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Research Article

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Uric Acid, Oxidative Stress and Inflammation in Chronic Heart Failure with Reduced Ejection Fraction

Acidul uric, stress-ul oxidativ şi inflamaţia în insuficienţa cardiacă cronică cu fracţie de ejecţie scăzută

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Abstract

***Background**. Oxidative stress (OS) and inflammation are major mechanisms involved in the progression of chronic heart failure (CHF). Serum uric acid (sUA) is related to CHF severity and could represent a marker of xanthine-oxidase activation. The relationship between sUA, oxidative stress (OS) and inflammation markers was assessed in patients with moderate-severe CHF and reduced left ventricular (LV) ejection fraction (EF).*

***Methods**. In 57 patients with stable CHF, functional NYHA class III, with EF<40%, the LV function was assessed by N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) levels and echocardiographically through the EF and E/e' ratio, a marker of LV filling pressures. The relationship between LV function, sUA, malondialdehyde (MDA), myeloperoxidase (MPO), paraoxonase 1 (PON-1) as OS markers and high sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) as markers of systemic inflammation was evaluated.*

***Results**. The mean sUA level was 7.9 ± 2.2 mg/dl, and 61% of the CHF patients had hyperuricemia. CHF patients with elevated LV filling pressures (E/e'≥ 13) had higher sUA (8.6 ± 2.3 vs. 7.3 ± 1.4, p=0.08) and NT-proBNP levels (643±430 vs. 2531±709, p=0.003) and lower EF (29.8 ± 3.9 % vs. 36.3 ± 4.4 %, p=0.001). There was a significant correlation between sUA and IL-6 (r = 0.56, p<0.001), MDA (r= 0.49, p= 0.001), MPO (r=0.34, p=0.001) and PON-1 levels (r= -0.39, p= 0.003).*

***Conclusion**. In CHF, hyperuricemia is associated with disease severity. High sUA levels in CHF with normal renal function may reflect increased xanthine-oxidase activity linked with chronic inflammatory response.*

***Keywords**: chronic heart failure, uric acid, left ventricular function, oxidative stress, inflammation*

Rezumat

***Introducere**. Stress-ul oxidativ (SO) şi inflamaţia sunt mecanisme importante implicate în progresia insuficienţei cardiace cronice (IC). Acidul uric seric (AUs) se corelează cu severitatea IC şi ar putea reprezenta un marker de*

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activare a xantin-oxidazei. Relaţia dintre AUs, SO şi markerii de inflamaţie a fost evaluată la pacienţi cu IC moderat-severă şi scăderea fracţiei de ejecţie (FE) a ventriculului stâng (VS).

***Metodă**. La 57 de bolnavi cu IC stabilă, în clasă funcţională NYHA III şi FE <40% a fost determinată funcţia VS prin nivelele fragmentului N-terminal al prohormonului peptidului natriuretic de tip brain (NT-proBNP) şi ecocardiografic prin FE şi raportul E/e', parametru al presiunilor de umplere ale VS. A fost evaluată relaţia dintre AUs, funcţia VS şi markerii de SO, malondialdehida (MDA), mieloperoxidaza (MPO), paraoxonaza 1 (PON-1) şi de inflamaţie, proteina C reactivă înalt sensibilă (hsCRP) şi interleukina 6 (IL-6).*

***Rezultate**. Valorile medii ale AUs au fost de 7,9 ± 2,2 mg/dL, iar hiperuricemia a fost prezentă la 61% din bolnavii cu IC. Bolnavii cu IC şi presiuni de umplere crescute ale VS (E/e' ≥ 13) au avut valori mai mari ale AUs (8,6 ± 2,3 vs. 7,3 ± 1,4, p=0,08) şi ale NT-proBNP (643 ± 430 vs. 2531±709, p=0,003) şi FE mai scăzută (29,8 ± 3,9 % vs. 36,3 ± 4,4 %, p=0,001). A existat o corelaţie semnificativă între AUs şi IL-6 (r = 0,56; p<0,001), MDA (r= 0,49, p= 0,001), MPO (r=0,34, p=0,001) şi PON-1 (r= -0,39, p= 0,003).*

***Concluzie**. Hiperuricemia se corelează cu severitatea IC. Nivelele crescute ale AUs în IC cu funcţie renală normală ar putea reflecta creșterea activității xantinoxidazei în asociere cu prezența inflamației cronice.*

***Cuvinte cheie**: insuficienţă cardiacă cronică, acid uric, funcţie ventriculară stângă, stress oxidativ, inflamaţie*

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Introduction

Chronic heart failure (CHF) is associated with neurohormonal activation, increased oxidative stress (OS), chronic inflammation and other mechanisms that contribute to continuous cardiac remodeling and heart failure progression. Despite impressive advances in the knowledge of heart failure mechanisms and the improvement of treatment, patients with CHF have a dismal prognosis.

