ORIGINAL PAPERS

The Effect of Allopurinol on Endothelial Function, Serum Uric Acid and NT-proBNP in Acute Decompensated Heart Failure

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Abstract

Background: Acute decompensated heart failure (ADHF) is a complex and heterogeneous syndrome, with increasing incidence and poor prognosis, being a major cause of hospital readmission and death and requiring urgent treatment. **Aim:** Assessing changes in serum uric acid (sUA), endothelial function (EF) and NT-proBNP for ADHF patients and the effect of Allopurinol on them. **Method:** Study group included 81 patients (mean age 71.23±10.22 years, 61% males) with ADHF (NYHA class III-IV) caused by ischemic cardiomyopathy. During hospitalization (10±4 days) Allopurinol 300 mg/day was randomly administered regardless of sUA level to 42 patients (ALLO+ group). NT-proBNP and sUA levels and EF were determined in all patients at baseline and release. EF was determined by flow mediated vasodilatation (FMD), values below 10% indicating endothelial dysfunction. **Results:** sUA levels significantly decreased in ALLO+ group and increased in ALLO-: from 7.44±2.77 mg/dL to 5.21±1.48 mg/dL vs from 6.63±2.51 mg/dL to 6.98±2.25 mg/dL. EF significantly improved in ALLO+ in comparison to ALLO-: an increase of 9.87±6.57 pp vs. 4.18±5.39 pp. NT-proBNP levels decreased for all subjects, with no difference between the groups: -1778±2005 µg/dL vs -2150±4196 µg/dL. **Conclusions:** In ADHF there is a strong relationship between hyperuricemia and endothelial dysfunction and Allopurinol decreases levels of sUA and improves EF.

Keywords: acute decompensated heart failure, Allopurinol, serum uric acid, endothelial function, oxidative stress

Rezumat

Introducere: Insuficiența cardiacă cronică acut decompensată (ADHF) formează un sindrom heterogen, complex, reprezentând o problemă majoră de sănătate publică cu o incidență în creștere și prognostic nefavorabil. **Obiective:** Evaluarea modificărilor acidului uric seric (AUs), a funcției endoteliale și a NT-proBNP-ului în ADHF și efectul Allopurinolului asupra acestora. **Material și metoda:** Au fost incluși 81 de bolnavi (vârstă medie 71±10 ani, 61% bărbați) cu ADHF (clasa NYHA III-IV) de etiologie ischemică. Pe parcursul internării (10±4 zile) s-a administrat aleatoriu Allopurinol 300 mg/zi, indiferent de nivelul AUs, la 42 de bolnavi (grupul ALLO+). Valorile NT-proBNP-ului și ale AUs și funcția endotelială au fost determinate la internare si externare. Funcția endotelială a fost evaluată prin vasodilatație mediată de flux, valori sub 10% indicând disfuncție endotelială. **Rezultate:** Nivelul AUs a scăzut semnificativ în grupul ALLO+ față de ALLO-: de la 7,44±2,77 mg/dL la 5,21±1,48 mg/dL vs de la 6,63±2,51 mg/dL la 6,98±2,25 mg/dL Funcția endotelială sa ameliorat semnificativ în ALLO+: o creștere de 9,87±6,57 pp față de 4,18±5,39 pp în ALLO. NT-proBNP a scăzut la externare pe întreg lotul, fără diferențe între cele două grupuri: 1778±2005 µg/dL vs 2150±4196 µg/dL. **Concluzii:** În ADHF există o relație puternică între hiperuricemie și disfuncția endotelială. Allopurinolul scade semnificativ nivelul AUs și îmbunătățește funcția endotelială.

Cuvinte cheie: insuficiența cardiacă cronică acut decompensată, Allopurinol, acid uric seric, funcție endotelială, stres oxidativ

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INTRODUCTION

Acute decompensated heart failure has an increasing incidence and poor prognosis, being a major cause of death and hospital readmission and requiring urgent optimized therapy[1]. Under the influence of some decompensation risk factor, such as infections, arrhythmias, decompensation of some comorbidities, lack of adherence to the treatment, patients with a history of heart failure may suffer a progressive symptomatology worsening; therefore, more than 70% of cases of acute heart failure represent the clinical worsening of chronic heart failure – ADHF[2].

