The Heart Surgery Forum 2022-4603
25 (2), 2022 [Epub April 2022]
doi: 10.1532/hsf.4603

Online address: http://journal.hsforum.com

The Impact of Serum Uric Acid on Postoperative Atrial Fibrillation in Coronary Artery Bypass Graft

Qian Zhang, MD, Yangyan Wei, MD, Jiwen Tang, BD, Siyang Huang, MD, Qing Chang, PhD

Department of Cardiology, Affiliated Hospital of Qingdao University, Qingdao, China

ABSTRACT

Background: Postoperative atrial fibrillation (POAF) after cardiac surgery is a common complication. We aimed to investigate the impact of serum uric acid level (UA) on the POAF of patients undergoing coronary artery bypass grafting (CABG).

Methods: A retrospective cohort study of patients undergoing CABG at the Hospital between January 2019 and December 2019 was performed. Hyperuricemia (HUA) was defined as serum UA levels >420 μmol/l in men and>360 μmol/l in women. The included patients were divided into the HUA group (103) and the normal UA group (306) based on serum uric acid levels before surgery. POAF was defined as atrial fibrillation that occurred within 7 days of cardiac surgery. We use COX regression analysis and Kaplan-Meier curves (log-rank test) for statistical analysis.

Results: The incidence of HUA was 25.2% (103/409). The rate of POAF was 28.61%. Univariate COX regression analysis showed the risk of POAF occurrence. It was revealed that UA was an independent predictor of POAF (HR=1.493, 95% CI1.007-2.212, $P = 0.046$). Kaplan-Meier curves showed that high serum UA was associated with the occurrence of POAF ($P = 0.034$). Moreover, age (HR=1.05, 95%CI 1.024-1.076, $P < 0.001$), AD (HR=1.567, 95%CI .015-2.42, $P = 0.043$), and CCB (HR=0.647, 95%CI 0.424-0.988, $P = 0.044$) also were independent predictors of POAF.

Conclusions: Preoperative UA level was significantly associated with POAF. Higher serum UA was an independent risk factor for POAF.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common arrhythmia after cardiac surgery, occurring in 20% to 40% of patients undergoing coronary artery bypass grafting surgery (CABG) [Benedetto 2020]. It usually occurs within the first 2-4 days after surgery [Echahidi 2008]. POAF can lead to increased short-term mortality and complications, such as cerebrovascular accidents, duration of hospital stay, and costs [Woldendorp 2020; Saxena 2012]. And compared with those with no POAF, long-term mortality and the incidence of long-term complications, such as ischemic stroke, heart failure, and long-term AF, is obviously higher in patients with POAF [Benedetto 2020; Woldendorp 2020; Thoren 2020; Taha 2021].

UA is a product of human body intake and endogenous synthesis of purines; it is catalyzed by xanthine oxidase (XO). Many studies have proven that in several pathological conditions, uric acid clearly was associated with oxidative stress and inflammation [Deng 2021; Spiga 2017; Kurajoh 2021]. This also is considered to be part of the POAF mechanism [Li 2010; Harada 2015]. Serum UA is closely related to the morbidity of cardiovascular diseases, such as hypertension, coronary artery disease [Gaubert 2020; Liu 2021; Saito 2021].

Many studies have proven the link between UA and atrial fibrillation in patients who have not undergone surgery [Hong 2020; Kwon 2018; Kawasoe 2018]. Memetoglu et al. reported patients with postoperative atrial fibrillation have higher levels of uric acid in a small population [Memetoglu 2015]. Considering the limitations of previous studies, this study was designed.