Increased serum uric acid (sUA) is strongly related to a poor prognosis in moderate - severe CHF (1,2). The risk of mortality markedly increases at sUA levels higher than 7 mg/dl (3,4,5,6). Hyperuricemia might be the consequence of increased xanthine-oxidase activity, which generates superoxide free radicals proportionally to uric acid synthesis (7,8,9). Thus, elevated sUA levels could be a marker of impaired oxidative metabolism linked to the chronic inflammatory response in CHF (10,11,12).

The aim of the study was to assess the relationship between sUA, OS and inflammation markers and the severity of left ventricular (LV) dysfunction in patients with moderate-severe, stable CHF and reduced systolic function, under optimal medical treatment according to current guidelines (13).

Study group and methods

Study population

Fifty-seven patients, 43 men and 14 women, with a mean age of 60 ± 12 years, with CHF NYHA class III and ejection fraction (EF) < 40% were included in the study. Patients with decompensated heart failure, evolving ischemia, significant valvular disease, and severe pulmonary or liver disease were not included in the study. Patients were clinically stable during the past four weeks before inclusion, without renal dysfunction, and under optimal medical therapy (betablockers, angiotensin converting enzyme inhibitors, furosemide, spironolactone and digoxin). None of the patients were taking urate lowering medication. The patients were informed about the methodology and purpose of the current research study and subsequently signed a written informed consent. The present study was approved by the local Ethics Committee.

Methods

Echocardiography and laboratory tests were performed in all patients, after a comprehensive clinical examination.

Echocardiographic Data

The echocardiographic examination was performed using an Aloka 4000 ultrasound machine with a 2.5 MHz probe. Echocardiography studies were performed according to standard recommendations of the European Association of Cardiovascular Imaging. The LV end-diastolic (LVEDV), LV end-systolic volumes (LVESV) and EF were assessed using the Simpson method. The mitral peak velocity of early filling (E), the deceleration time of early filling velocity (DTE) and the peak velocity of late filling (A) were evaluated. The septal and lateral annular velocities (e') were measured using tissue Doppler echocardiography. One third of the patients had atrial fibrillation and the E/A ratio was not available. Therefore, the LV diastolic function and LV filling pressures were estimated using the E/e'ratio, i.e. the ratio between early filling velocity (E) and the averaged annular velocities (e'). A value of E/e' ratio ≥ 13 was considered a marker of elevated LV filling pressures.

Laboratory evaluation

sUA levels were assessed using enzymatic-colorimetric methods using Roche Diagnostics (normal range: ≤ 7.2 mg/dL).

The N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) was measured using Roche Cardiac Reader kit (normal range: <125 pg/mL).

Malondialdehyde (MDA) levels and myeloperoxidase (MPO) activity, as serum markers of OS, and paraoxonase-1 (PON-1) activity, as a marker of serum antioxidant activity, were assessed.

MDA was measured by ELISA OxiSelect™ MDA Adduct kit from CELL BIOLABS, INC. The MDA concentration was expressed in nmol/mL (normal range: 0.27-1.02 nmol/mL).

Myeloperoxidase (MPO) activity was determined spectrophotometrically at a wavelength of 405 nm, using o-Dianisidin as substrate, the enzymatic activity being expressed in IU/L (normal range 225-271 IU/L) (14).

Paraoxonase-1 (PON-1) arylesterase activity was determined at a wavelength of 270 nm, the enzymatic activity being expressed in IU/L using phenyl acetate as substrate; one unit of paraoxonase activity was defined as a μM phenyl acetate hydrolyzed /min/ mL serum (normal range: 76.1 to 100.2 U/mL) (15).

High sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL6) levels were assessed as markers of systemic inflammation.

hsCRP levels were measured with the high sensitive CRP ELISA IL International GMBH kit. The method used the ELISA immunoenzymatic technique (normal range: 1-3 mg/L).