ADHF is a heterogeneous and complex syndrome, with multiple pathophysiological mechanisms, being dominated by signs of systemic congestion. There is a growing body of evidence suggesting that increased oxidative stress contributes to ventricular and vascular remodeling and disease progression[3].

Numerous epidemiological and clinical studies[4] have shown a strong association between sUA level and cardiovascular pathology[5]: from risk factors to target organ damage and ultimately to heart failure[6,7]; situations in which oxidative stress is an important physiopathological link[8,9].

The pathogenesis of hyperuricemia in heart failure is most likely multifactorial[10] oxidant-producing enzymes, in particular xanthine oxidase (XO, involving oxidative metabolism abnormalities, activation of cytokines, insulin resistance and impaired kidney function[11]. However, an increase of the uric acid production seems to be the dominant factor[12-14]. Thus, sUA level in these patients is a witness of the degree of XO activation[15-16], leading to increased production of superoxide[17].

Studies on animal models have demonstrated the reduction of the antioxidant activity and the increase in oxidative stress in ADHF: the reactive oxygen species contribute to the progression of heart failure by myocardial fibrosis and decreasing muscle fiber performance[18].

The uric acid is in normal circumstances an anti-oxidant, but becomes pro-oxidant in the atherosclerotic medium with ROS generation. Therefore, the "sUA paradox" consists in the association of high sUA levels with an increased cardiovascular risk[19]. It is conceivable that, in these conditions, the antioxidant activity of sUA is overcome by the pro-oxidant and pro inflammatory effects of ROS accumulation[20]; with decreased synthesis and release of nitric oxide (NO)[21].

Therefore, hyperuricemia is associated with a worse prognosis in heart failure[22]; the sUA level beeing independently correlated with mortality[14,23], heart failure severity (assessed by NYHA functional class and exercise duration)[24] and functional capacity indicators such as maximum oxygen consumption[11].

The endothelial dysfunction[25] is characterized by abnormal pro-inflammatory, pro-thrombotic[26] and pro-vasoconstrictor[27] status; all well known as pathophysiologic processes in ADHF. The endothelial dysfunction is associated with decreased synthesis of NO and bradykinin, important platelet activation inhibitors[28], thus bringing the platelets in a state of hyperactivation.

Testing the endothelial function with the brachial artery flow-mediated vasodilatation method has become one of the most used methods[29], beeing non-invasive[30,31] and validated by comparative studies with the standard method[32]. However, the place of uric acid is not well established in ADHF[33], prospective studies are required for identifying the cutoff value to predict poor prognosis. Also, considering the pathophysiological mechanisms involved in ADHF such as endothelial dysfunction and oxidative stress, Allopurinol seems to be a promising therapeutic perspective by XO inhibiting[8,34], the key enzyme in oxidative metabolism, which catalyzes the conversion of xanthine into free oxygen radicals and uric acid[35-38].

The aim of the study was to assess the changes in the endothelial function (EF), serum uric acid (sUA) and NT-proBNP for ADHF patients and the effect of Allopurinol (ALLO) on these parameters.

Method: The study group included 81 patients with ADHF caused by ischemic cardiomyopathy, treated according to 2012 ESC guidelines. The decompensation of heart failure was proved clinically: NYHA functional class III and IV and at least 2 signs of congestion and biologically: increasing of NT-proBNP level and required hospitalization.

Exclusion criteria were: stroke in the last 3 months, cor pulmonale, significant valvular disease, severe pulmonary, renal or liver disease. None of the patients were taking Allopurinol before admission.

ECG, laboratory tests and echocardiography were performed in all patients, after a comprehensive clinical examination[1].

Echocardiography studies were performed according to standard recommendations of the *European Association of Cardiovascular Imaging*. SUA levels were assessed using enzymat¬ic-colorimetric methods (normal range: ≤7 mg/dL for men and ≤6 mg/dL for women). The N-terminal fragment of the prohor¬mone brain natriuretic peptide (NT-proBNP) was immunologically measured using Roche Cardiac Reader kit (normal range: <125 μg/dL).