METHODS

Study population: The present study is a cohort study among the patients who have undergone CABG at the Hospital between January 2019 and December 2019. Our cohort uses a mixed cohort of off-pump CABG and on-pump CABG. Such a cohort is more in line with the current situation of coronary artery bypass surgery in China, mainly off-CABG, and there also is a small part of on-pump CABG. This heart center is a tertiary referral center, and all operations are independently performed by experienced physicians. Retrospective studies were exempted from informed consent by the Ethics Committee of the the Hospital. The inclusion criteria were an age >18 years and patients with isolated coronary artery bypass. The exclusion criteria were listed as follows: (1) preoperative diagnosis of atrial fibrillation; (2) history of pacemaker implantation or implantation of a pacemaker during surgery; (3) minimally invasive CABG; (4) missing data. (Figure 1) Consequently, 409 patients were stratified and included in the analyses. Preoperative and operative data retrospectively were collected for each patient. All laboratory data were last recorded before surgery. Emergency

Received February 2, 2022; accepted February 14, 2022.

Correspondence: Qing Chang, MD, Department of Cardiovascular Surgery, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao 266003. (e-mail: changqing20671@163.com).

surgery (ES) is defined as surgery performed within 48 hours of admission to the hospital. Palpitations are a sensory symptom, defined as an unpleasant awareness of an abnormal beating of the heart.

Definition of hyperuricemia: Hyperuricemia (HUA) was defined as serum UA levels >420 μmol/l in men and>360 μmol/l in women [Nan 2006; Wang 2020].

Detection of atrial fibrillation: The endpoint of this study was the new onset of atrial fibrillation within 7 days after surgery. POAF is defined as patients who were in sinus rhythm before surgery and developed new AF after heart surgery. AF was defined as irregular heart rhythm without a repetitive pattern and distinct P wave for at least 30 seconds. Each patient underwent continuous electrocardiograph (ECG) monitoring for more than 7 days.

Perioperative period management: All patients have undergone CABG. The patient did not undergo any treatment for arrhythmia prior to surgery. The same anesthetic medication and surgical techniques were used for all surgeries. During surgery, the left internal mammary artery can be used to bypass the anterior descending branch, or the diagonal branch and other blood vessels can be anastomosed sequentially, according to the condition. Great saphenous vein bridge was used for other diseased vessels. After the operation, the patient's vital signs were closely observed and recorded through ECG monitoring. Patients did not undergo any treatment to prevent arrhythmia prior to surgery.

Statistical analysis: Continuous variables are presented as the mean (SD) or median (interquartile range) and compared by t-test or Mann-Whitney U test. Categorical data are presented as counts with proportions and analyzed by $\chi 2$ test. Univariate Cox analysis was used to test all variables. Variables included in the final multivariable model were $P < 0.2$ in the univariable Cox model. Kaplan-Meier curve was drawn to estimate the incidence of POAF and the log-rank test was used for comparison. Statistical significance was defined by two-tailed P-values of <0.05. Data analysis was performed using R 4.1.0 and SPSS 26.0.

RESULTS

From January 2019 to December 2019, 459 patients who had undergone CABG were consecutively enrolled in the study. According to exclusion criteria, a total of 409 patients were included in the final analysis. Baseline characteristics of both the normal UA group and high UA group are presented in Table 1. Among 409 patients, 294 (71.9%) were male, 267 (65.3%) had hypertension, and 208 (50.9%) had diabetes mellitus. The incidence of HUA was 25.2% (103/409). In the entire study population, the incidence of POAF 7 days after CABG surgery was 28.61% (117/409). The incidence of POAF in the normal UA group and the high UA group was 25.82% (79/306) and 36.90% (38/103), respectively. Table 2 shows the results of univariate and multivariate COX regression. (Table 2) All clinical variables were entered into univariate Cox analysis. (Appendix incorporates factors with $P < 0.2$ in univariate analysis into multivariable Cox regression.) The univariate Cox analysis results show that UA is a risk factor of POAF. On multivariable Cox regression (Table 2), UA (HR=1.493, 95% CI 126 1.007-2.212, $P = 0.046$), age (HR=1.05, 95% CI 1.024-1.076, $P < 0.001$), AD (HR=1.567, 127 95% CI 1.015-2.42, $P = 0.043$), and CCB (HR=0.647, 95% CI 0.424-0.988, $P = 0.0$ were found to independently predict POAF. The Kaplan-Meier curves were used to determine the relationship between serum UA and the incidence of POAF. Using log-rank tests, high serum UA was associated with POAF ($P = 0.034$).