IL-6 levels were assessed using the R&D Systems human IL-6 ELISA immunoassay kit, the results being expressed in pg/mL (normal range: 2.0 -10.9 pg/mL).

Serum creatinine levels were measured using Jaffe's method (normal range: 0.5-1.2 mgl/dL) and the glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) equation.

Data analysis

Results are presented as mean ± standard deviation (SD) or median (min, max) for continuous numerical variables and percentages for categorical variables. The $\chi 2$ test, Fisher test were used to compare categorical variables, while Student t test was the test of choice for numerical variables. The Mann-Whitney with a 2-tailed hypothesis was used for variables with an independent (non-gaussian) distribution. Significant correlations between continuous variables were evaluated using Pearson's method. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistics, version 21.0.

Results

Among the fifty-seven patients diagnosed with NYHA III stable CHF with reduced EF (<40%), 43 patients (75%) had ischemic cardiomyopathy (Table I). 18 (32%) CHF patients had permanent atrial fibrillation. The mean level of creatinine was 1.07 ± 0.19 mg/dL and the estimated glomerular filtration rate (eGFR) was 75.7 ± 16.05 mL/min/1.73m^2. All patients were treated with betablockers and angiotensin converting enzyme inhibitors, 48 patients (84%) with loop diuretics (furosemide), 27 patients (47 %) with spironolactone and 20 patients (35 %) with digoxin.

The mean LVEF measured by echocardiography was 33.2 ± 6.1 % and the mean E/e' ratio was 11.5 ± 6.7 (Table I). Based on the E/e' values, 38 patients (66 %) were classified as having high LV filling pressures (E/e ' ≥ 13) and 19 patients (34%) had normal LV filling pressures (E/e ' < 13).

The mean level of sUA was 7.9 ± 2.2 mg/dL, 61% of the patients having hyperuricemia. sUA was positively correlated to NT-proBNP levels (r = 0.44, p<0.001), and inversely correlated with LVEF (r = -0.24, p=0.048) (Figure 1).

Table II emphasizes the LVEF, NT-proBNP and sUA mean values in the study population and in relation to LV filling pressures. NT-proBNP was 1625 ± 1268 pg/dL, significantly higher in patients with E/e'>13 (2531 ± 709 pg/mL vs 643.8 ± 430 pg/mL, p<0.003). EF was significantly lower in patients with E/e' > 13 (29.8 ± 3.9 % vs 34.6 ± 4.4 %, p<0.001). The mean sUA level was higher in patients with E/e' > 13 (8.6 ± 2.2 mg/dL vs 7.3 ± 1.4 mg/dL, p=0.08).

The values of OS markers, MDA, MPO and PON-1, and inflammatory markers, hsCRP and IL-6, in the study group and according to LV filling pressures are shown in Table II. MDA was significantly higher in patients with E/e' ≥ 13 (1.3 ± 0.2 vs 0.9 ± 0.2 nmoL/ml; p=0.04).

Table I. Demographics, clinical characteristics, pharmacological treatment and echocardiographic parameters of the study population.

Demographic and Clinical Data	
Mean age (years)	60 ± 12
Men (No.)	43 (75 %)
Functional NYHA class III (No.)	57 (100%)
Ischemic CHF (No.)	43 (75 %)
Atrial fibrillation (No.)	18 (32%)
Systolic BP (mmHg)	126 ± 18
Diastolic BP (mmHg)	78 ± 11
Heart rate (beats/min)	70 ± 13
Serum creatinine	1.07 ± 0.19
eGFR (mL/ min/1.73 m^2)	75.7 ± 16.0
Serum uric acid (mg/dL)	7.9 ± 2.2
Pharmacological treatment	
Beta-blocker (Bisoprolol 5-10 mg/day)	57 (100%)
ACEI (Trandolapril 2-4 mg/day)	57 (100%)
Loop diuretics (Furosemide 40 mg/day)	48 (84%)
Spironolactone (25-50 mg/day)	27 (47 %)
Digoxin (0.25 mg/day)	20 (35%)
Echocardiographic parameters	
LVEDV (mL)	198 ± 60.5
LVESV (mL)	131 ± 44
LVEF %	33.2 ± 6.1
E (m/s)	0.7 ± 0.2
DTE (ms)	169 ± 45
Mean e' (cm/s)	6.5 ± 1.7
E/e'	11.5 ± 6.7

ACEI – angiotensin converting enzyme inhibitors, BP – blood pressure, eGFR - estimated glomerular filtration rate, LVEDV – left ventricular end-diastolic volume, LVESV- left ventricular end-systolic volume, LVEF – left ventricular ejection fraction, E - peak velocity of early mitral filling, DTE – E deceleration time, e' –tissue Doppler annular velocities.

