Serum uric acid as a metabolic regulator of endothelial reparative processes in heart failure patients

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Serum uric acid (SUA) is considered a marker and possible factor of nature progression of chronic heart failure (CHF) mediated cardiovascular remodelling. Recent investigations have shown that SUA is independent and strong predictor of outcome in the general population as well as in patients with cardiovascular and non-cardiovascular diseases, such as myocardial infarction, acute coronary syndrome, acute and chronic cardiac failure, type 2 diabetes mellitus, atherosclerosis, the metabolic syndrome, chronic kidney disease, and obstructive sleep apnea syndrome. It has suggested that SUA may contribute in controversial mechanisms that relate with prooxidative and antioxidative state. Because uric acid is able to activate intracellular signaling system affected Akt / STAT / MAP-kinase mechanisms, there is predisposition that SUA may mediate with mobbing and differentiation of mononuclear progenitor cells (MPCs). The review is addressed to discussion of one of possible mechanism of effect realizing of SUA in heart failure affected endogenous reparation via endothelial proangiogenic MPCs.

Keywords: Serum uric acid; heart failure; circulating mononuclear progenitor cells; cardiovascular remodelling; tissue repair

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Introduction

Chronic heart failure (CHF) is considered a global medical problem that strongly associate with cardiovascular morbidity and mortality worldwide [1]. Although pathogenesis of cardiac failure appears to be in-depth sophisticated and not completely understood, contemporary strategy of the prevention and treatment of CHF is able to improve clinical outcomes, quality of life and well being of the patients [2]. Nevertheless, there are some expectations that risk stratification of the patients at early stage of CHF development and exact determination of drug giving response within CHF evolution might contribute in choosing optimal approaches of the treatment [3]. In this context a continued discover of specific diagnostic and predictive biomarkers reflected different faces of cardiac failure development is being remained very attractive and probably may improve clinical outcomes [4, 5]. Moreover, serial measurements of circulating biomarkers are considered a pivotal definition of biomarker-guided therapy of CHF as strategy alternated to clinical-based approach [6, 7]. Importantly that ideal biomarker should relate with some requirements, such as low cost, high specificity and sensitivity, low biological variability, low frequency of analytical errors, high reproducibility in follow up etc. [8, 9].

Serum uric acid (SUA) is simple well known routine measured biomarker that is frequently elevated in CHF patients [10]. Recent investigations have shown that SUA is independent and strong predictor of outcome in the general population as well as in patients with cardiovascular and non-cardiovascular diseases, such as myocardial infarction,
acute coronary syndrome, acute and chronic cardiac failure, type 2 diabetes mellitus, atherosclerosis, the metabolic syndrome, chronic kidney disease, and obstructive sleep apnea syndrome \[11-15\]. However, the innate molecular mechanisms regarding effect of SUA on cardiovascular remodeling and as result in CHF development are still not clear and current clinical evidences on SUA in nature progression of cardiac failure are controversial. The review is addressed to discussion of one of possible mechanism of effect realizing of SUA in heart failure affected endogenous reparation through mobbing and differentiation of endothelial proangiogenic MPCs.

Hyperuricemia in CHF

Hyperuricemia defined as elevation of SUA upper reference limit that is referred 360 \(\mu\text{mol/L} (6 \text{ mg/dL})\) and 400 \(\mu\text{mol/L} (6.8 \text{ mg/dL})\) for women and men respectively. Currently hyperuricemia is common for majority patients admitted in the hospital due to acute and acutely decompensated heart failure \[16\]. In is well known that increased production of uric acid is result from activity of xanthine oxidase (XO), which is up-regulated by inflammation, oxidative stress and neurohormonal activation that are suitable for heart failure \[17\]. Therefore, SUA is attributing of decreased excretion due to renal failure, which can be a consequence of cardio-renal syndrome, renal congestion, or comorbidities \[18\].

