Editorial

Hyperuricemia in US Population with Heart Failure: Causal or Incidental Bystander?

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Increased level of uric acid (UA) has been associated with a higher prevalence of cardiovascular diseases (CVD), and European Society of Cardiology (ESC) guidelines highlight UA measurement as an additional marker to stratify cardiovascular risk [1]. Increased UA levels have been observed in 5–20% of the general population, and this rate increases up to 25% in hospitalized patients. In patients affected by heart failure (HF), both in acute and chronic settings, the prevalence of hyperuricaemia ranges from 30 to 60% [2, 3]. This analysis of the National Health and Nutrition Examination Survey (NHANES) confirmed that the prevalence of hyperuricaemia (defined as UA levels >7.0 mg/dL for men and >5.7 mg/dL for women) is around 50% in HF patients [4]. Although current findings confirm previous analyses, further elements should be taken into account/further observations should be made. Firstly, HF diagnosis was not performed by physicians but only through patient interviews. This did not permit to distinguish HF aetiology (such as coronary artery disease, valvular heart diseases, idiopathic cardiomyopathy, etc.) and HF subtype (HF with reduced [HFrEF] or preserved [HFpEF] ejection fraction) which usually reflects different pathogenesis and cardiovascular risk burden. Indeed, a high prevalence of increased UA levels has been found in both HFrEF and HFpEF, although prognostic power has been found only in HFpEF patients [5]. Secondly, the current study did not evaluate the potential role of UA in HF development and progression. Hyperuricaemia and HF are strictly related, but whether it is the cause or the effect of metabolism alteration or increased systemic endothelial dysfunction and increased vascular stress is far from being established. Current and other studies demonstrated that almost 50% of HF patients experienced increased UA serum levels; this association is due to both oxidant stress and pro-inflammatory overdrive in HF, which could worsen clinical status symptoms by

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anaerobic threshold decrease. Systemic organ hypoperfusion, reduced energetic substrate by ATP depletion in the sarcoplasmic reticulum, and mitochondrial dysfunction due to decreased GMPc and nitroxide availability are all potential features of impaired outcomes [6]. Moreover, a significant percentage of HF patients with hyperuricemia have some degree of renal dysfunction. Accordingly, *in patients affected by HF, may hyperuricaemia be the result of an increased production of UA, altered excretion, or the combination of both mechanisms?* Perhaps the picture could change in relation to HF typology, metabolic substrate, and associated comorbidities. Currently, the combination of both mechanisms may be hypothesized. The increase of xanthine oxidase (XO) action could be assumed as the trigger that leads to increased cytokine levels, endothelial dysfunction, apoptosis, and energetic alterations in myocardial cells. Contemporarily, the worsening renal function and the diuretic up-titration linked to HF severity could be related to the reduced UA excretion. By similar mechanisms, hyperuricaemia enhances cardiovascular risk burden and has a different role (or different roles) in hypertension and diabetes progression. Increased UA levels in hypertension trigger oxidative stress, endothelial dysfunction, and renin-angiotensin-aldosterone system activity. The consequent vasoconstriction leads to hypertension development, left ventricular hypertrophy, and systemic arterial stiffening. Accordingly, hyperuricaemia should precede insulin resistance in diabetic subjects; insulin reduces renal UA excretion by direct effects on distal tubular reuptake and by reducing UA substrate utilization. The current alteration came from both vasoconstriction and the related reduction of glucose uptake from peripheral tissue and skeletal muscle; the UA affects adipocytes in which pro-thrombotic and pro-inflammatory factors are overexpressed, and negatively modulates the expression of PPAR- γ receptors. Thus, the physiologic activity of PPAR receptors regarding the reuptake of polyunsaturated acid from circulation to adipocytes is modulated by insulin sensitivity [6, 7]. Although the association of UA with cardiovascular risk factors and HF was well demonstrated, contradictory data exist about the relation between hyperuricaemia and cardiovascular events. Whereas the MRFIT and Rotterdam studies showed that hyperuricaemic patients had an increased risk of developing coronary artery disease, other studies, such as Framingham and ARIC, did not confirm this relation [2, 7–9]. Current discrepancies may be related to gender and race or clinical characteristics in a different sample size of patients. Women are much more prone to develop hyperuricaemia than men. Moreover, hyperuricaemia in post-menopausal women seems to be strongly related to cardiovascular events. This relation could be explained by the reduction of oestrogens and the consequent reduction in renal tubular UA excretion. Conversely, the increased prognostic power of UA in the Asiatic and Afro-American population could be related to dietary and genetic factors causing some enzymatic dysfunction in the XO cascade [6]. Another question that needs to be elucidated is the relation occurring between renal and increased UA serum levels. Indeed, renal dysfunction is more frequent in HF and this condition could contribute to the development of hyperuricaemia. However, different mechanisms may be involved. Firstly, UA increase through endothelial dysfunction and hypertension and diabetes progression could cause glomerular dysfunction, which could be responsible for poor UA filtration and then hyperuricaemia. Secondly, the systemic venous congestion and subsequent diuretic up-titration could cause a reduced excretion of UA, which in turns is related to hyperuricaemia development and worsening renal function. Thirdly, the UA concentration in the distal tubule could be related (or is related) to the decrease of Na and water resorption. Lastly, elevated UA level could mirror an increased protein catabolism and simply reflects the pre-cachectic status in the more advanced HF stages. For these reasons, UA should be considered both the bystander and the actor of decline in renal function in HF patients [10]. Because of the strict liaison between CVD and UA, many trials involving lowering UA drugs used cardiovascular endpoints to test the potential efficacy of this treatment with contrasting results. Although several studies with UA-lowering drugs did not report cardio-

vascular side effects, these drugs did not improve clinical symptoms, the 6-min walking test, left ventricular ejection fraction, and cardiovascular mortality [3]. More recently, a post hoc analysis emphasized the potential deleterious effects of drugs acting on the XO view showing a significant increase of cardiovascular events in active arms [11]. Current findings are likely to be related to the different pathophysiological pathways of UA increase in CVD. Ongoing trials with UA-lowering drugs will test the association between UA reduction and clinical benefit in HF patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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