MPO activity was increased (310 ± 11 IU/L) not related with the E/e ' ratio (312 ± 10 U/L vs 307 ± 11 IU/L, p=0.34). There was no statistically significant difference between PON-1 activity (41.9 ± 15 U/mL) and E/e' (38.2 ± 10 U vs 37.5

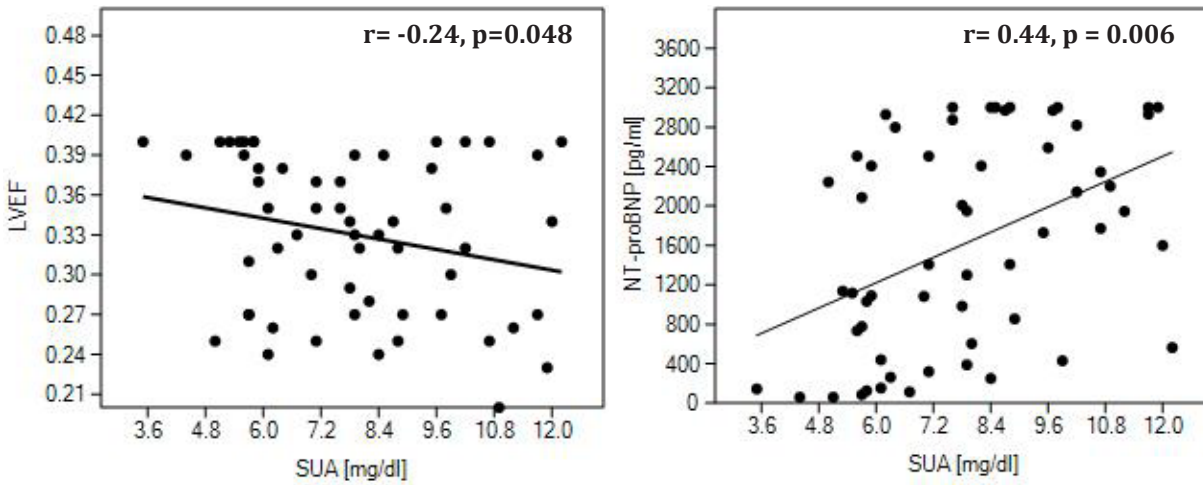

Figure 1. Scatterplots of sUA against markers of LV function in the Study Population
sUA=serum uric acid, LVEF=left ventricular ejection fraction, r=Pearson correlation coefficient

± 16 U, p=0.88). There were significant correlations between sUA and serum markers of OS (MDA r=0.49, p=0.001; MPO r=0.34, p=0.001 and PON-1 r = -0.39, p= 0.003) (Figure 2).

The median value of hsCRP was 6.1 (1.9, 23.8) mg/L, while the median value of IL-6 was 12 (0.7, 122.6) pg/mL. There was a significant correlation between sUA and IL-6 (r=0.56, p<0.001) (Figure 2).

Discussion

Many epidemiological studies found a relationship between sUA levels and cardiovascular diseases, such as arterial hypertension or coronary heart disease (16,17,18). In patients with CHF the prevalence of hyperuricemia varies between 37% and 54% in patients with CHF, being higher, up to 70 % in patients hospitalized for worsening CHF with reduced EF (12,19,20,21).

Table II. sUA, EF, NT-proBNP, oxidative stress and inflammation markers in the Study Population and according to E/e' ratio.
Values expressed in mean ± standard deviation or median (min, max).

