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Uric Acid in Chronic Heart Failure

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The pathophysiologic understanding of chronic heart failure (CHF) has shifted from a mere hemodynamic disorder to a much more complex approach including changes and imbalances in neurohormonal, immune, and metabolic functions. Among metabolic abnormalities, hyperuricemia is a constant finding in CHF. The xanthine oxidase metabolic pathway increasingly is appreciated as an important contributor to both symptoms of CHF as well as progression of the disease. Recent data suggest hyperuricemia to be an independent marker of impaired prognosis in CHF. In this article, the significance of the xanthine oxidase metabolic pathway in CHF is discussed. Data on xanthine oxidase inhibition are reviewed, which suggest a beneficial effect of therapeutically targeting this enzymatic pathway.
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Chronic heart failure (CHF) is a leading cause of both morbidity and mortality in Western society with increasing numbers in prevalence and health care costs. During the past 10 to 15 years, our understanding has changed from a mere hemodynamic disorder to a much more complex approach, including neuroendocrine and immune activation. Not only the cardiovascular system is affected in the long-term course of the disease, but also peripheral tissues and organs contribute to both symptoms and progression of the disease. Recent findings on metabolic imbalances and hormonal abnormalities occurring in CHF[1] add further to the increasingly complex picture of CHF pathophysiology. Hyperuricemia is a constant finding in CHF.[2] Uric acid levels increase in parallel to disease severity (Fig 1) and are associated with main clinical symptoms such as impaired exercise capacity[3] and decreased peripheral blood flow and vascular resistance.[2] Those data suggest a role of the xanthine oxidase metabolic pathway in the pathophysiology of CHF. More recently, prognostic implications for hyperuricemia in CHF are discussed. This article focuses on the role of hyperuricemia and of the xanthine oxidase metabolic pathway in CHF.

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The Xanthine Oxidase Metabolic Pathway in CHF

In humans, uric acid is the metabolic end point of purine degradation. The last metabolic steps in this process (from hypoxanthine to xanthine and from xanthine to uric acid) are promoted by the enzyme xanthine oxidoreductase (EC1.1.3.22). This enzyme is a flavoprotein that contains both iron and molybdenum and uses NAD^+ as an electron acceptor. It exists in 2 interconvertible forms: xanthine dehydrogenase and xanthine oxidase (XO). In its oxidase form, this enzyme can transfer the decreasing equivalent to molecular oxygen as redox partner generating free oxygen radicals (superoxide anion and hydrogen peroxide, which can be converted to free hydroxyl radicals). In 1968, the cytosolic XO was the first documented putative biologic generator of oxygen-derived free radicals.[4] Since then, it has been established that XO is a major source of free oxygen radical production in the human body.[5,6,7] This metabolic pathway is of particular significance in conditions of tissue hypoxia and ischemia/reperfusion[8] because increased degradation of adenosine triphosphate via adenosine leads to increased substrate load for XO.[9] Accordingly, an increase in serum uric acid level has been observed in hypoxic states such as obstructive pulmonary disease,[10] neonatal hypoxia,[11,12] cyanotic heart disease,[13,14] and acute heart failure.[15] Uric acid levels have been shown to increase also in the coronary sinus after consecutive balloon inflations during angioplasty[16,17] and during coronary bypass surgeries.[18] Simultaneously, in ischemia/hypoxia, xanthine dehydrogenase increasingly is converted to XO, which further adds to accelerated radical production.[5,19]

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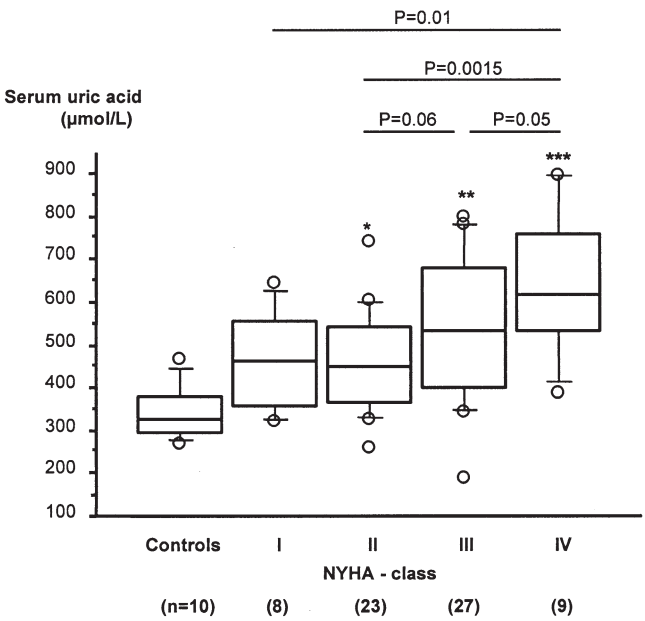