DISCUSSION

In the cohort of patients undergoing CABG, we found a significant association between UA and the risk of POAF, and this association continued after controlling for potential confounders. And compared with the normal UA group, the high UA group has a higher incidence of POAF. (Figure 2) Memetoglu et al. previously explored the role of uric acid in postoperative AF through prospective studies [Memetoglu 2015]. But the study was a case-control trial of small samples, with only 39 patients in the case group. On this basis, the present retrospective study was conducted in a larger heart center, including 117 patients with POAF and 103 patients with HUA. The inclusion of more patients can reduce selection bias. The present study is a cohort study in which all patient information was extracted from medical records and electronic advanced care record sheets. Adjusted Cox regression analysis revealed that preoperative UA elevation is an independent risk factor for POAF. The incidence of POAF in the seven days after CABG was 28.61% (117/409) among the study population. This is consistent with prior research reports on the incidence of POAF [Mathew 2004]. Of note, a systematic review and meta-analysis reported that the incidence of HUA in mainland China is 13.3%, while our incidence of HUA is 25.2%, which is significantly higher. However, a study in Qingdao reported that the incidence of HUA was 25.3% [Nan 2006], which is consistent with our study. This may partly be explained by Qingdao's location along the coast, with high intake of purine-rich seafood. The purine in food is one of the main sources of human UA [Kang 2011].

The relationship between uric acid and atrial fibrillation in nonoperative patients has been supported by numerous studies. Studies from South Korea and Japan in large populations both show that UA is significantly related to AF [Kwon 2018; Kawasoe 2018]. Meanwhile, the evaluation of the meta-analysis also provided evidence of the association between AF and serum UA [Tamariz 2014]. On the other hand, the meta-analysis results of Zhao et al. showed that elevated serum UA is not associated with increased risk of AF recurrence after catheter ablation [Zhao 2016].

Higher uric acid levels may increase the incidence of AF in patients through the following mechanisms. Elevated UA induced cardiac remodeling including electrophysiology and structural changes may be associated with the emergence of POAF. UA is produced by the action of XO, and XO is an important source of ROS. Animal experiments have shown

Table1. Baseline Characteristics according to serum UA. (n=409)

	Normal UA group n=306	High UA group n=103
Baseline parameters		
Age(year)	64.5 (7.8)	64.0 (8.8)
Male, n (%)	229 (74.8)	65 (63.1)
BMI	25.1 (3.1)	25.9 (2.9)
Smoking, n (%)	130 (42.5)	40 (38.8)
Drinking, n (%)	83 (27.1)	27 (26.2)
Diabetes mellitus, n (%)	114 (27.3)	32 (31.1)
Hypertension, n (%)	184 (60.1)	83 (80.6)
Palpitations, n(%)	35 (11.4)	20 (19.4)
Heart failure, n (%)	9 (2.9)	6 (5.8)
OMI, n (%)	26 (8.5)	20 (19.4)
Diagnosis, n (%)		
Stable angina	7 (2.3)	2 (1.9)
Unstable angina	193 (63.1)	55(53,4)
AMI	106 (34.7)	46 (44.7)
Pre-operative laboratory values		
creatinine	77.0 [63.6,90.8]	90.2 [74.2,105.4]
LDLC	2.4 [1.9, 3.0]	2.4 [2.0, 3.0]
Triglycerides	1.4 [1.0, 1.8]	1.9 [1.2, 2.6]
glucose	5.4 [4.8, 7.1]	5.6 [5.0, 6.6]
Echocardiogram		
LVEF	57.7 (7.1)	54.9 (8.9)
VWM, n (%)	172 (56.4)	69 (68.3)
AD, n (%)	192 (62.7)	76 (73.8)
Preoperative medication, n (%)		
ACEI	41 (13.4)	10 (9.7)
CCB	99 (32.4)	36 (35.0)
BRB	211 (69.0)	66 (64.1)
Surgery information		
ES, n (%)	19 (6.2)	6 (5.8)
LITA, n (%)	260 (85.0)	80 (77.7)
OPERATIVETIME	263.7 (85.5)	258.1 (85.0)
CPB, n (%)	30 (9.8)	11 (10.7)
IABP, n (%)	29 (9.5)	7 (6.8)