Parameter	Global population	Filling pressures		P
		E/e'<13*	E/e'>13*	
EF (%)	33.2 ± 6.1	34.6 ± 4.4	29.8 ± 3.9	0.001
NT-proBNP (pg/mL)	1625 ± 1268	643.8 ± 430	2531 ± 709	0.003
SUA (mg/dL)	7.9 ± 2.2	7.3 ± 1.4	8.6 ± 2.2	0.08
MDA (nmol/mL)	1.1 ± 0.3	0.9 ± 0.2	1.3 ± 0.2	0.04
MPO (IU/L)	310 ± 11	307 ± 11	312 ± 10	0.34
PON-1 (U/mL)	41.9 ± 15	37.5 ± 16	38.2 ± 10	0.88
hsCRP (mg/L)	6.1 (1.9, 23.8)	6.1 (1.9, 20.5)	7.7 (1.9, 23.8)	0.75
IL6 (pg/mL)	12 (0.7, 122.6)	7.5 (0.7, 122.6)	14.2 (3.4, 97.7)	0.56

sUA=serum uric acid, MDA= malondialdehyde, MPO= myeloperoxidase, PON-1= paraoxonase-1, IL6= interleukin 6

*P values for comparisons between E/e'<13and E/e'>13; P<0.05

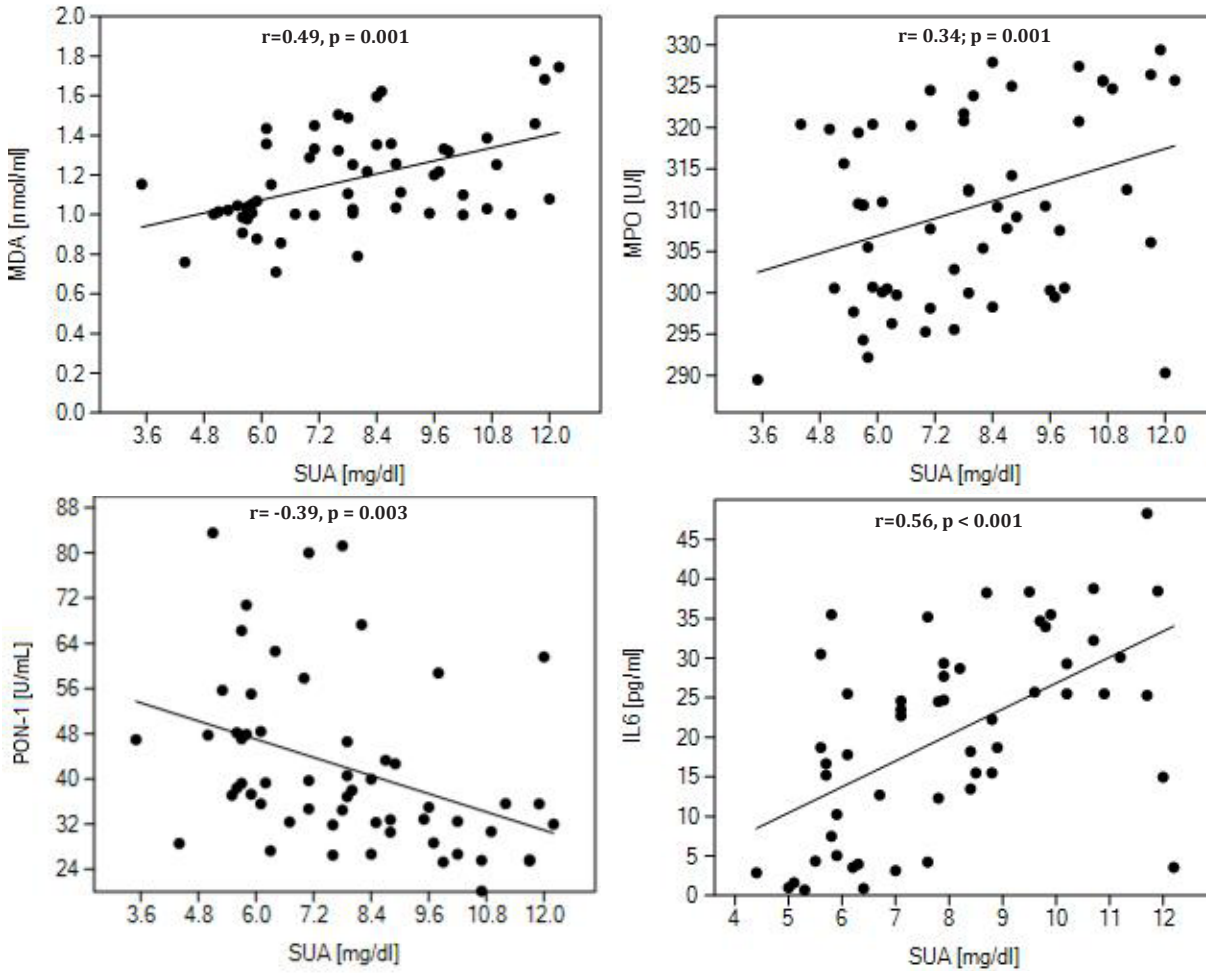

Figure 2. Scatterplots of sUA against markers of oxidative stress and systemic inflammation in the Study Population. sUA=serum uric acid,MDA= malondialdehyde, MPO= myeloperoxidase, PON-1= paraoxonase-1, IL6= interleukin 6, r=Pearson correlation coefficient.

