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Uric Acid in Heart Failure: Controversy Factor in The Multiple Pathogenesis of The Disease

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Abstract

The majority of individuals with traditional cardiovascular risk factors contributing in heart failure (HF) risk exhibited increased serum levels of uric acid. The role of SUA in HF manifestation appears to be controversial. First controversy affects the fact that SUA plays an important role in inducing oxidative stress, inflammation, neuro humoral activation, and endothelial dysfunction. Being natural antioxidant uric acid contributes in prevention of cell damage and thereby may restore vascular function leading to reversion of endothelial dysfunction. Interestingly, there is a large body of evidence regarding that uric acid is able to regulate an activity of endogenous repair system through epigenetic mechanisms and activation of intracellular signaling, such as STAT3 and Akt. Indeed, uric acid mediates a survival of endothelial precursors, mediate their mobbing and differentiation, as well as coordinate a turn-over effect of metabolic memory phenomenon into repair capability of cell precursors. Probably, these controversies could have taken into consideration when clinical results of several studies are discussed. Although elevated SUA levels were found a strong predictor of adverse clinical outcomes in HF patients, there is assumption that final result of elevated uric acid may depend on cooperation between metabolic and epigenetic factors contributing in HF evolution. The short communication is depicted the importance of new clinical data to confirm the emerging reparative ability of SUA in HF and its role as promising target for treatment in cardiac failure.

Keywords: Serum Uric Acid, Heart Failure, Endothelial Dysfunction, Biomarker

Introduction

There is a large body of evidence regarding the role of serum uric acid (SUA) in pathogenesis of cardiovascular diseases (CVD) including heart failure (HF). Recent clinical studies and some meta-analysis have shown that elevated SUA was associated with an increased risk of incident HF, observed in majority of patients with established chronic HF and relate to adverse clinical outcomes in HF [1-4]. However, the impact of SUA on all-cause mortality and HF-related death was insured by co-existing disease predominantly hypertension, abdominal obesity, pred iabetes / diabetes mellitus, kidney disease as well as female sex [2,5-7]. Whether SUA could be an independent predictor of HF development is not fully clear. Moreover, there are data clarifying that even asymptomatic hyperuricemia associated strongly with long-term survival of CVD patients and individuals with chronic kidney disease throughout pre-dialysis period and whose who undergoing hemodialysis procedures. In the Rotterdam Study high quartiles of normal rages of SUA and mild increased SUA level were more closely related to early-phase mechanisms of insulin resistance and diabetes mellitus rather than CV complications due to target organ damage progression [5]. Thus, predictive value of SUA in different patients at risk of HF is controversial and requires to be elucidated.

The potential molecular mechanisms that explain the role of SUA in development and advance of HF are traditionally structured in follow schematic consequences that are appeared to be counter directed. On the one hand, the hyperuricemia causes inflammation due to direct vascular injury and a production of various inflammatory cytokines and monocyte chemo attractant protein-1, inducing oxidative stress and activation of the local rennin-angiotensin system [8,9]. Additionally, all these factors lead to endothelial dysfunction by a reduction in endothelial levels of vasodilator substances such as nitric oxide, inducing cellular proliferation, accelerating atherosclerosis, activating insulin resistance and microvascular inflammation [10]. On the other hand, urates are physiological substrate for myeloperoxidase acting as regulator of oxidative stress, but molecule of uric acid may act as intracellular scavenger of free radicals diminishing pro-

inflammatory effect and increasing cell survival [11]. Thus, SUA links in vascular damage, endothelial dysfunction and oxidative stress that play important role across all stages of HF development and contributes in an impact of co-morbidities on risk of HF onset and advance.

Another way that could probably explain the role of uric acid in pathogenesis of HF relates to an ability of uric acid to epigenetically regulate survival of endothelial precursors, mediate their mobbing and differentiation, as well as coordinate a turn-over effect of metabolic memory into repair capability of cell precursors [12,13]. Indeed, SUA independently and inversely associated with number of circulating endothelial progenitor cells in HF individuals [14]. Moreover, SUA contributed in shaping of altered ability of endothelial precursors to activate by several stimuli, release secretom, regulate endothelial reparation and turn into mature endothelial cells [15,16]. Consequently, SUA may consider as an endogenous regulator of vascular repair system that undoubtedly opens new sign on the role of uric acid metabolism as integrative asset explaining an impact of various comorbidities on a risk of HF manifestation. As an evidence of the opinion it has been allowed presenting data, which confirm higher predictive value of elevated SUA in HF patients beyond etiology of disease, cardiac pump function, traditional risk factors and estimated glomerular filtration rate [17-19]. Interestingly, large numbers of clinical and observational studies have shown that elevated SUA levels are associated with reduced survival in in-patients and out-patients with several phenotypes of chronic HF, as well as in acute / actually decompensated HF [20-22]. In contrast, in recent meta-analysis lowering SUA levels under treatment (allopurinol, oxypurinol, febuxostat) did not predict improved surrogate clinical outcomes in HF [23]. Moreover, there was not convincing evidence regarding associations of SUA levels with increased risk of HF and other disease at higher risk of HF (hypertension, impaired fasting glucose or diabetes mellitus, chronic kidney disease, coronary heart disease) and HF mortality [24].

All these facts clarify that SUA is multiple player with controversial activities that concurrently contribute in HF pathogenesis [25]. SUA modalities cannot be discussed as unconditionally harmful effects supporting inflammation and cell death, but they may produce a favorable result on reparative activity of endothelium and restoring endothelium function and vascular integrity [26]. Whether SUA is a therapeutic target to reduce HF risk in vulnerable population is not fully clear and requires to be explained in the large clinical trials. In conclusion, there is no an available evidence regarding only harmful effect of SUA in vulnerable population patients at higher risk of HF as well as in individuals with established HF irrespective left ventricular ejection fraction or isolating diastolic abnormality. The importance of new clinical data to confirm the emerging reparative ability of SUA and its antioxidant activities across HF development require to be cleared in large investigations. The results of these trials would be intriguing and could open new perspective to use xanthine oxidase inhibitors as adjuvant care in HF management.

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