

ARTICLE

Uric acid in Chronic Heart Failure; Correlation with Prognostic Markers

Fathia Ehmouda¹, Hamid Elbrasai², Ali M Elneihoum¹

¹Department of Medicine, 7th October University Hospital and ²Benghazi Cardiac Center, Benghazi, Libya

Corresponding author: Professor Ali M Elneihoum Email: alineihoum@hotmail.com

Published: 12 October 2014

Ibnosina J Med BS 2014;6(5):208-212

Received: 16 July 2013

Accepted: 03 April 2014

This article is available from: <http://www.ijmbs.org>

This is an Open Access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Chronic heart failure (CHF) is a leading cause of both morbidity and mortality worldwide. The pathophysiologic understanding of chronic heart failure (CHF) has shifted from a mere hemodynamic disorder to a much more complex approach including changes and imbalances in neurohormonal, immune, and metabolic functions. Hyperuricemia is a constant finding in CHF.

Aim: To estimate the level of uric acid (UA) in patients with CHF, and to explore the possible relationship with established prognostic markers in these patients. **Patients**

and Methods: Ninety-five patients with CHF were studied. Detailed clinical assessment, ECG, laboratory investigations and echocardiography were performed for all patients. Serum UA level >7.0 mg/dl was considered high. **Results:** The age range of patients was 28-85 years (median age 67). Of this group, 54 were males. The duration of the disease ranged from 113 years. In addition, 56% of patients were diabetic, 64% were hypertensive, and 74%

had ischemic heart disease. 41 patients were class III New York Heart Association (NYHA) functional calcification, whereas 34 patients and 12 patients were in class II & IV respectively. The following diagnostic information was obtained: 1) blood pressure readings were 60 -123mmHg (mean=87.9±14.4). 2) atrial fibrillation (AF) was noted in 36 patients (38%) 3) left ventricular ejection fraction (EF %) was 13-68% (mean=37.9±20.1) 4) blood urea ranged from 13-197 mg/dl (mean=64.7±42.6) 5) serum creatinine was 0.4-5.5mg/dl (mean=1.4±0.9) 6) serum sodium was 119-148 (mean=134.2±5.9) 7) Elevated serum uric acid levels were found in 73% of our patients. We found a significant inverse correlation between serum uric acid level and mean arterial blood pressure ($r = -0.42$, $p = 0.019$) and with left ventricular ejection fraction (EF%) ($r = -0.31$, $p = 0.003$). We also demonstrated a direct correlation between serum UA and blood urea ($r = +0.21$, $p = .042$), serum Cr ($r = +0.21$, $p = 0.051$) and age ($r = +0.37$, $p = 0.034$). No significant differences were noted in serum UA level

in different (NYHA) functional subgroups. **Conclusions:** High serum UA was observed in 73% of patients with CHF. The observed significant correlation between UA level and some established prognostic markers in these patients may indicate that serum UA could provide additional prognostic information in this population. We propose that such a simple marker that can be measured anywhere at a low cost to help identify high-risk patients with CHF.

Key Words: Uric acid, hyperuricemia, chronic heart failure, CHF, prognosis

Introduction

Chronic heart failure (CHF) is a leading cause of both morbidity and mortality worldwide, with increasing both prevalence and health care costs. Recently, our understanding has changed from a mere hemodynamic disorder to a much more complex approach, including neuroendocrine and immune activation. Not only is the cardiovascular system affected in the long-term course of heart failure, but peripheral tissues and organs contribute to both symptoms and progression of the disease. Current findings on metabolic imbalances and hormonal abnormalities occurring in CHF further contribute to the complex picture of this disease pathophysiology (1).

Increasing body of evidence suggests that UA, a product of xanthine oxidase (XO), may be a useful marker for metabolic, hemodynamic, and functional staging in CHF and a valid predictor of survival in these patients. Recent data supports an expanded role for UA evaluation and the XO pathway in the pathogenesis of HF (2). Moreover isolated hyperuricemia (irrespective of renal function and administration of drugs) appears to be a marker of altered oxidative metabolism, associated with tissue hypoxia. Uric acid levels reflect the degree of circulating XO activity characterized by elevation of levels of free radicals and inflammatory markers which could further damage cardiomyocytes and vascular endothelium. In addition, this can induce disturbances of myocardial contractility, vasoconstriction and may negatively affect the cardiovascular system and potentially worsen the prognosis in patients with CHF (3-6). Numerous population studies have previously reported that elevated UA levels are an independent predictor of cardiovascular mortality. Recent evidence suggests that lowering serum levels of UA may lead to improved outcomes in HF patients (7-10). The question of whether UA is only a marker rather than a causal factor in the pathogenesis of HF remains and will

require further evaluation.

We hypothesized that in CHF serum uric acid levels might be a simple, widely available and significant predictor of disease severity & could be added to the known prognostic indicators of this disease. The objective of our study was to estimate the level of uric acid (UA) in patients with CHF, and to determine the possible correlation with established prognostic markers in those patients.