BMI: body Mass Index; OMI: old myocardial infarction; AMI: acute myocardial infarction; LDLC: Low Density Lipoprotein Cholesterol; LVEF: Left ventricular ejection fraction; VWM: ventricular wall motion abnormal; AD: atrial dilation; ACEI: angiotensin-converting enzyme inhibitor; CCB: Calcium Channel Blockers; BRB: β-receptor blockers ES emergency surgery LITA: left internal mammary artery bypass; CPB: cardiopulmonary bypass; IABP :intra-aortic balloon pump.

Table2.COX regression analysis for predicting POAF after GABG

	Univariate			Multivariate		
	HR	95%CI	*P*	HR	95%CI	*p*
AGE	1.06	1.03-1.09	<0.001	1.05	1.024-1.076	<0.001
OMI	1.45	0.87-2.42	0.157			
UA	1.52	1.03-2.24	0.034	1.493	1.007-2.212	0.046
LVEF	0.97	0.95-0.99	0.002	-	-	-
VWM	1.5	1.02-2.21	0.04	-	-	-
AD	1.74	1.14-2.64	0.01	1.567	1.015-2.42	0.043
CCB	0.66	0.44-1	0.051	0.647	0.424-0.988	0.044
BRB	0.73	0.5-1.06	0.098	-	-	-
ES	1.59	0.83-3.05	0.159	-	-	-
LITA	0.65	0.42-0.99	0.047	-	-	-
OPERATIVETIME	1	1-1	0.039	-	-	-
IABP	1.56	0.91-2.68	0.109	-	-	-

OMI: old myocardial infarction; LVEF: left ventricular ejection fraction; VWM: ventricular wall motion abnormal; AD: atrial dilation; CCB: Calcium Channel Blockers; BRB: β-receptor blockers ES emergency surgery CPB: cardiopulmonary bypass; LITA: left internal mammary artery bypass; IABP: intra-aortic balloon pump.

that UA can cause oxidative damage and inhibit cardiomyocyte activity, further progressing to myocardial remodeling [Chen 2011]. Researchers also found that the use of XO-inhibiting drugs for four weeks in infarcted rats weakened sympathetic innervation and reduced the arrhythmia vulnerability [Lee 2016].

Studies have proven that the circulating and local renin-angiotensin-aldosterone system (RAAS) in the cardiovascular system can be stimulated by UA, which in turn causes atrial inflammation and oxidative stress [Perlstein 2004; Corry 2008]. UA has been proven to increase the level of inflammation in the body through a variety of pro-inflammatory pathways [Yu 2020; Maharani 2016].

Inflammation can increase the risk of POAF by modulating atrial electrophysiological, altering atrial conduction, and facilitating re-entry [Ishii 2017; Ishii 2005]. Meanwhile, the inflammatory factors produced by UA stimulation also can lead to the remodeling of atrial structure, thereby stimulating the occurrence of POAF [Deng 2021; Ishii 2017]. In addition, animal models indicate that HUA can lead to apoptosis of atrial myocytes, atrial fibrosis, and over-innervation of sympathetic nerves, thereby significantly increasing the susceptibility to AF and the duration of AF [Wang 2021]. During cardiac surgery, the negative effects of HUA on patients may be amplified by the shock of surgery and the increase in sympathetic nerve excitability.