After adjustment of renal function, age, and drug given among CHF patients even mild isolated increased SUA is considered a marker of vascular calcification, altered oxidative metabolism, elevated production of cytokines and free radicals, which associates with insulin resistance, tissue damage due to hypoxia, vascular integrity disorders, endothelial dysfunction, and declined endogenous repair capacity \[19, 20\]. Although exiting hyperuricemia is able to effect negatively on cardiovascular system and prognosis in CHF patients \[21\], SUA is discussed one of the major circulating scavenger of free radicals with high antioxidant capacity \[22\]. Moreover, SUA-induced oxidative stress seems to be paradoxical and data regarding the clinical implication of hyperuricemia are confused \[22\]. Meta-analysis provided by Huang H et al \[23\] showed that hyperuricaemia was associated with an increased risk of suffering from CHF (hazard ration [HR] 1.65, 95% confidence interval [CI] 1.41–1.94) and that for every 1 mg/dL increase in SUA, the odds of development of CHF increased by 19% (HR 1.19, 95% CI 1.17–1.21). Tamariz L et al \[24\] reported that SUA predicts all-cause mortality in CHF. There are evidences regarding beneficial effect of xanthine oxidase inhibitor for the vascular inflammation in animal models \[25\]. Therefore, recent clinical trials have been shown that allopurinol is able to effect positively on heart failure outcomes \[26\]. Surprisingly, elevated SUA was independently associated with mortality in CHF patients, even when accounting for allopurinol use \[27\]. Taken together data among causality value of SUA in CHF patients reflect that SUA is not only a “phenotypic” marker of metabolic disorders and a tenderness of reparative processes affected vascular wall and contributed endothelial function, but SUA might be prognostic factor or even novel therapeutic target in CHF patients \[28\]. Less is known about the association between SUA level and circulating mononuclear progenitor cells (MPCs), which have an effect on angiogenesis and tissue reparation \[29\].

Circulating mononuclear progenitor cells in heart failure

Currently it is well established that MPCs might be recruited resulting in exaggerated production of proinflammatory cytokines that are suitable for CHF \[30, 31\]. Recent studies have demonstrated that circulating MPCs are declined progressively depending severity of CHF \[32-34\]. However, it has been postulated that depletion of MPC numerous in circulation may link SUA with inflammatory response and outcomes in CHF \[35\]. Although CD34+ MPC populations are not associated with cardiac and vasculature remodelling or prognosis in CHF patients \[36\], recent evidence suggests levels of circulating proangiogenic MPCs labelled CD14+CD309+ and CD14+CD309+Tie2+ cells were decreased in stable CHF patients \[37\]. In fact, a sufficient negative association of proangiogenic MPC level with SUA in CHF patients was found \[38\]. Arguing against a pure protective role of SUA in cardiovascular disease \[39\], it was found the levels of SUA remained independently associated with lowered proangiogenic MPCs after adjusting for parameters with known impact on concentrations of MPCs. Moreover, even tendency to increase of SUA in CHF patient population associated with progressively declining proangiogenic MPCs, which have a tremendous tissue repair capacity. Probably, these findings might be taken into consideration to be explaining controversial role of SUA in CHF evolution and outcomes. Overall, the exact underlying mechanism that leads to decline circulating level of proangiogenic MPCs contributed in vascular repair and modulating of endothelial function is still not clear. It has suggested that tissue ischemia determines an increase in XO, which leads to an increase in SUA levels, and mediates suppression of recruitment, mobbing, differentiation and functional status of MPCs through STAT and Akt / MAP-kinase mechanisms, that is reflection of chronic inflammatory, oxidative stress and, probably, catabolic state suitable for CHF. It is well known that STAT (signal transducer and activator of transcription) especially STAT-3 is an acute-phase response factor, which is activated by various cytokines and growth factors including interleukin
(IL)-5, IL6, and interferon γ. Through expression of a variety of genes in response to cell stimuli, MPCs may differentiate into mature endothelial cells and thereby contribute in cellular processes such as endothelial cell growth, apoptosis, angiogenesis, and vasculature reparation \[39\]. In fact, number and migratory activity of MPCs obtained from CHF patients demonstrated low capacity to differentiation after stimulation of potent pro-angiogenic factors, such as fibroblast growth factor-4 and vascular endothelial growth factor, and as well as decreased resistance to hypoxic stress conditions \[40\]. Probably uric acid limits proangiogenic capacity of MPCs, especially in subjects with exiting comorbidities, such as insulin resistance, metabolic syndrome \[32, 41\]. However, the exact mechanism of escape phenomenon of MPCs under control of physiological stimuli is unclear and uric acid might be the real candidate for explanation of this phenomenon. Finally, significant confounder impacting SUA levels on population of proangiogenic MPCs with involving several pathogenetic mechanisms are predisposed.

Thus, on the one hand, SUA may be considered a directly inductor of tissue damage that realizes through oxidative and probably catabolic state. On the other hand, uric acid may suppress a tissue repair through involvement of proangiogenic MPCs via activation of intracellular signalling systems.

Conclusions

In conclusion, exaggerated SUA is probably not only marker of CHF development and it is a factor contributed lowering of endogenous repair mechanism affected mobility and differentiation of MPCs. Therefore, uric acid is able to induce tissue damage through oxidative mechanism. The interrelationship between elevated SUA and declined MPCs allows explaining the causality role of uric acid in CHF advance. Speculations around antioxidative capacity of uric acid in heart failure and it clinical significance is remained beyond recently obtained evidences and require more investigations. However, measurement of SUA is very simple analytical method that may help to stratify the patients with CHF at high risk of unfavorable clinical outcomes.

References