In our study, 61% patients with NYHA class III CHF and reduced EF had hyperuricemia. sUA was higher in patients with increased LV filling pressures (8.6 ± 2.2 mg/dL in patients with E/e'ratio ≥ 13 vs 7.3 ± 1.4 mg/dL, p=0.08). The relationship between sUA and the hemodynamic compromise in CHF was demonstrated invasively and non-invasively by the measurement of E/A ratio of the mitral inflow at echocardiography (2,6,22,23,24). sUA correlated with severe diastolic dysfunction defined echocardiographically by restrictive mitral filling pattern (25).

sUA level was associated with lower EF, both in stable and worsening heart failure (6,26). The significant relationship in between sUA and LVEF found in the present study (r = -0.24, p=0.048) has also been demonstrated in several CHF studies (24,27,28). sUA level was related to NT-proBNP levels (24,26). Our data was similar to OPT-CHF trial results (29).

The significant relationship between sUA and the severity of LV systolic and diastolic

dysfunction in moderate-severe CHF qualifies sUA as a marker of CHF severity. In a validation study, sUA was the most powerful predictor of survival for patients with severe CHF, functional class III or IV, with a 7.4 relative risk of death in patients with sUA levels higher than 9.5 mg/dl (1).

Hyperuricemia in CHF is attributed to multiple factors. Renal failure or long-term diuretic therapy reduce uric acid excretion. However, diuretic-induced hyperuricemia is more common with thiazides and uric acid retention under diuretic treatment is dose-dependent.

In CHF with normal kidney function, hyperuricemia is a consequence of increased production rather than reduced renal clearance (6,26). sUA is a marker of xanthine-oxidase up-regulation, triggered by local tissue ischemia or hypoxia, and generating free radicals proportionally to uric acid synthesis (12). Large cohort studies demonstrated that hyperuricemia is a prognostic marker for poor outcomes for all cause mortality and CHF hospitalizations only in CHF patients without chronic kidney disease (6,21). In a recent meta-analysis of thirty-three studies assessing the relation between sUA and heart failure, the incremental elevation in sUA, by 1 mg/dL, increased risk of all cause mortality by 4% in patients with existing CHF and the odds of incident HF by 19% in the general population (26, 30).

There is an imbalance of the oxidative metabolism in CHF. In our study MDA, a marker of lipid peroxidation, was higher in CHF patients with lower EF and increased LV filling pressures. Increased MDA levels were related CHF functional severity, the highest values being reported in patients with functional NYHA class III and IV (31,32). MPO activity was also increased, recent data suggesting a correlation between high MPO activity and CHF functional severity (33). PON-1, a HDL-associated glycoprotein with antioxidant function, was reduced in CHF patients. Lower levels of PON-1 activity were also found in patients with idiopathic dilated cardiomyopathy and CHF (24). The diminished PON-1 activity in CHF with low EF was a marker of worse prognosis, predicting a higher risk of incident long-term adverse events (34).

The relationship between sUA, increased OS and reduced serum antioxidant capacity suggests that sUA is a marker of xanthine-oxidase up-regulation in CHF.

The markers of chronic inflammatory response were increased in CHF patients and IL-6 correlated with sUA levels($r=0.56$, $p<0.001$). The correlation between sUA and inflammatory cytokines (IL-6, TNF alpha), adhesion molecules and their soluble receptors was demonstrated in another study (4). sUA emerged as the strongest predictor for inflammatory response, independent of diuretic dose and serum creatinine (4). Uric acid levels parallels the chronic inflammatory response which occurs with increasing CHF severity (11).

The correlations between sUA and OS and inflammation markers suggest that increased OS induces activation of leukocytes and endothelial cells, while promoting endothelial dysfunction. Activation of pro-inflammatory cytokines also contributes to increased sUA production (35).

Study limitations

The limitations of this study are its small sample size, and a lack of a control group. However, these are only preliminary results, and the study will be extended to a larger number of CHF patients.