The endothelial function was assessed by flow-mediated vasodilatation method using the 2 dimensions vascular ultrasound of the brachial artery at the brachial artery (FMD), as recommended by international guidelines[32]. Percentage variation in the diameter of the brachial artery before and after ischemic stimulus (tensiometer cuff inflation over 50 mmHg systolic BP value) was calculated, values below 10% indicating endothelial dysfunction.

$$\text{FMD (\%)} = \frac{\text{(final diametre- initial diametre)*100}}{\text{initial diametre}}$$

Forty-two patients were randomly assigned to receive ALLO 300 mg, daily, regardless of their sUA level added to the standard treatment (ALLO+ group). The rest of 39 patients were treated according to the ESC Guideline (ALLO – group). All patients were re-evaluated during hospitalization and at discharge (10 ± 4 days after admission).

Length of stay was 10 ± 4 days for ALLO+ group and 10 ± 5 days for ALLO- group (p=0.87).

Statistical analysis: The results were presented as mean ± standard deviation for numeric variables and as absolute numbers and percentages for categorical variables. For the analysis of numeric variables, parametric (Student's *t*-test, ANOVA) or non-parametric (Mann-Whitney, Kruskal-Wallis) tests were used. Linear regression and Pearson correlation coefficient r were used for correlations between numerical variables. The statistical significance was considered for a p-value<0.05. The statistical analysis was performed by using 20.0.SPSS.

RESULTS

Table 1. Characteristics of the two groups of patients at initial assessment

	Overall 81	ALLO + 42	ALLO – 39	p
Demographics				
Age - years	71.23 ± 10.22	70.88 ± 9.07	71.62 ± 11.44	0.75
Male - n (%)	49 (61%)	26 (62%)	23 (59%)	0.79
Clinic				
NYHA class III - n (%)	44 (54%)	24 (57%)	20 (51%)	0.76
NYHA class IV - n (%)	37 (46%)	18 (43%)	19 (49%)	0.60
Heart rate - beats/min	91 ± 26	90 ± 27	91 ± 24	0.79
Systolic Blood pressure– mmHg	134 ± 25	132 ± 22	135 ± 27	0.51
Life Quality				
MLHF - points	53 ± 12	52 ± 13	53 ± 11	0.82
Length of stay - days	10 ± 4	10 ± 4	10 ± 5	0.87
Cardiovascular risk factors				
Family history - n (%)	18 (22%)	11 (26%)	7 (18%)	0.38
MI history - n (%)	19 (23%)	9 (21%)	10 (26%)	0.66
Diabetes - n (%)	28 (35%)	18 (42%)	10 (26%)	0.11
Hypercholesterolemia - n (%)	43 (53%)	23 (55%)	20 (52%)	0.76
Obesity - n (%)	26 (32%)	16 (38%)	10 (26%)	0.17
Atrial fibrillation - n (%)	56 (69%)	29 (69%)	27 (69%)	0.99
Hypertension - n (%)	62 (77%)	31 (74%)	31 (80%)	0.55
LBBB - n (%)	22 (27%)	12 (29%)	10 (26%)	0.76
CKD - n (%)	22 (27%)	12 (29%)	10 (26%)	0.64

Legend: NYHA – New York Heart Association Classification; MLHF –Minnesota Living With Heart Failure questionnaire; MI – myocardial infarction; LBB – left bundle block; CKD – chronic kidney disease

The baseline characteristics of the 2 study groups are presented in table 1 and 2: they were similar in terms of age, clinical presentation, cardiovascular risk factors and paraclinics. The mean sUA level was 7.05±2.66 mg/dL at admission, 41 subjects having hyperuricemia. The mean NTproBNP level was 5311±5417 μg/dL, demonstrating decompensated heart failure. Also, the mean FMD was 7.18±6.04%, 59 subjects (73%) presenting endothelial dysfunction at admission.

A significant correlation between the NT-proBNP level and the sUA level (r=0.239, p=0.032) was noticed. Also, there was an inverse correlation between the NT-proBNP level and the FMD percentage (r =-0.252, p=0.023) and between the FMD percentage

Table 2. Paraclinic characteristics of the 2 groups of patients at initial assessment