Figure 1 Serum uric acid levels in healthy subjects and in CHF patients subgrouped according to New York Heart Association (NYHA) functional class. $*P < .05$, $**P < .001$, $***P < .0001$ versus control group. Adapted from Doehner et al.[2]

In CHF, increased uric acid levels therefore might be expected because patients with CHF have impaired uptake of oxygen at rest and during exercise. This has been confirmed by the consistent finding of hyperuricemia in CHF being a direct measure of impairment of oxidative metabolism.[3,20] High serum uric acid levels indicate the degree of XO activation in CHF[21] and occur independently of the effects of diuretics and renal dysfunction.[3] Indeed, measurement of soluble plasma XO[22] and of endothelium-bound XO[23] have shown increased XO enzyme activity in CHF compared with healthy controls. As described earlier, an increased free radical oxygen load can be predicted in patients with CHF, which indeed has been observed.[24,25,26]

In CHF, endothelial dysfunction and decreased vasodilator capacity are characteristic features that relate closely to prominent clinical symptoms such as decreased exercise capacity and early muscle fatigue.[27,28] Decreased perfusion of skeletal muscle in CHF is neither primarily related to central hemodynamic abnormalities[29,30] nor to arterial hypotension,[31] but, more importantly, to endothelial dysfunction[32] and inflammatory activation.[33] Increased oxidative stress is a major factor responsible for the impaired regulation of vascular tone because it diminishes vasoactive nitric oxide.[34,35] XO-generated free oxygen radicals interact with endothelium-derived nitric oxide to form peroxynitrite (in itself a highly active oxygen radical), starting a cascade of detrimental oxygen radical effects (Fig 2). Endothelial dysfunction has been shown to be related to increased scavenging (ie, degradation) of nitric oxide by free oxygen radicals rather than impaired generation of nitric oxide.[6] Notably, in humans the tissue with the highest activity of XO (besides the epithelium of the mammary gland) is the capillary endothelium and the endothelium of the small arteries.[36,37]

Increasing evidence suggests that the xanthine oxidase metabolic pathway is not merely the final step in the purine degradation with the formation of uric acid as a metabolically inert waste product. In humans, the organs with the highest XO activity are the intestine and the liver, with low or undetectable levels in the brain, kidney, lung, and muscle.[38] The localization of XO primarily in the endothelial cells of the capillaries suggests that XO is involved in specific functions of the vascular system.[36] Given the capacity to generate free oxygen radicals, this enzyme might have a role in bactericidal defense mechanisms,[39,40] especially at the barrier between intestinal lumen and the body tissues. This physiologic mechanism may provide an acute adaptive response to environmental factors. One could hypothesize, however, that long-term stimulation of XO may result in chronic activation of this mechanism, leading to maladaptive processes and eventually damaging effects. The latter provides the pathophysiologic link of hyperuricemia with a large variety of detrimental processes, including increased cytokine production, cell apoptosis, and endothelial dysfunction, all of which occur in CHF patients.[41,42,43] Indeed, in a prospective series of studies on patients with CHF, it has been shown that hyperuricemia is a marker of impaired oxidative metabolism and hyperinsulinemia,[3] inflammatory cytokine activation,[44] and impaired vascular function.[2,45]

XO Inhibition—a Therapeutic Target in CHF?

The therapeutic option to inhibit increased XO activity in CHF might be useful to counteract maladaptive chronic upregulation of the XO metabolic pathway. In fact, it has been shown that in CHF patients with hyperuricemia, treatment with the XO inhibitor allopurinol improved endothelial function and peripheral blood flow,[46,47] whereas markers of free oxygen radical generation were decreased.[46] In a placebo-controlled, randomized, double-blinded, cross-over study we showed that allopurinol (100 mg/d) after 1 week of treatment decreased uric acid levels by 39%, while vasodilator capacity improved in arm and leg vascular beds by 24% and 23%, respectively.[46] Plasma XO activity was decreased by 49%.[48] It was found that the treatment-induced decrease of uric acid significantly correlated with the improvement of vasodilator capacity. This raises the possibility that independent of the oxygen radicals, uric acid itself may have an adverse effect on the regulation of peripheral vascular tone (see later). It has been shown that allopurinol treatment can improve forearm blood flow and endothelial dysfunction also in other conditions such as type 2 diabetes mellitus and mild hypertension.[49] In the context of reperfusion injury, XO-derived free oxygen radicals are a major contributor to impaired blood flow and tissue damage; allopurinol may exert protective effects against these reperfusion injuries.[50] Beneficial effects of allopurinol treatment for reperfusion injury after digital reimplantation surgery has been reported (de-

