Invited commentary

Uric acid in chronic heart failure: marker or therapeutic target?

Commentary on

Uric acid and xanthine oxidase: perspectives in chronic heart failure

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Heart failure is one of the leading medical problems in modern medicine regardless of whether we view it from the clinical, prognostic, epidemiological or socio-economic perspective. While current treatment strategies are targeting exclusively the neurohormonal activation, our pathophysiologic understanding has advanced significantly towards an increasingly complex picture including metabolic, inflammatory, and hormonal pathways.

Recently, an increasing interest in uric acid (UA) has emerged, as a number of studies have shown that hyperuricaemia is a constant feature of metabolic imbalance within heart failure pathophysiology. In contrast to many other novel biomarkers, UA is an easily measured parameter with wide availability at low costs. The former perception of UA as the inert end product of the purin degradation has changed as recent evidence suggests a significant role of the purine degradation pathway within metabolic and immunologic regulation. In this issue, Patel and Arora provide a broad overview of current knowledge on UA and the xanthine oxidase metabolic pathway [1]. In combining the findings from pre-clinical and clinical studies the authors present a comprehensive picture of the diagnostic and therapeutic implications regarding UA metabolism in the context of CHF.

In the ongoing discussion on hyperuricaemia in CHF several questions remain controversial. Fundamentally, the nature of UA as a good or bad guy in the field is still on debate. On one side, the enzyme xanthine oxidase (XO) has been established as a major source of oxygen radical accumulation and hence originator of a wealth of detrimental effect in acute and chronic disease conditions. In fact, XO was first documented biological generator of reactive oxygen species (ROS) [2]. On the other hand, UA accounts for much of the protective antioxidant capacity in plasma [3]. So a chicken and egg conundrum emerges if one looks at these two factors (i.e. XO and UA) separately.

While several studies observed that exogenous administration of UA exerts protective effects against oxidative damage and endothelial dysfunction, it should be noted that in CHF hyperuricemia results mainly from up regulated XO activity [4] with the inevitable effect of increased ROS generation. Accordingly, inhibition of XO and hence preventing ROS accumulation yielded multiple protective effects on functional and metabolic capacity in CHF [5]. The specific organ distribution of XO with the highest activity (apart from the lactating mammary glands) in the capillary endothelial cells [6] of intestine and the liver [7] suggests a specific function in the vascular system. Given the toxic effect of ROS, a role as defence mechanism seems plausible such as to protect the inner surface (i.e. the barrier between intestinal lumen and the body tissues) from bacterial intrusion [8]. The protective antioxidant capacity of UA may then act as a negative feedback principle to the ROS accumulation by XO. As seen in other physiologic response mechanisms, the well-tuned short-term adaptive response may fail in long-term activation such as in chronic disease leading to maladaptive processes and eventually harmful effects.

A second currently unresolved question addresses the role of UA itself as an active player or a mere marker of XO activity. The demonstrated quality of hyperuricaemia as a strong and independent predictor of symptomatic status and prognosis in CHF [9] ensures the characteristic of UA as disease *marker*. This does, however, not presume a causal contribution of UA. Data on the *causal* involvement of UA to CHF pathophysiology are inconclusive: UA has recently been observed as an endogenous danger signal that mediates immune response following cell injury [10]. The immune activation capacity of UA is supported by the finding of increased production of tumour necrosis factor-a upon endotoxin challenge, after infusion of UA, in mice [11]. On the other hand, recent studies in humans have shown that lowering UA without blocking XO activity (i.e. by stimulated increased UA excretion or further degradation) did not result in the beneficial effect seen with direct XO inhibition [12]. Further studies are required to fully uncover the role of UA in this context.

A third aspect and probably most interesting is the question as to the role of UA as potential novel target for therapy. A substantial body of evidence has been accumulated to support this intriguing therapeutic concept. A range of surrogate markers of myocardial and peripheral functional and metabolic capacity has shown to improve after XO inhibition in both animal models and patients [5]. In contrast, however, in a recent randomized controlled trial using oxypurinol for XO inhibition in CHF (OPT-CHF) no beneficial effect on CHF disease severity or survival could be observed [13]. While this disappointing result puts the overall therapeutic concept into question, some aspects should be discussed. In the OPT-CHF study, UA was not part of the inclusion criteria, which may contribute to the lack of effect. Notably, pilot studies on XO inhibition repeatedly failed in those patients with normal UA levels and it has been suggested that only patients with high UA levels – demonstrating up-regulated XO activity – may be suitable for this therapy [14]. Interestingly, in the subgroup with elevated UA levels, the OPT-CHF study showed the anticipated results, however, lacking the power and prospective character of the overall study analysis.

The work by Patel and Arora provides a detailed overview of the currently available data and conceptual understanding. Several questions are, however, still under discussion and further studies should be encouraged to advance our understanding of the XO metabolic pathway.

The metabolic facet within CHF pathophysiology is increasingly appreciated and the XO inhibition as novel metabolic approach in CHF therapy is still a promising target.

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