Laboratory	Overall 81	ALLO + 42	ALLO – 39	p
Hemoglobin -g/dL	12.71 ± 2.04	12.66 ± 2.27	12.78 ± 1.78	0.80
Sideremia -mg/dL	57.4 ± 28.93	54.39 ± 29.14	60.64 ± 28.72	0.33
BUN -mg/dL	56.48 ± 26.05	56.69 ± 26.9	56.27 ± 25.56	0.95
Creatinine -mg/dL	**1.15 ± 0.47**	**1.13 ± 0.32**	**1.17 ± 0.6**	**0.68**
Cl. Creatinine -ml/min/1.73 m²	66.33 ± 22.14	66.04 ± 19.38	67.96 ± 3.82	0.69
sUA -mg/dL	**7.05 ± 2.66**	**7.43 ± 2.77**	**6.64 ± 2.51**	**0.18**
Na -mmoli/L	135.74 ± 4.55	135.34 ± 4.99	136.18 ± 4.03	0.41
K -mmoli/L	4.35 ± 0.52	4.29 ± 0.53	4.43 ± 0.51	0.24
total Cho -mg/dL	159.94 ± 49.38	162.07 ± 47.95	157.64 ± 51.41	0.69
CRP -mg/L	16.37 ± 3.45	18.92 ± 3.90	13.63 ± 2.94	0.50
NT-proBNP -µg/dL	**5311 ± 5417**	**4593 ± 4941**	**6085 ± 5852**	**0.22**
Ecocardiography				
LVEF -%	**37.09 ± 11.59**	**37.16 ± 12.27**	**36.87 ± 10.95**	**0.91**
LV mass index -g/m²	147.06 ± 16	130.7 ± 46.27	165.15 ± 27.27	0.34
Flow mediated vasodilatation				
FMD -%	**7.18 ± 6.04**	**6.27 ± 4.52**	**8.14 ± 7.27**	**0.17**

Legend: BUN – blood urea nitrogen; Cho – colesterol; CRP – C-reactive protein; LVEF – left ventricle ejection fraction

and NYHA class (r=-0.266, p=0.016) or the MLHF questionnaire score (r=-0.424, p<0.001).

After two days of hospitalization, in ALLO+ group, the sUA level significantly decreased from 7.44±2.77 mg/dL to 6.74±2.37 mg/dL (p=0.004) and the FMD percentage significantly increased from 6.27±4.52% to 8.46±4.73 (p<0.001) showing the improvement of the endothelial function.

On the day 5 re-evaluation, there was observed a gradual improvement of endothelial function in ALLO+ group, the FMD percentage increasing to 12.73±6.34% (p<0.001) while the sUA level decreased to 6.05±2.18 mg/dL (p=0.001). This trend continued at discharge, the FMD percentage reaching to 16.26±7.50% (p<0.001) and the sUA level to 5.21±1.48 mg/dL (p<0.001).

The variation of sUA level did not correlate with the improvement of the endothelial function in ALLO+ group during hospitalization (r=-0.181, p=0.258) or at discharge (r=0.277, p=0.079).

In ALLO- group a slight improvement in endothelial function was observed during hospitalization: from 8.15±7.27 pp to 12.51±8.84 pp (p<0.001). Also, a slight increase (but not significant) of the sUA level was observed: from 6.63±2.51 mg/dL to 6.98±2.25 mg/dL (p=0.054).

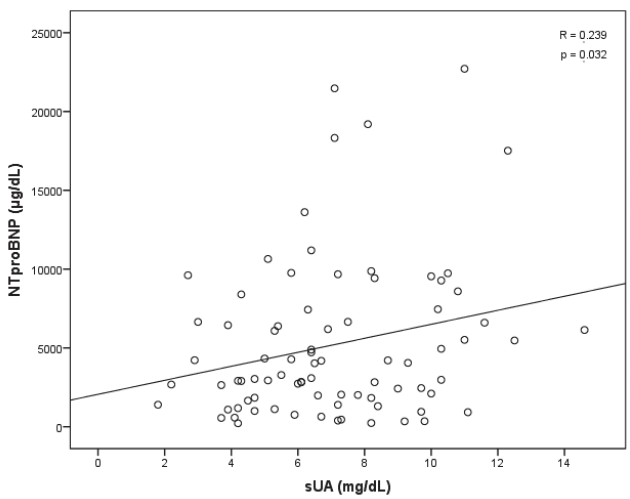

Figure 1. The correlation between sUA level (mg/dL) and NTproBNP level (µg/dL) at admission.