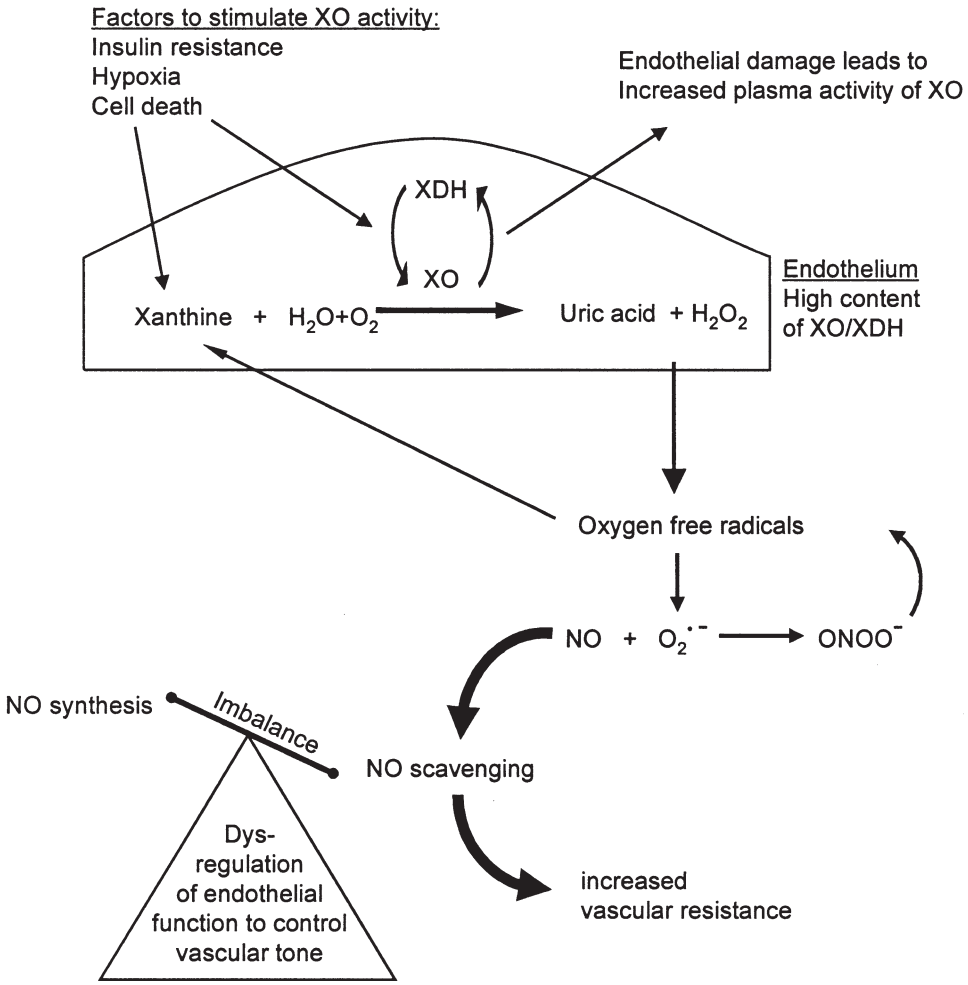

Figure 2 Endothelial effects of XO-derived free radicals. In CHF, increased substrate supply and XO/XH imbalance lead to up-regulated XO activity, resulting in increased free oxygen radical production. Superoxide anions react with endothelium-derived nitric oxide, causing impaired nitric oxide–dependent regulation of vascular tone and hence increased peripheral vascular resistance.

creased infection rate, postoperative pain, and chronic swelling).[51]

Besides its effect on peripheral vascular tone, inhibition of XO appears to directly influence myocardial performance in CHF. In animal models, allopurinol decreases myocardial oxygen consumption[52] and improves systolic function,[53,54] resulting in increased myocardial energy efficiency. Recently, this has been confirmed in human CHF.[55] Although the underlying mechanism is not yet understood fully, some investigators have suggested a specific effect of allopurinol to sensitize cardiac myofilaments to Ca^{2+}.[56] Treatment with allopurinol is, however, not free of problems. It can induce attacks of gout, kidney dysfunction, or skin reactions. Whether new, more specific, XO antagonists will be established in the future as a regular treatment option remains to be seen.