Allopurinol is a competitive inhibitor of xanthine oxidase (XO) that can reduce the concentration of UA in the blood. Many studies have shown that allopurinol can reduce inflammation levels, improve oxidative stress and endothelial function [Alem 2018; Zhang 2021]. Research shows that the electrical and structural remodeling of the atrium can be attenuated by allopurinol [Yang 2018]. However, there is a lack of corresponding clinical trials to prove that allopurinol can reduce the production of postoperative AF. In this study, it was also found that age is an independent risk factor for POAF in patients undergoing CABG; HR=1.05. Advanced age has been widely reported and accepted as a risk factor for postoperative AF. Results from a study by Mathew et al. demonstrated that for every 10 years of atrial fibrillation, the probability of POAF increases by 75% [Mathew 2004]. Shen et al. reported there is a non-linear relationship between age and the prevalence of POAF after cardiac surgery, and the prevalence of POAF is sharply increased over 55 years of age [Shen 2011]. Age was significantly related to atrial fibrosis and nonuniform anisotropic conduction may be a good explanation. In addition, our study confirms that preoperative CCB use, and AD also are independent risk factors for POAF.

According to our research, we recommend investigating uric acid in blood as a routine investigation in all CABG. For whether it is recommended to control uric acid before an operation, further prospective studies of multicenter cohorts are needed to assess the postoperative effects of controlling serum uric acid levels on patients and whether patients benefit. The present analysis has several limitations. First, this study is a single-center retrospective cohort study, and the data has not been collected prospectively, which may lead to selection bias and retrospect bias. Therefore, prospective studies are needed to further verify. Second, because it is a retrospective study, the duration of atrial fibrillation cannot be collected. We cannot assess the association between UA and POAF duration. Third, due to emergency surgery and other reasons, 5% of data was missing, which may affect the results.

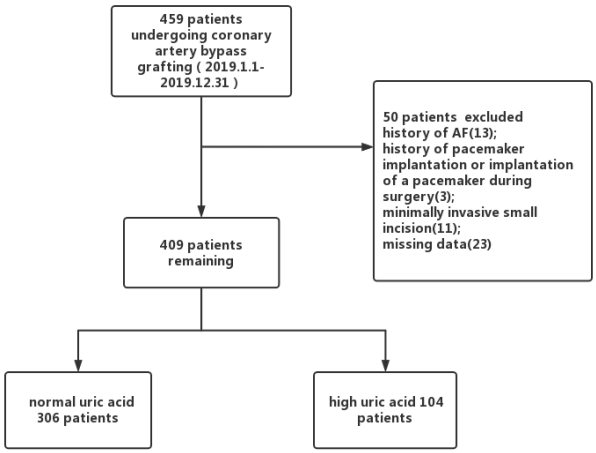

Figure 1. Flow chart of subject selection.

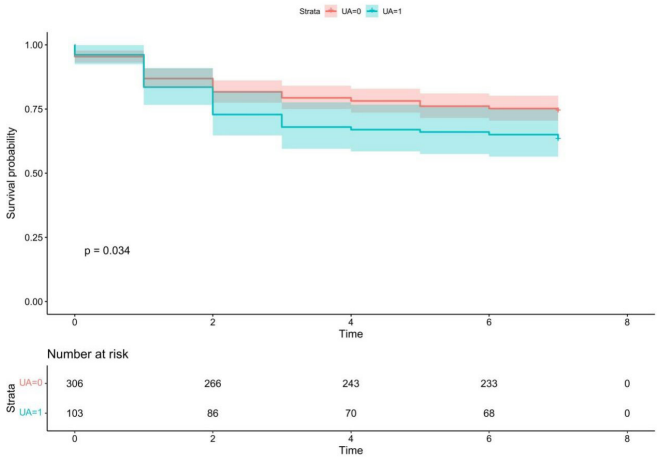

Figure 2. Kaplan-Meier curve of POAF in total population according to serum uric acid level.

CONCLUSIONS

The results of this study suggest that the serum UA was an independent risk factor for POAF following CABG. This connection emphasizes the importance of early intervention and management of UA to reduce the incidence of POAF and improve patient prognosis.