Patients and methods

The study was conducted at The 7th October University Hospital and Benghazi Cardiac Center between July, 2009, and June, 2010. All patients recruited were diagnosed with CHF based on detailed history, clinical assessment, ECG, Chest X-ray & echocardiography evaluation of left ventricular ejection fraction (EF%) & LV diastolic function. Blood samples were collected from all patients & analyzed in standard methods for blood urea, serum creatinine and electrolytes. Serum uric acid level was measured, after overnight fasting by enzymatic methods using chemical analyzer. Hyperuricemia was defined as a serum UA level >7.0 mg/dl. The significant differences between serum uric acid levels in different patients' subgroups were tested by the parametric or non-parametric tests as appropriate. The correlation coefficients between serum UA and different prognostic markers were calculated using Pearson's correlation coefficient. Results were presented as percentage (%), range (median), range (mean \pm 2SD) or correlation coefficient (r). Statistical significance was defined as $P < 0.05$.

Results

The age of patients ranged from 28 to 85 years; median age was 67 years. 54 patients were males. Disease duration ranged from 1 to 13 years. 56% of the patients had diabetes, 64% were hypertensive, 74% had ischemic heart disease, 60% had dyslipidemia, and 9.5% had chronic renal failure. It is noteworthy that 42 patients were in class III New York Heart Association (NYHA) functional calcification whereas 34 patients & 12 patients were in class II & IV respectively. Patients' mean blood pressure (MBP) was 60-123 mmHg (mean = 87.9 ± 14.4), atrial fibrillation (AF) was found in 36 patients (38%). Left ventricular ejection fraction (EF %) range was 13-68% (37.9 ± 20.1). Blood urea range was 13-197mg/dl (64.7 ± 42.6), serum creatinine was 0.4-5.5mg/dl (1.4 ± 0.9), serum sodium was 119-148 (134.2 ± 5.9). Ninety three patients (98%) were on diuretics, 32 patients (34%) on beta-blockers, 87 patients

Table 1. Patients' clinical characteristics, cardiac and general biochemical data, and concomitant medications

| | |
|--|--------------------------------------|
| Age | Range=28-85 years (median= 67years) |
| Males | 54/95 (57%) |
| Disease duration | 1-13 yrs (mean 6±5.5) |
| History of Diabetes | 53/95 (56%) |
| Hypertension | 61/95 (64%) |
| Hyperlipidemia | 56/95 (60%) |
| CRF | 9/95 (9.5%) |
| IHD | 70/95 (74%) |
| QRS prolongation | 47/95 (49.4%) |
| Atrial fibrillation | 36/95 (37.8%) |
| Mean blood pressure (MBP) | Mean=87.9±14.4 |
| Pulse (beat/mint) | Mean= 78.8±12.7 |
| NYHA class I | 8/95 (8.4%) |
| NYHA class II | 34/95 (35.7%) |
| NYHA class III | 41/95 (43.2%) |
| NYHA class IV | 12/95 (12.6%) |
| Left ventricular ejection fraction (%) | Mean=38±20 |
| uric acid >6.5mg/dl | 69/95 (73%) |
| Blood Urea mg/dl | Mean=64.7±42.6 |
| Serum Creatinine mg/dl | Mean= 1.4±0.9 |
| Sodium | Mean=134.2±5.9 |
| Diuretic | 93/95 (80%) |
| ACE | 87/95 (92%) |
| B- Blocker | 32/95 (34%) |
| Aspirin | 79/95 (83%) |

Table 2. Correlation coefficient between serum uric acid and different variables:

| Variable | Correlation coefficient | P value |
|--|-------------------------|---------|
| Age | + 0.37 | 0.037 |
| Mean blood pressure (mmHg) | - 0.42 | 0.019 |
| Mean pulse rate | + 0.12 | 0.295 |
| Left ventricular ejection fraction (%) | - 0.31 | 0.003 |
| Urea | + 0.21 | 0.042 |
| Creatinine | + 0.20 | 0.051 |
| Sodium | + 0.01 | 0.958 |

(92%) on ACE-inhibitors or angiotensin receptor blockers (ARB) and 79 patients (83%) on aspirin (Table 1). Mean uric acid level in the study patients was 8.8 mg/dl. Sixty-nine patients (73%) had hyperuricemia. We demonstrated (Table 2) a significant inverse correlation between serum uric acid level, mean arterial blood pressure ($r = -0.42$, $p=0.019$), and left ventricular ejection fraction ($r = -0.31$, $p=0.003$). We also demonstrated a positive correlation between serum UA and blood urea ($r = +0.21$, $p = .042$), serum Cr ($r = +0.21$, $p = 0.051$) and age ($r = +0.37$, $p = 0.034$). No significant difference was found in serum UA levels in different (NYHA) functional subgroups. We found no significant difference in the levels of uric acid in different CHF sub groups by sex, DM, HTN or AF.