Hyperuricemia in CHF

Recent experimental studies suggest that uric acid itself might contribute to cardiovascular pathophysiology. The direct association between a decrease in uric acid level and improved vasodilator capacity was described earlier. We previously showed that high uric acid levels in CHF predict impaired peripheral blood flow and decreased vasodilator capacity.[2] Notably, these findings are independent of renal dysfunction and diuretic dose, which are known to contribute to increasing the serum uric acid level and this may partly account for higher uric acid levels in patients with CHF. Thiazide and loop diuretics in particular, by increasing tubular reabsorption of uric acid, may cause decreased excretion. It has been shown that in hypertensive patients, bendrofluazide at a dose of 2.5 mg/d may cause an increase in serum uric acid levels of 9%.[57] However, this is not sufficient to explain the substantial increase of uric acid level observed in CHF patients. For furosemide treatment in CHF patients[58] as well as for torasemide,[59] even in larger doses (100-400 mg) as used in the treatment of chronic renal failure, changes in uric acid levels were reported as clinically insignificant. Similar renal impairment might increase serum uric acid levels owing to diminished excretion. However, this might not be a dominant factor for hyperuricemia observed in CHF patients because associations of uric acid with pathophysiologic alterations in CHF (see earlier) constantly were found independent of parameters of renal function[2,3]

A detrimental impact of chronic hyperuricemia has been reported. Uric acid 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.[60,61,62] In a mouse model it

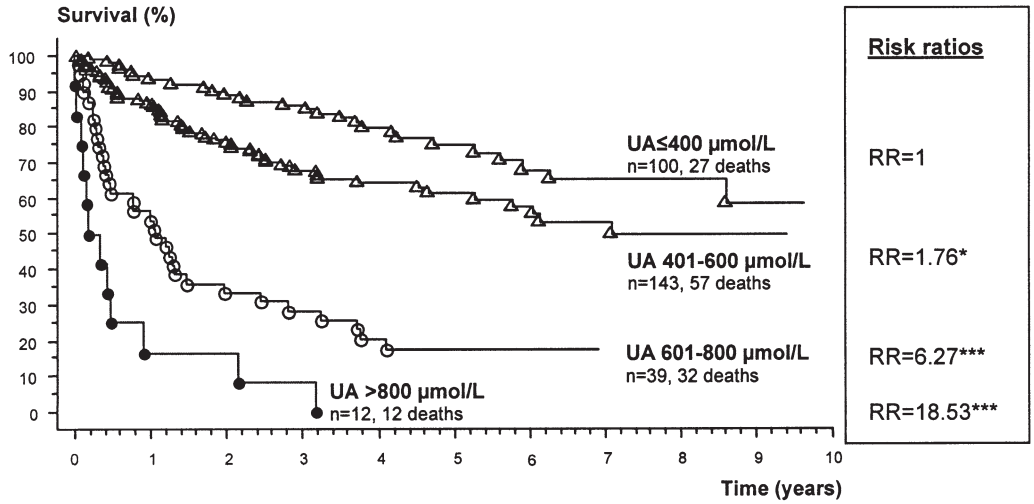

Figure 3 The graded relationship between serum uric acid level (in μmol/L) and survival in 294 patients with CHF. Kaplan-Meier survival plot and hazard ratios (relative risk) are shown. Relative risk compared with uric acid $\leq$ 400 μmol/L. *P = .016 versus patients with uric acid levels $\leq$ 400 μmol/L; ***$P <$ .0001 versus patients with uric acid levels $\leq$ 400 μmol/L. Adapted from Anker et al.[65]

was shown that uric acid infusion caused increased endotoxin-stimulated tumor necrosis factor-α production and hence proinflammatory immune activation.[63] Recently, uric acid was identified as an endogenous danger signal to activate the immune system.[64] However, the discussion is ongoing whether there is also an antioxidant effect and hence a protective effect of uric acid.

Hyperuricemia as a Novel Prognostic Marker

There is increasing evidence suggesting prognostic significance for the XO metabolic pathway. Recently, it was shown that in CHF patients high uric acid levels are a predictor of impaired survival, independently of and better than other well-established parameters such as the clinical status, exercise capacity, parameters of kidney function, and effect of diuretic therapy.[65] Data indicated a stepwise increase of mortality risk in parallel to increasing uric acid levels (Fig 3). This is in line with the finding in a recent retrospective study that examined the effect of allopurinol in CHF on mortality and hospitalization.[66] In these patients, long-term high-dose allopurinol ($\geq$300 mg/d) was associated with a better all-cause mortality (adjusted relative risk, .59; 95% confidence interval, .37-.95; $P <$ .05) than low-dose allopurinol ($<$300 mg/d), assuming a dose-related effect of allopurinol.

Summary

The traditional view of CHF as a mere pumping disorder has shifted to a more complex approach including hormonal, immune, and metabolic aspects, and secondary changes. Increasing data suggests that the XO metabolic pathway is a significant contributor to the pathophysiology of CHF with both symptomatic and prognostic implications. Preliminary results suggest a beneficial effect of decreasing uric acid by XO inhibition. Whether one also could use uricosuric treatments (to increase excretion of uric acid) or newer, more selective XO inhibitors potentially with less side effects in acute or chronic heart failure needs further study.

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