ACKNOWLEDGEMENTS

We would like to thank all contributors to the study of clinical staff. Ethical approval and informed consent: The Ethics Committee of the the Hospital approved the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki. The need for consent was waived by our institutional review board due to the retrospective nature of the study. Patient data confidentiality was protected.

REFERENCES

Alem MM. 2018.Allopurinol and endothelial function: A systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther. Aug 36(4):e12432.

Benedetto U, Gaudino MF, Dimagli A, et al. 2020. Postoperative Atrial Fibrillation and Long-Term Risk of Stroke After Isolated Coronary Artery Bypass Graft Surgery. Circulation. Oct 6. 142(14):1320-1329.

Chen CC, Hsu YJ, Lee TM. 2011. Impact of elevated uric acid on ventricular remodeling in infarcted rats with experimental hyperuricemia. Am J Physiol Heart Circ Physiol. Sep 301(3):H1107-17.

Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. 2008. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens. Feb 26(2):269-75.

Deng Y, Liu F, Yang X, Xia Y. 2021. The Key Role of Uric Acid in Oxidative Stress, Inflammation, Fibrosis, Apoptosis, and Immunity in the Pathogenesis of Atrial Fibrillation. Front Cardiovasc Med. 8:641136.

Echahidi N, Pibarot P, O'Hara G, Mathieu P. 2008. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. Feb 26 51(8):793-801.

Gaubert M, Bardin T, Cohen-Solal A, et al. 2020. Hyperuricemia and Hypertension, Coronary Artery Disease, Kidney Disease: From Concept to Practice. Int J Mol Sci. Jun 6 21(11).

Harada M, Van Wagoner DR, Nattel S. 2015. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J. 79(3):495-502.

Hong M, Park JW, Yang PS, et al. 2020. A mendelian randomization analysis: The causal association between serum uric acid and atrial fibrillation. Eur J Clin Invest. Oct 50(10):e13300.

Ishii Y, Schuessler RB, Gaynor SL, et al. 2005. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation. Jun 7 111(22):2881-8.

Ishii Y, Schuessler RB, Gaynor SL, Hames K, Damiano RJ, Jr. 2017. Postoperative atrial fibrillation: The role of the inflammatory response. J Thorac Cardiovasc Surg. Jun 153(6):1357-1365.

Kang DH, Chen W. 2011. Uric acid and chronic kidney disease: new understanding of an old problem. Semin Nephrol. Sep 31(5):447-52.

Kawasoe S, Kubozono T, Yoshifuku S, et al. 2018. Uric Acid Level and New-Onset Atrial Fibrillation in the Japanese General Population- Longitudinal Study. Circ J. Dec 25 83(1):156-163.

Kurajoh M, Fukumoto S, Yoshida S, et al. 2021. Uric acid shown to contribute to increased oxidative stress level independent of xanthine oxidoreductase activity in MedCity21 health examination registry. Sci Rep-Uk. Apr 1 11(1).

Kwon CH, Lee SH, Lee JY, Ryu S, Sung KC. 2018. Uric Acid and Risk of Atrial Fibrillation in the Korean General Population. Circ J. Oct 25 82(11):2728-2735.

Lee TM, Lin SZ, Chang NC. 2016. Effects of urate-lowering agents on arrhythmia vulnerability in post-infarcted rat hearts. J Pharmacol Sci. May 131(1):28-36.

Li J, Solus J, Chen QX, et al. 2010. Role of inflammation and oxidative stress in atrial fibrillation. Heart Rhythm. Apr 7(4):438-444.

Liu CW, Ke SR, Tseng GS, Wu YW, Hwang JJ. 2021. Elevated serum uric acid is associated with incident hypertension in the health according

to various contemporary blood pressure guidelines. Nutr Metab Cardiovasc Dis. Apr 9 31(4):1209-1218.