Discussion

In this study of Libyan patients with different functional stages of CHF, we demonstrated that 73% of these patients had elevated serum UA levels. On the other hand, a significant negative correlation between high UA levels to low blood pressure and low left ventricular ejection could indicate that UA levels in patients with CHF is correlated with the severity of the disease. Hence this could be a reliable prognostic marker. Increased UA levels have consistently been reported in patients with CHF, and recent clinical data supports the possibility that UA adds important prognostic information alone and in combination with other measures of cardiac function and patient functional status in this group (4). Numerous studies have reported that hyperuricemia carries an increased relative risk of all-cause mortality in patients with CHF, independent of other risk factors. In a recent meta-analysis of 1456 patients with HF, high UA levels increased all-cause mortality in patients with both acute and chronic HF (11). Our findings are consistent with previous observations which found hyperuricemia was common in patients with HF. Higher uric acid level was independently associated with long-term adverse outcomes in these patients (12).

Several studies have shown an association between increased serum UA levels in CHF and morbidity and mortality (13-15). Data from the Beta-Blocker Evaluation of Survival Trial took a different approach (16) assuming that hyperuricemia without CRF is primarily due to increased production of uric acid from the failing heart. Their conclusion was that hyperuricemia is associated with poor outcome in CHF without CRF. This finding suggests that hyperuricemia in CHF without CRF might be linked to increased XO activity. Although, the role of XO in CHF

is not clearly established, its relation to tissue hypoxia, circulating free radicals, inflammatory mediators, & endothelial & cardiomyocyte dysfunction could all have a negative effect on the cardiovascular system leading to poor outcomes in CHF patients (5). Moreover, it appears that the inhibition of XO activity in patients with hyperuricaemia may have a beneficial effect on endothelial cell function, myocardial function and ejection fraction. Gotsman, et al found in a heart failure register-based study that treatment with allopurinol in CHF was associated with improved survival. (15). Another retrospective study examined the effect of allopurinol on mortality and hospitalization in this patient population (17). Long-term high-dose allopurinol (300 mg/d) was associated with a better all-cause mortality (adjusted relative risk 0.59; 95% confidence interval, 0.37-0.95; $P=0.05$).

In conclusion, hyperuricemia was observed in 73% of our patients with congestive heart failure. The significant correlation between the level of uric acid and low left ventricular ejection fraction in patients with established heart failure may indicated the important role of uric acid level as a prognostic marker. Regardless of whether UA levels are ready for routine clinical use, either as a prognostic factor or novel therapeutic target, further prospective studies are necessary to demonstrate that routine measurement or reduction of UA levels improves outcomes in HF patients.

References

1. American Heart Association. Heart disease and stroke statistics - 2007 update. Dallas, Texas: American Heart Association; 2007.
2. 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;107:1991-7.
3. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from two placebo-controlled studies. *Circulation* 2002;105:2619-24.
4. 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.
5. Leyva F, Anker S, Swan JW, Godsland IF, Wingrove

- CS, Chua TP, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *European Heart Journal* 1997;18(5):858-65.
6. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: Insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation* 2003;107:1951-3.
 7. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med.* 1999;131:7-13.
 8. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. *National Health and Nutrition Examination Survey. JAMA.* 2000;283:2404-10.
 9. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concini H, et al. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. *Int J Cardiol.* 2008;125:232-9.
 10. Meisinger C, Koenig W, Baumert J, Doring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population. The MONICA/KORA Cohort Study. *Arterioscler Thromb Vasc Biol.* 2008;28(6):1186-92.
 11. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J. et al. UA as a predictor of all cause mortality in HF: a meta-analysis. *Congest Heart Fail.* 2011;17:25-30.
 12. Niizeki T, Takeishi Y, Arimoto T, Okuyama H, Nozaki N, Hirono O, et al . Hyperuricemia associated with high cardiac event rates in the elderly with chronic heart failure. *J Cardiol.* 2006;47(5):219-28.
 13. Tamariz L, Verma S: Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. *Congest Heart Fail.* 2011;17(1):25-30.
 14. Hamaguchi S, Furumoto T, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, et al, for the JCARE-CARD Investigators: Hyperuricemia predicts adverse outcome in patients with heart failure. *Internat J Cardiol* 2011;151(2):143-7.
 15. Gotsman I, Kern A, Lotan C, Zwas DR: Changes in uric acid levels and allopurinol use in chronic heart failure: association with improved survival. *J Cardiac Failure* 2012;18(9):694-701.
 16. Filippatos GS, Ahmed MI, Gladden JD, Aban IB, Love TE, Sanders PW, et al. Hyperuricemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. *Eur Hear J.* 2011;32(6):712-20.
 17. Erdogan D, Tayyar S, Uysal BA, Icli A, Karabacak M, Ozaydin M, et al. Effects of allopurinol on coronary microvascular and left ventricular function in patients with idiopathic dilated cardiomyopathy. *Can J Cardiol.* 2012;28(6):721-7.