. Int J Cardiol 228:151–157
10. Nishino M, Mori N, Yoshimura T, Nakamura D, Lee Y, Taniike M, Makino N, Kato H, Egami Y, Shutta R, Tanouchi J, Yamada Y (2014) Higher serum uric acid and lipoprotein(a) are correlated with coronary spasm. Heart Vessels 29:186–190
11. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F (2014) 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press 23:3–16
12. Murase T, Nampei M, Oka M, Miyachi A, Nakamura T (2016) A highly sensitive assay of human plasma xanthine oxidoreductase activity using stable isotope-labeled xanthine and LC/TQMS. J Chromatogr B Analyt Technol Biomed Life Sci 1039:51–58
13. Sugano Y, Anzai T, Yagi T, Noma S (2010) Impact of high-density lipoprotein cholesterol level in patients with variant angina pectoris. Int J Cardiol 140:175–181
14. Li YH, Lin GM, Lin CL, Wang JH, Chen YJ, Han CL (2013) Relation of serum uric acid and body mass index to mortality in high-risk patients with established coronary artery disease: a report from the ET-CHD registry, 1997-2006. J Cardiol 62:354–360
15. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, Tang Z (2016) Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep 6:19520
16. Puddu P, Puddu GM, Cravero E, Vizioli L, Muscari A (2012) Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. J Cardiol 59:235–242
17. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA (2005) Uric acid and oxidative stress. Curr Pharm Des 11:4145–4151
18. Cantu-Medellin N, Kelley EE (2013) Xanthine oxidoreductase-catalyzed reactive species generation: a process in critical need of reevaluation. Redox Biol 1:353–358
19. Hellsten-Westing Y (1993) Immunohistochemical localization of xanthine oxidase in human cardiac and skeletal muscle. Histochemistry 100:215–222
20. Chen C, Lü J-M, Yao Q (2016) Hyperuricemia-related diseases and xanthine oxidoreductase (XOR) inhibitors: an overview. Med Sci Monit 22:2501–2512
21. Forstermann U, Xia N, Li H (2017) Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circ Res 120:713–735
22. Lefroy DC, Crake T, Uren NG, Davies GJ, Maseri A (1993) Effect of inhibition of nitric oxide synthesis on epicardial coronary artery caliber and coronary blood flow in humans. Circulation 88:43–54
23. Spiekermann S (2003) Electron spin resonance characterization of vascular xanthine and NAD(P)H oxidase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. Circulation 107:1383–1389
24. Radi R, Beckman JS, Bush KM, Freeman BA (1991) Peroxynitrite oxidation of sulfhydryls. The cytotoxic potential of superoxide and nitric oxide. J Biol Chem 266:4244–4250
25. George J, Carr E, Davies J, Belch JJ, Struthers A (2006) High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 114:2508–2516
26. Nakagawa H, Morikawa Y, Mizuno Y, Harada E, Ito T, Matsui K, Saito Y, Yasue H (2009) Coronary spasm preferentially occurs at branch points: an angiographic comparison with atherosclerotic plaque. Circ Cardiovasc Interv 2:97–104
27. Morita S, Mizuno Y, Harada E, Nakagawa H, Morikawa Y, Saito Y, Katoh D, Kashiwagi Y, Yoshimura M, Murohara T, Yasue H (2014) Differences and interactions between risk factors for coronary spasm and atherosclerosis–smoking, aging, inflammation, and blood pressure. Intern Med 53:2663–2670
28. Ishii M, Kaikita K, Sato K, Tanaka T, Sugamura K, Sakamoto K, Izumiya Y, Yamamoto E, Tsujita K, Yamamuro M, Kojima S, Soejima H, Hokimoto S, Matsui K, Ogawa H (2015) Acetylcholine-provoked coronary spasm at site of significant organic stenosis predicts poor prognosis in patients with coronary vasospastic angina. J Am Coll Cardiol 66:1105–1115
29. Yamagishi M, Miyatake K, Tamai J, Nakatani S, Koyama J, Nissen SE (1994) Intravascular ultrasound detection of atherosclerosis at the site of focal vasospasm in angiographically normal or minimally narrowed coronary segments. J Am Coll Cardiol 23:352–357
30. Battelli MG, Polito L, Bolognesi A (2014) Xanthine oxidoreductase in atherosclerosis pathogenesis: not only oxidative stress. Atherosclerosis 237:562–567
31. Tsushima Y, Nishizawa H, Tochino Y, Nakatsuji H, Sekimoto R, Nagao H, Shirakura T, Kato K, Imaizumi K, Takahashi H, Tamura M, Maeda N, Funahashi T, Shimomura I (2013) Uric acid secretion from adipose tissue and its increase in obesity. J Biol Chem 288:27138–27149
32. Patetsios P, Song M, Shutze WP, Pappas C, Rodino W, Ramirez JA, Panetta TF (2001) Identification of uric acid and xanthine oxidase in atherosclerotic plaque. Am J Cardiol 88(188–191):a186
33. Shimokawa H, Takeshita A (2005) Rho-kinase is an important therapeutic target in cardiovascular medicine. Arterioscler Thromb Vasc Biol 25:1767–1775
34. Crea F, Lanza GA (2011) New light on a forgotten disease: vasospastic angina. J Am Coll Cardiol 58:1238–1240
35. George J, Struthers AD (2009) Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. Vasc Health Risk Manag 5:265–272