Conclusions

sUA is a metabolic biomarker of heart failure severity. Hyperuricemia in CHF without impairment of renal function may reflect an imbalance in oxidative stress, with increased xanthine-oxidase activity linked with chronic inflammatory response. Lowering sUA with xanthine-oxidase

inhibitors may be a therapeutic option for heart failure treatment.

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Conflict of interest

None

References

1. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107(15):1991–7. DOI: 10.1161/01.CIR.0000065637.10517.A0
2. Kittleson MM, St John ME, Bead V, Champion HC, Kasper EK, Russell SD, et al. Increased levels of uric acid predict haemodynamic compromise in patients with heart failure independently of B-type natriuretic peptide levels. Heart 2007;93(3):365–7. DOI: 10.1136/hrt.2006.090845
3. Cengel A, Turkoglu S, Turfan M, Boyaci B, et al. Serum uric acid levels as a predictor of in-hospital death in patients hospitalized for decompensated heart failure. Acta Cardiologica 2005;60(5):489–92. DOI: 10.2143/AC.60.5.2004969
4. Sakai H, Tsutamoto T, Tsutsui T, Tanaka T, Ishikawa C, Horie M, et al. Serum level of uric acid, partly secreted from the failing heart, is a prognostic marker in patients with congestive heart failure. Circ J. 2006;70(8):1006–11. DOI: 10.1253/circj.70.1006
5. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J, et al. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail. 2011;17(1):25–30. DOI: 10.1111/j.1751-7133.2011.00200.x
6. Gotsman I, Keren A, Lotan C, Zwas DR. Changes in uric acid levels and allopurinol use in chronic heart failure: association with improved survival. J Card Fail. 2012;18(9):694-701. DOI: 10.1016/j.cardfail.2012.06.528
7. Ashraf M, Samra ZQ. Subcellular distribution of xanthineoxidase during cardiac ischemia and reperfusion: an immunocytochemical study. J Submicrosc Cytol Pathol 1993; 25(2):193–201.
8. Terada LS, Guidot DM, Leff JA, Willingham IR, Hanley ME, Piermattei D, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci USA. 1992;89(8):3362–6. DOI: 10.1073/pnas.89.8.3362
9. Lazzarino G, Raatikainen P, Nuutinen M, Nissinen J, Tavazzi B, Di Pierro D, et al. Myocardial release of malondialdehyde and purine compounds during coronary bypass surgery. Circulation. 1994;90(1):291–7. DOI: 10.1161/01.CIR.90.1.291
10. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, et al. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998;19(12):1814–22. DOI: 10.1053/euhj.1998.1188
11. Anker SD, Leyva F, Poole-Wilson PA, Kox WJ, Stevenson JC, Coats AJ. Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure. Heart. 1997;78(1):39–43. DOI: 10.1136/hrt.78.1.39
12. Doehner W, Rauchhaus M, Florea VG, Sharma R, Bolger AP, Davos CH, et al. Uric acid in cachectic and noncachectic patients with chronic heart failure: relationship to leg vascular resistance. Am Heart J. 2001;141(5):792–9. DOI: 10.1067/mhj.2001.114367
13. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur J Heart Fail 2008;10(10):933–989. DOI: 10.1016/j.ejheart.2008.08.005
14. Buchmann R, Hasilik A, Van Dyke TE, Lange DE. Amplified Crevicular Leukocyte Activity in Aggressive Periodontal Disease. J Dent Res. 2002. 81(10):716-721. DOI: 10.1177/154405910208101012
15. Cabana VG, Reardon CA, Feng N, Neath S, Lukens J, Getz GS. Serum paraoxonase: effect of the apolipoprotein composition of HDL and the acute phase response. J Lipid Res. 2003; 44(4):780-792. DOI: 10.1194/jlr.M200432-JLR200
16. Krishnan E. Interaction of inflammation, hyperuricemia, and the prevalence of hypertension among adults free of metabolic syndrome: NHANES 2009-2010. J Am Heart Assoc. 2014;3(2):e000157. DOI: 10.1161/JAHA.113.000157