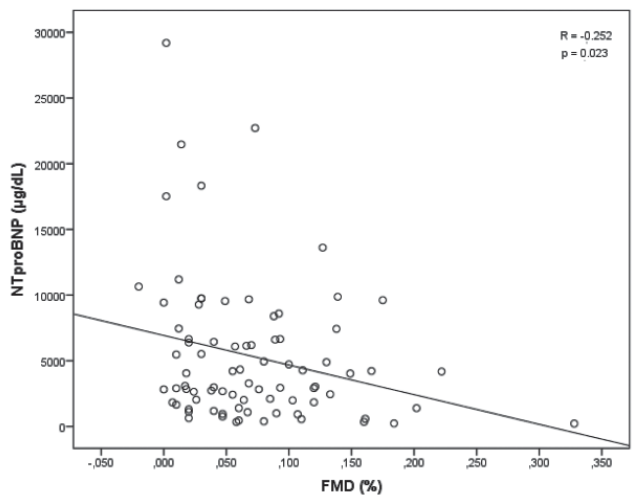

Figure 2. The correlation between FMD level (%) and NTproBNP level (µg/dL) at admission.

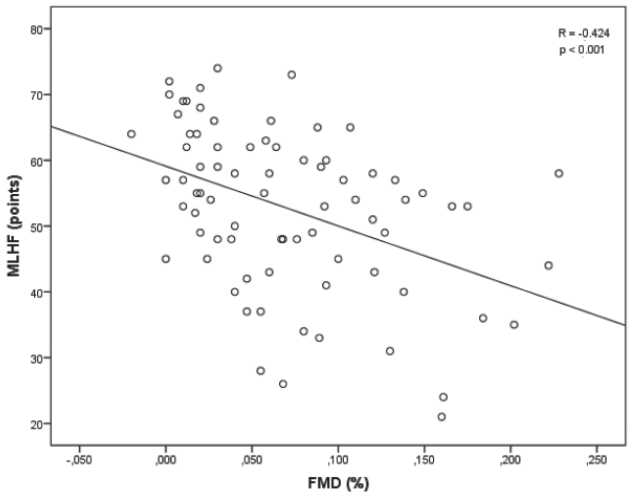

Figure 3. The correlation between FMD level (%) and MLHF (points) at admission.

Table 3. The sUA level variation (mg/dL) in the 2 groups during hospitalization

	admission	day 2	day 5	discharge
ALLO+	7.44 ± 2.77	6.74 ±2.37	6.05 ±2.18	5.21 ± 1.48
		p=0.004	**p=0.001**	**p<0.001**
ALLO-	6.63 ± 2.51	6.86 ±2.24	7.10 ±2.16	6.98 ± 2.25
		p=0.16	p=0.57	p=0.12

Table 4. The hyperuricemia variation (no. of subjects [%]) in the 2 groups during hospitalization

	admission	day 2	day 5	discharge
ALLO+	25 (60%)	20 (48%)	16 (38%)	6 (14%)
		p=0.02	p=0.26	**p=0.002**
ALLO-	16 (41%)	16 (41%)	18 (46%)	20 (51%)
		p=1	p=0.26	p=0.33

Table 5. The creatinine level variation (mg/dL) in the 2 groups during hospitalization

	admission	day 2	day 5	discharge
ALLO+	1.13 ±0.32	1.14±0.29	1.16±0.30	1.14±0.27
		p=0.81	p=0.54	p=0.72
ALLO-	1.18 ± 0.60	1.18±0.53	1.20±0.52	1.19±0.50
		p=0.74	p=0.75	p=0.76

Table 6. The FMD percentage variation (percentage points) in the 2 groups during hospitalization

	admission	day 2	day 5	discharge
ALLO+	6.27±4.52	8.46±4.73	12.73±6.34	16.26±7.50
		p<0.001	**p<0.001**	**p<0.001**
ALLO-	8.15 ± 7.27	9.63±8.10	12.22±9.63	12.51±8.84
		p=0.005	**p=0.02**	p=0.96

Table 7. The endothelial dysfunction variation (no of subjects (%)) in the 2 groups during hospitalization

	admission	day 2	day 5	discharge
ALLO+	35 (83%)	27 (64%)	15 (36%)	6 (14%)
		p=0.003	**p=0.005**	**p<0.001**
ALLO-	24 (62%)	21 (54%)	16 (41%)	18 (46%)
		p=0.18	p=0.42	p=0.57

