Uric acid in chronic heart failure - current pathophysiological concepts

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Letter Title: Uric acid in chronic heart failure: looking at the elephants tails.

Re Article: Serum uric acid correlates with extracellular superoxide dismutase activity in patients with chronic heart failure
By Alcaino et al Eur J Heart Failure 10; 2008: 646-651

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To the Editor

In their recent article Alcaino et colleagues report a beneficial effect of hyperuricaemia in patients with chronic heart failure towards prevention of oxidative stress and improved endothelium function. The conclusions from this observational study in 38 patients with CHF are opposite to a substantial body of evidence. Therefore, we would like to make up for the authors' shortfall to discuss these discrepancies and put the findings in perspective to current data.

Most importantly, based on the presented background the hypothesis of the study reveals a serious misconception of the character of hyperuricaemia in CHF pathophysiology. Several studies are cited to support the role of UA as antioxidant to prevent oxidative damage including endothelium dysfunction. All these studies, however, tested the impact of administration of exogenous uric acid not the impact of endogenous physiologically derived uric acid. While exogenous uric acid may indeed function to scavenge free oxygen radicals, it is of utmost importance to appreciate the origin of elevated UA levels in CHF. It has sufficiently been shown by direct assessment of xanthine oxidase XO [i] as well as indirectly from allopurinol therapy studies [ii] that elevated XO activity the predominant cause of hyperuricaemia in CHF. Importantly, the uric acid generating enzyme XO is one of the major sources of oxygen free radicals in human physiology. In fact, as early as 1968 the cytosolic XO was the first documented biological generator of oxygen derived free radicals [iii]. It seems an indefensible hypothesis to suggest hyperuricaemia as an adaptive process in response to the increased ROS accumulation if the UA and ROS are generated in parallel by up-regulated XO. Moreover, the suggestion that this process in CHF “is leading to a raise in ecSOD activity and thus preserving endothelial function” has clearly been disproved as SOD and endothelium dysfunction are decreased in CHF well in parallel to disease severity.

The idea that elevated (endogenous) UA levels may exert a beneficial effect on endothelium function and prognosis as discussed by the authors is in contrast to a large number of studies on vascular function [i, ii, iv, v] and mortality [vi, vii, viii] in heart failure patients and several
other cardiovascular diseases including stroke [ix], cardiovascular risk [x], hypertension and renal disease [xi] as well as in normal populations [xii, xiii, xiv, xv]. Any attempt to include a representative number of all papers that provide data and conclusions that are opposite to the paper by Alcaino et al. would be stopped short due to limitation of space.

Similarly the interpretation of UA as a risk marker at early CHF but as beneficial factor at advanced stages does not withstand reality as studies show linear associations of UA with disease severity [iv, xvi, xvii], mortality and impaired vascular function [v].

While the ongoing scientific discussion regarding the role of uric acid as active contributor vs passive marker is indeed ongoing, Alcaino et al slipped in the misinterpretation of the absence of evidence as evidence of absence: If previous studies using allopurinol treatment could not prove a detrimental effect of UA itself this may by no means allow to conclude for a compensatory (i.e. beneficial) role of uric acid. The references quoted by Alcaino et al in support of their view are at least in part [xviii, xix] neither stating nor intending this message. In fact, a recent study to test the effect of UA lowering without XO inhibition using uricase has shown no effect on endothelial function [xx].

Alcaino et al seemingly base their study on the theory by Reyes that diuretic dependent increase in UA conveys improved prognosis in cardiovascular patients [xxi]. Whether the rise of uric acid caused by diuretic treatment may exert beneficial effect on antioxidant capacity is, however, the wrong question to ask and resembles the attempt to describe an elephant from looking at its tail. The potential contribution of this particular cause to elevated UA cannot be looked at separately from other mechanisms to increase UA in CHF. Elevated UA levels in CHF result likely from a combination of increased XO activity (i.e. overproduction, see above) and to some degree impaired excretion following impaired renal function and diuretic use. The isolated effect of the diuretic dependent UA increase in this context is, however, negligible as only the effect of total UA elevation may - or may not – be clinically relevant. The theory by Reyes that diuretic dependent increase in UA conveys improved prognosis in cardiovascular patients has previously been challenged [xxii] an is convincingly refuted by a multitude of studies that show
that (global) hyperuricaemia is a strong marker of disease severity and impaired prognosis (see above).

Further, the assertion of the authors to address a previously not investigated association between UA, SOD activity and endothelium function is in negation of several papers that particularly evaluated these interactions [i, ii, v]. Notably, the findings on the impact of UA in CHF in these previous studies were opposite to the results by Alcaino. Unfortunately, these discrepancies were not discussed. The authors comment that UA levels in their study were within normal limits in the majority of patients, however, not such data is presented. In the studied CHF patient group UA levels were abnormally elevated (7.3±2.3 mg/dl) and the comparison with the control subjects revealed significantly elevated UA levels in CHF patients (p<0.04). Moreover, the references to underscore conformity with the other CHF populations are not applicable in this context [xxiii, xxiv]. Notable, elevated uric acid levels are a common finding in CHF with increasing UA in parallel to CHF severity [iv, xvi, xvii].

Despite the overwhelming evidence from previous studies against the conclusion by Alcaino et al, the current data need to be explained. On factor may rest with the small size of the study population and the statistical possibility of 5% to observe random associations. More importantly, the pre-specified selection of patients with significantly reduced endothelium function prevents a realistic reflection of the association over the normal pathophysiological range of patient. Looking at the limited part of the spectrum may results in a distorted association.

It can be concluded that the findings and interpretation of the data by Alcaino are diametrically opposed to the current pathophysiological concepts. The lack of discussing the discrepancy with the vast body of evidence against these data is dissatisfactory particularly given the nature of this study as a small observational study showing mere correlations that do not allow for causal interpretations. The lack of relating the hypothesis and findings of the study to recent literature together with insufficient and in part incorrect referencing with previous studies
highlight of course the responsibility of the Journal to ensure a thorough and high quality peer reviewing process.

A rope is a rope is a rope. To recognise the shape and nature of the elephant might not be possible from the isolated gaze at its tail but requires an integrative inter-coordinated and repeatedly verified approach.

REFERENCES


Reyes AJ. The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. Eur J Heart Fail. 2005;7:461-7.