Maharani N, Kuwabara M, Hisatome I. 2016. Hyperuricemia and Atrial Fibrillation. Int Heart J. Jul 27 57(4):395-9.

Mathew JP, Fontes ML, Tudor IC, et al. 2004. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. Apr 14 291(14):1720-9.

Memetoglu ME, Kehlibar T, Yilmaz M, et al. 2015. Serum uric acid level predicts new-onset atrial fibrillation after coronary artery bypass graft operation. Eur Rev Med Pharmaco. Mar 19(5):784-789.

Nan H, Qiao Q, Dong Y, et al. 2006. The prevalence of hyperuricemia in a population of the coastal city of Qingdao, China. J Rheumatol. Jul 33(7):1346-50.

Perlstein TS, Gumieniak O, Hopkins PN, et al. 2004. Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney Int. Oct 66(4):1465-70.

Saito Y, Tanaka A, Node K, Kobayashi Y. 2021. Uric acid and cardiovascular disease: A clinical review. J Cardiol. Jul 78(1):51-57.

Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. 2012. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). Am J Cardiol. Jan 15 109(2):219-25.

Shen J, Lall S, Zheng V, Buckley P, Damiano RJ, Jr., Schuessler RB. 2011. The persistent problem of new-onset postoperative atrial fibrillation: a single-institution experience over two decades. J Thorac Cardiovasc Surg. Feb 141(2):559-70.

Spiga R, Marini MA, Mancuso E, et al. 2017. Uric Acid Is Associated With Inflammatory Biomarkers and Induces Inflammation Via Activating the NF-kappaB Signaling Pathway in HepG2 Cells. Arterioscler Thromb Vasc Biol. Jun 37(6):1241-1249.

Taha A, Nielsen SJ, Bergfeldt L, et al. 2021. New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting and Long-Term Outcome: A Population-Based Nationwide Study From the SWEDEHEART Registry. J Am Heart Assoc. Jan 5 10(1):e017966.

Tamariz L, Hernandez F, Bush A, Palacio A, Hare JM. 2014. Association between serum uric acid and atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm. Jul 11(7):1102-8.

Thoren E, Wernroth ML, Christersson C, Grinnemo KH, Jideus L, Stahle E. 2020. Compared with matched controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischemic stroke, heart failure and mortality even after adjustment for AF. Clin Res Cardiol. Oct 109(10):1232-1242.

Wang D, Sun L, Zhang G, et al. 2021. Increased Susceptibility of Atrial Fibrillation Induced by Hyperuricemia in Rats: Mechanisms and Implications. Cardiovasc Toxicol. Mar 21(3):192-205.

Wang Y, Weng P, Wan H, et al. 2020. Economic Status Moderates the Association Between Early-Life Famine Exposure and Hyperuricemia in Adulthood. J Clin Endocrinol Metab. Nov 1 105(11).

Woldendorp K, Farag J, Khadra S, Black D, Robinson B, Bannon P. 2020. Postoperative atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg. Dec 16.

Yang Y, Zhao J, Qiu J, et al. 2018. Xanthine Oxidase Inhibitor Allopurinol Prevents Oxidative Stress-Mediated Atrial Remodeling in Alloxan-Induced Diabetes Mellitus Rabbits. J Am Heart Assoc. May 2 7(10).

Yu W, Cheng JD. 2020. Uric Acid and Cardiovascular Disease: An Update From Molecular Mechanism to Clinical Perspective. Front Pharmacol. 11:582680.

Zhang YS, Lu LQ, Jiang YQ, et al. 2021. Allopurinol attenuates oxidative injury in rat hearts suffered ischemia/reperfusion via suppressing the xanthine oxidase/vascular peroxidase 1 pathway. Eur J Pharmacol. Jul 22 908:174368.

Zhao J, Liu T, Korantzopoulos P, et al. 2016. Association between serum uric acid and atrial fibrillation recurrence following catheter ablation: A meta-analysis. Int J Cardiol. Feb 1 204:103-5.