Table 8. The NT-proBNP variation (µg/dL) in the 2 groups during hospitalization

	admission	discharge
ALLO+	4593+/-4941	2745+/-3550 **p<0.001**
ALLO-	6085+/-5852	3951+/-4990 **p=0.003**

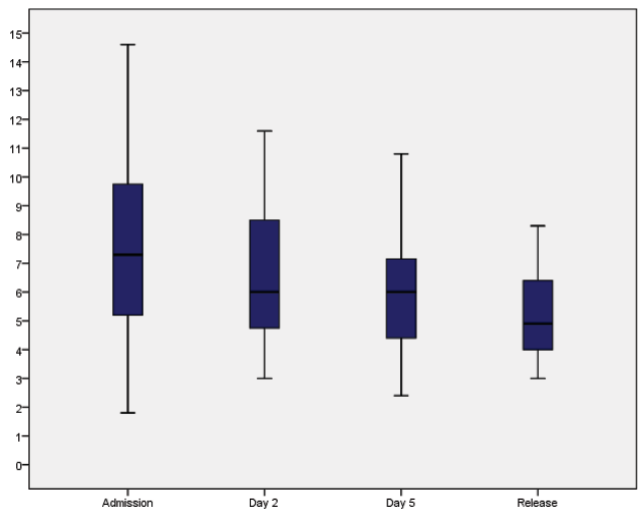

Figure 4. The sUA variation (mg/dL) during hospitalization in ALLO+ group.

The NT-proBNP level decreased by 1957±3232 g/dL at discharge overall, without a significant difference between the two groups: -1778±2005 μg/dL in ALLO+ vs 2150±4196 μg/dL in ALLO- (p=0.62).

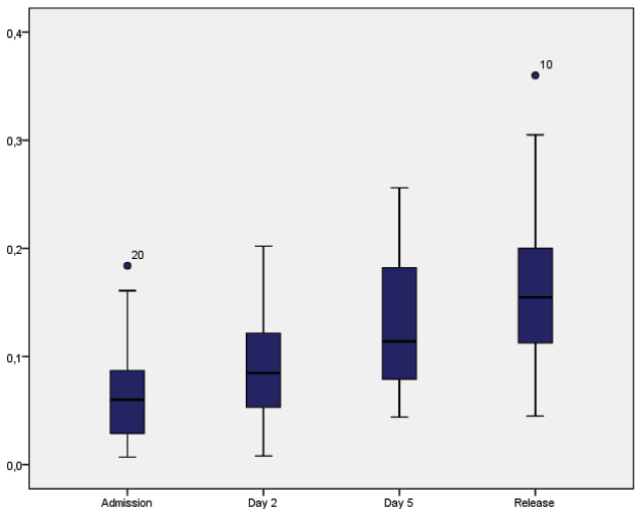

Figure 5. The FMD variation (%) during hospitalization in ALLO+ group.

DISCUSSIONS

The results confirm the high prevalence of hyperuricemia (>50%) in ADHF patients, consistent with previous studies[8,9]. Hyperuricemia in this case has two main causes: an increase of the uric acid production because of higher abundance of purines and reduced renal function clearance[26]. Thus we can consider the sUA level a witness of XO activation, experimental evidence demonstrating the increased XO activity in ADHF, generating a superoxide increase10oxidant-producing enzymes, in particular xanthine oxidase (XO.

The mean sUA level was 7.05±2.66 mg/dL; similar to the results of the cohort study AHEAD[39] that enrolled ADHF patients with same characteristics: mean age 73.4 years, 43% female, mean NT-proBNP 5510 μg/dL. The mean sUA level was 7.26 mg/dL and levels greater than 8.67 mg/dL were associated with in-hospital mortality. In another cohort study where patients hospitalized for ADHF were included[40] (the Japanese Registry of acute heart failure) and followed them for a period of 2.1 years for fatal or non-fatal cardiovascular events, 56% of the subjects had hyperuricemia at admission (mean sUA level 7.3±2.4 mg/dL). Patients with a level greater than 7.4 mg/dL had higher rates of cardiac and non-cardiac rehospitalization and mortality. The multivariate analysis showed that sUA level is an independent predictor for death or rehospitalization, the risk of death increasing with 6.8% for every 1 mg/dL increase.