17. Sinan Deveci O, Kabakci G, Okutucu S, Tulumen E, Aksoy H, Baris Kaya E, et al. The association between serum uric acid level and coronary artery disease. Int J Clin Pract. 2010; 64(7):900-7. DOI: 10.1111/j.1742-1241.2009.02263.x
18. Duran M, Kalay N, Akpek M, Orscelik O, Elcik D, Ocak A, et al. High levels of serum uric acid predict severity of coronary artery disease in patients with acute coronary syndrome. Angiology. 2012;63(6):448-52. DOI: 10.1177/0003319711426868
19. Gotsman I, Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. Curr Pharm Des. 2005;11(32):4145-51. DOI: 10.2174/138161205774913255
20. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16(1):15-24. DOI: 10.1093/eurjhf/hft132
21. Filippatos GS, Ahmed MI, Gladden JD, Mujib M, Aban IB, Love TE, et al. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. Eur Heart J. 2011;32(6):712-20. DOI: 10.1093/eurheartj/ehq473
22. Amin A, Vakilian F, Maleki M. Serum uric acid levels correlate with filling pressures in systolic heart failure. Congest Heart Fail. 2011;17(2):80-4. DOI: 10.1111/j.1751-7133.2010.00205.x
23. Zhang YH, Lü R, Zhao XY, Kang LM, Yang YJ, Zhang J. Association of serum uric acid, plasma NT-proBNP, Hs-C reactive protein and invasive hemodynamic parameters in patients with heart failure. Zhonghua Xin Xue Guan Bing Za Zhi. 2009;37(2):126-9.
24. Wojciechowska C, Romuk E, Tomasik A, Skrzep-Poloczek B, Nowalany-Kozielska E, Birkner E, Jache W. Oxidative stress markers and c-reactive protein are related to severity of heart failure in patients with dilated cardiomyopathy. Mediators Inflamm. 2014;2014:147040. DOI: 10.1155/2014/147040
25. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Elevated serum uric acid levels are associated with diastolic dysfunction in patients with dilated cardiomyopathy. Am Heart J. 2002; 143(6):1107-11. DOI: 10.1067/mhj.2002.122122
26. Vaduganathan M, Greene SJ, Ambrosy AP, Mentz RJ, Subacius HP, Chioncel O, et al. Relation of serum uric acid levels and outcomes among patients hospitalized for worsening heart failure with reduced ejection fraction (from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan trial). Am J Cardiol. 2014;114(11):1713-21. DOI: 10.1016/j.amjcard.2014.09.008
27. Pinelli M, Bindi M, Filardo FP, Moroni F, Castiglioni M. Serum uric acid levels correlate with left ventricular ejection fraction and systolic pulmonary artery pressure in patients with heart failure. [Article in Italian] Recenti Prog Med. 2007;98(12):619-23.
28. Borghi C, Cosentino ER, Rinaldi ER, Cicero AF. Uricaemia and ejection fraction in elderly heart failure outpatients. Eur J Clin Invest. 2014;44(6):573-8. DOI: 10.1111/eci.12273
29. Hare JM, Mangal B, Brown J, Fisher C Jr, Freudenberger R, Colucci WS, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol. 2008; 51(24):2301-9. DOI: 10.1016/j.jacc.2008.01.068
30. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk ofheart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16(1):15-24. DOI: 10.1093/eurjhf/hft132
31. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, et al. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol. 1998;31(6):1352–6. DOI: 10.1016/S0735-1097(98)00101-6
32. Díaz-Vélez CR, García-Casti-eiras S, Mendoza-Ramos E, Hernández-López E. Increased malondialdehyde in peripheral blood of patients with congestive heart failure. Am Heart J. 1996;131(1):146-52. DOI: 10.1016/S0002-8703(96)90063-0
33. Reina-Couto M, Carvalho J, Valente MJ, Vale L, Afonso J, Carvalho F, et al. Impaired resolution of inflammation in human chronic heart failure. Eur J Clin Invest. 2014; 44(6):527-38. DOI: 10.1111/eci.12265
34. Wilson Tang WH, Wu Y, Mann S, Pepoy M, Shrestha K, Borowski AG, et al. Diminished Anti-Oxidant Activity of High-Density Lipoprotein-Associated Proteins in Systolic Heart Failure. Circ Heart Fail. 2011;4(1):59–64. DOI: 10.1161/CIRCHEARTFAILURE.110.958348
35. Landmesser U, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, et al. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine-oxidase and extracellular superoxide dismutase. Circulation. 2002;106(24):3073–8. DOI: 10.1161/01.CIR.0000041431.57222.AF