Uric Acid Predicts Clinical Outcomes in Heart Failure
Insights Regarding the Role of Xanthine Oxidase and Uric Acid in Disease Pathophysiology
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In the current issue of Circulation, Anker and colleagues\(^1\) report that elevated levels of uric acid (UA) predict mortality and the need for heart transplantation in patients with congestive heart failure (HF). Serum concentrations of UA added important prognostic information alone and when combined with measures of cardiac function (ejection fraction) and patient functional status (maximal oxygen consumption with exercise) and were independent of renal function, serum sodium, serum urea, diuretic usage, and patient age. Receiver operating curve analysis identified a cutoff of 585 \(\mu\)mol/L (9.8 mg/dL) as the best mortality predictor. This finding is not only potentially of value in patient management but also raises extremely interesting questions regarding the pathophysiological underpinnings of this finding.

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A consideration of the mechanism of UA production and metabolism offers insight into the relationship between UA levels and HF outcomes. Indeed, accumulating data support the idea that UA, in addition to being a potentially valuable prognostic marker, possesses specific toxic or other properties that could contribute to HF pathophysiology. Moreover, UA levels may reflect xanthine oxidase (XO) pathway activity, which has the potential to contribute to the progression of left ventricular dysfunction by interfering with myocardial energetics\(^2\) and myofilament calcium sensitivity.\(^3\)

Potential Mechanisms for Increased Uric Acid in Heart Failure

UA is a metabolic byproduct of purine metabolism (Figure). Serum UA may increase in the failing circulation because of increased generation, decreased excretion, or a combination of the 2 factors. There are several possible contributors to increased UA production in HF, including increased abundance and activity of XO,\(^4\) increased conversion of xanthine dehydrogenase (XDH) to XO,\(^5\) or increased XO substrate resulting from enhanced ATP breakdown to adenosine and hypoxanthine. As UA is excreted primarily by the kidney, decreased renal perfusion could lead to increased UA levels. To the extent that HF leads to tissue ischemia (in advanced HF) and a rise in serum lactate, renal UA excretion can be further impaired as lactate competes with urate via an organic anion exchanger in the proximal tubule.\(^6\)

Pathophysiological Role of the Xanthine Oxidase Pathway in Heart Failure

There is increasing evidence that strongly supports a direct pathophysiological role for the metabolic pathway leading to UA production in the failing circulation.\(^2,7\) In regard, the 2 terminal steps in urate production are catalyzed by XO, which also produces a molecule of superoxide for each reaction\(^5\) (Figure). XO is the product of the xanthine oxidoreductase gene that encodes XDH, an 150 Kda protein, which functions as a homodimer. XDH is converted to XO by proteolytic cleavage or sulfhydryl modification.\(^5\)

The elevation in serum UA may reflect increased XO pathway activity and in turn the generation of superoxide and...
resultant oxidative stress via the XO system.\(^9\) XO is upregulated within the heart in both experimental\(^4,9\) and human\(^2\) heart failure. Much had previously been made of the difficulty in identifying XO within the hearts of certain mammalian species, including humans;\(^10\) nevertheless, it is clear that XO, which is produced in highest abundance in the liver and gut, may circulate in the blood and adhere to endothelium in distant sites.\(^11\) Moreover, XO is expressed in cardiac myocytes, as shown by immunohistochemistry and may participate in intracellular signaling.\(^12\)

From a functional standpoint, XO activity participates in both mechanoenergetic uncoupling and vascular dysfunction in the failing circulation. Mechanoenergetic uncoupling is the process whereby cardiac energy consumption remains the same or increases while cardiac work falls dramatically, and is increasingly being perceived as a potential key lesion in the failing heart. Inhibition of XO with allopurinol restores depressed myocardial energetics toward normal, and this effect can be mimicked by the antioxidant ascorbate.\(^12\) Furthermore, several recent studies have demonstrated that XO inhibition improves endothelial dysfunction in patients with congestive heart failure in association with reduction in circulating markers of oxidative stress,\(^13,14\) thereby providing evidence that XO inhibition reduces oxidant generation.

Pathophysiological Role of Uric Acid in Heart Failure

Beyond XO activity, recent experimental studies suggest that UA itself may have a role in cardiovascular and renal pathophysiology. This might seem surprising, as UA can function as an antioxidant, both by itself and by promoting superoxide dismutase activity,\(^15,16\) and might therefore be considered potentially protective. However, UA potently stimulates vascular smooth muscle cell proliferation in vitro, an effect mediated by stimulation of mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor.\(^7,17,18\) Furthermore, rats with mild experimentally-induced hyperuricemia develop intrarenal vascular disease with increased renin expression, systemic and glomerular hypertension, and renal injury in the absence of intrarenal crystal deposition.\(^19,20\) These hemodynamic and structural changes can be prevented if UA elevation is prevented by allopurinol.\(^19,20\)

Interaction of Xanthine Oxidase and Uric Acid With Nitric Oxide Pathways

Both XO activity and UA may also affect cardiac and renal nitric oxide signaling,\(^12,19\) which exerts key cardiac and vascular effects. The impact of XO inhibition to restore depressed myocardial energetics requires intact NO pathway activity.\(^12\) UA may also impair NO production directly, as suggested by the finding that UA infusion into forearm veins of humans attenuates acetylcholine-stimulated vasodilation.\(^22\) Likewise, the hypertension associated with hyperuricemia in rats is associated with reduced expression of macula densa neuronal nitric oxide synthase (NOS) and can be partially reversed by the NOS substrate L-arginine.\(^19\) This finding has interesting implications for cardiac function, as neuronal NOS plays a key role in modulating cardiac excitation-contraction coupling by facilitating sarcoplasmic reticulum calcium release.\(^22\)

Clinical Utility of Uric Acid Measurements

From a clinical perspective, the current study raises the issue of whether serum UA levels should be routinely measured in HF patients. Indeed this is likely to be a controversial issue, and one which will require evaluation in the context of measurement of brain natriuretic peptide (BNP), a serum marker that also possesses prognostic and diagnostic value in HF patients.\(^23\) Much in the same way as BNP has been evaluated, it will be of great value to assess whether UA levels change in response to HF therapy in a manner that predicts clinical outcome.

Whether or not UA levels are ready for clinical use, the observation that UA levels possess prognostic information adds an extremely intriguing finding to mounting evidence that XO and UA play pathophysiological roles in HF and its precursor, hypertension. Indeed, the amassing data have led to the planning of a clinical trial entitled A Phase II–III Prospective, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients with NYHA Class III-IV Congestive Heart Failure (OPT-CHF), initiated in 2003, which will test clinical outcomes using a composite endpoint comprising measures of heart failure morbidity, exercise capacity, and mortality. The findings of Anker and colleagues,\(^1\) therefore, not only bring to light a potentially new diagnostic test but also provide a novel line of evidence that the XO pathway and/or UA itself may be of pathophysiological importance in heart failure progression.

Acknowledgments

This work was supported by National Institutes of Health grants RO1 HL-65455 (to Dr Hare) and RO1 HL68607 (to Dr Johnson). Dr Hare is the recipient of a Paul Beeson Physician Faculty Scholars in Aging Research Award.

References


**KEY WORDS:** Editorials ■ antioxidants ■ nitric oxide ■ cardiovascular diseases ■ kidney
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_Circulation_. 2003;107:1951-1953
doi: 10.1161/01.CIR.0000066420.36123.35
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/15/1951

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