The sUA level was correlated with the NT-proBNP level at admission (r=0.239, p=0.032). This weak correlation was observed in previous studies, the authors[41] considering that the uric acid may provide complementary information to natriuretic peptides on the prognosis of ADHF patients.

The endothelial dysfunction[42] is another important pathophysiological mechanism in HF decompensation: in our study 73% of subjects had endothelial dysfunction at admission.

The results of this study confirm the beneficial effect of Allopurinol on the endothelial function in ADHF patients. The effect seems to settle quickly, a significant improvement was seen even after 2 days of treatment: mean FMD increased from 6.27±4.52% to 8.46±4.73%; and continued in day 5 to 12.73±6.34% and at discharge to 16.26±7.50%. These data suggest a rapid and continuous effect of Allopurinol, with progressive improvement throughout hospitalization. It remains to be studied whether the magnitude of this effect is maintained in the medium and long term, especially in the vulnerable period, up to 3 months after hospitalization when rehospitalization and mortality rate are very high.

Farquharson et al[36] showed a net improvement in endothelial function and a decrease of the oxidative stress markers after Allopurinol (300 mg daily) in patients with heart failure. George et al[43] demonstrated the dose-dependent effect of Allopurinol on the endothelial function, the best results being obtained at a dose of 600 mg daily, without any notable adverse effects.

The EXACT-HF study[44] randomly assigned 253 high-risk patients with symptomatic left ventricular dysfunction and serum uric acid levels ≥9.5 mg/dL to receive high-dose Allopurinol or placebo in a double-blind, multicenter trial. Allopurinol safely lowered sUA levels in comparison with placebo, but had no detectable benefits on clinical status, exercise capacity, quality of life or left ventricular structure and function. Despite a strong pathophysiological rationale for XO inhibition, positive physiological end points in previous studies may have been poor surrogates for the clinical end points that were measured. Alternatively, this study may have been too short, or the study population too sick to observe a benefit. Also, the mean sUA level was 11 mg/dL and the mean creatinine level 1.5 mg/dL; therefore, hyperuricemia was probably also due to impairment of renal excretion. Filippatos et al.[13] demonstrated the impact of hyperuricemia in patients with HF

only when CKD was not associated. The same results were confirmed by a post-hoc analysis of the EVEREST study: hyperuricemia is a predictor for all-cause mortality for patients with eGFR >30 mL/min/1.73 m^2. In patients with eGFR <30 ml/min/1.73 m^2, sUA levels have not been correlated with death or rehospitalization of cardiac or non-cardiac causes[45]. Also, other studies proved that if hyperuricemia is caused by impaired renal excretion and not by increased xanthine oxidase activity, the use of xanthine oxidase inhibitors is unlikely to improve outcomes.

In the ALLO- group, a slight improvement of the endothelial function was observed during hospitalization, this confirming that the endothelial dysfunction is an important pathophysiological mechanism[46] in heart failure decompensation that seems to improve with clinical improvement[43].

Also, the improvement of endothelial function did not correlate with the decrease of the sUA level (r=-0.181, p=0.258), suggesting that the effect of Allopurinol on the endothelial function improvement is in part independent of the sUA-lowering effect. This comes in line with previous studies[47] that have shown that the effect of Allopurinol on the endothelial function is not secondary to the decrease of sUA level, but to reduction of the vascular oxidative stress. Using equivalent doses of Allopurinol and Probenecid, that produced similar reductions of the sUA level, the authors[43] proved that Probenecid practically had no effect on the endothelial function.

NT-proBNP levels decreased with more than 50% from admission to release overall, with no difference between the groups; natriuretic peptides and oxidative stress markers being complementary in the ADHF physiopathology[35].

CONCLUSION

In ADHF patients hyperuricemia had a high prevalence - 51% of the subjects with a mean sUA level of 7.05±2.66 mg/dL. The endothelial dysfunction was observed in 73% of the subjects and was improving with clinical improvement during hospitalization.

There was a strong relationship between hyperuricemia and endothelial dysfunction, the sUA level being a witness of the oxidative stress that is causing endothelial dysfunction. Allopurinol (300 mg daily) decreased the sUA level and improved the endothelial function, but did not influence the NTproBNP level (probably different pathophysiological mechanisms).

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