Uric acid and xanthine oxidase: perspectives in chronic heart failure

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Abstract

Heart failure continues to be one of the major causes of morbidity and mortality in the western world. Advances in cardiovascular medicine have lead to unearth the possible markers of disease progression. Hyperuricemia is one of the potential metabolic markers for heart failure. In this review, we discuss the beneficial and deleterious role of uric acid and xanthine oxidase in the pathophysiology and management of chronic heart failure. Measurement of this readily available inexpensive marker may be included in the routine protocol and xanthine oxidase inhibition in addition to correct hyperuicemia may improve the vascular function and oxidative stress in patients with chronic heart failure.

Key words: heart failure, uric acid, xanthine oxidase.

Introduction

Despite advances in understanding the pathophysiology and management of heart failure (HF), it still constitutes one of the major public health problems. From 1979 to 2005 there was 171% increase in hospital discharge for HF. The estimated direct and indirect cost of HF in the United States for 2008 is $34.8 billion [1]. A high level of uric acid (UA) has been associated to be predictor of cardiovascular mortality [2-4]. Serum UA has been reported to be high in patients with chronic heart failure (CHF) [5, 6]. However no mechanism whereby excessive UA could damage heart or the vasculature has been identified. Xanthine oxidase (XO) might be the possible link between UA and its effects seen in HF [7] as UA levels reflect the degree of activation of XO in HF [6].

Formation of uric acid – role of xanthine oxidoreductase

Traditionally UA is being considered to be a metabolically inert end-product of purine metabolism in humans, without any physiological value. Later this ubiquitous compound has proven to be a selective antioxidant, capable especially of reaction with hydroxyl radicals and hypochlorous acid [8]. The transformations of hypoxanthine into xanthine and of this metabolite UA are catalyzed by xanthine oxidoreductase (XOR), rate-limiting enzyme of the purine degradation pathway [9]. XOR is a ubiquitous metalloflavoprotein that appears in two interconvertible forms: xanthine dehydrogenase (XD), which is constitutively expressed *in vivo*; and XO, which is generated by the posttranslational modification of XD which occurs at low oxygen tension and in the presence of several proinflammatory mediators. Functionally, both

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XD and XO catalyze the oxidation of purines to UA. However, whereas XD requires NAD^+ as an electron acceptor for these redox reactions, thereby generating the stable product NADH, XO is unable to use NAD^+ and reduces molecular oxygen generating the highly reactive superoxide free radical [10]. XO may contribute to impaired vasodilator capacity in patients with CHF via upregulated oxidative stress [11]. Superoxide radical can combine with endothelium-dependent nitric oxide (NO) to form peroxynitrite ($ONOO^-$), a potent non-radical oxidant species [12]. This superoxide aninons can inhibit endothelium-dependent vasorelaxation [13]. Negative regulators of XOR activity are superoxide [14], hydrogen peroxide and hydroxyl radical [15]. Such product-mediated regulation may play a role in XOR inactivation in hyperoxia.

In lower mammals, urate oxidase enzyme further metabolizes UA to allantoin, but this enzyme is inactivated in most primates. Humans lack urate oxidase because of a defective gene that is not transcribed [16]. Watanabe et al. [17] hypothesized that the mutation provided a survival advantage because of the ability of hyperuricemia to maintain blood pressure under low-salt dietary conditions. During primate evolution, UA may have a role in lengthening life-span and decreasing age-specific cancer rates in humans [18]. Most serum UA is excreted via urine by processes of glomerular filtration, tubular reabsorption, tubular secretion and again reabsorption in late proximal tubule [19].

Uric acid, xanthine oxidase and chronic heart failure

In patients with HF raised UA levels may be considered as a marker of hyperinsulinemia, inflammatory cytokine activation [6, 20], endothelial dysfunction, cardiac cachexia, exercise intolerance [21, 22], and worse cardiac function [23]. Among echocardiographic parameters, patients with raised UA have elevated filling pressures both in acute [24] and chronic heart failure [23].

Hyperuricemia seen in HF is independent of the effects of diuretics and renal impairment. There is an inverse relationship between serum UA levels and measures of functional capacity like Maximal oxygen uptake (MVO_2), regression slope relating to minute ventilation to carbon dioxide output, exercise time and New York Heart Association (NYHA) class in patients with HF [6].

The principal sites for XO production are liver and gut but it may circulate in the blood and adhere to endothelium in distant sites [25]. XO is expressed in cardiac myocytes, as evident by immunohistochemistry and may participate in autocrine signaling [26]. In patients with CHF, XO (a potent radical producing enzyme) activity is increased >200% and endothelium-dependent SOD (Superoxide dismutase, a major vascular antioxidant enzyme; a scavenger of su-

peroxide) activity is decreased and both are closely associated with increased vascular oxidative stress. This loss of vascular oxidative balance may represent a novel mechanism contributing to endothelial dysfunction in CHF [27]. UA preserves the activity of superoxide dismutase thereby providing a protective mechanism [28].

In the study by Waring et al acute exposure of high concentrations of UA levels did not impair haemodynamic variables, basal forearm blood flow and nitric oxide dependent endothelial function in healthy men suggesting that there may be no causal role of UA in the development of atherosclerosis. However in that study all the subjects were free of established cardiovascular risk factors [29]. In coronary system, a major site of production of UA is the microvascular endothelium, and there is generally a net release of UA from the human myocardium. UA prevents oxidative inactivation of endothelial enzymes (cyclooxygenase, angiotensin converting enzyme) and preserves the ability of the endothelium to mediate vascular dilatation in the face of oxidative stress [8].

However *in vitro* studies have shown that hyperuricemia may stimulate vascular smooth muscle cell proliferation via activation of mitogen-activated protein kinases and stimulation of cyclooxygenase-2 and platelet-derived growth factor [17, 30] and can induce platelet secretion [31]. In a study on mouse model UA increased endotoxin-stimulated tumor necrosis factor-alpha production suggesting its role in proinflammatory cytokine activation [32].

Possible explanations for raised uric acid in heart failure

Serum UA is raised in HF, probably due to increased activity of XO [33, 34], increased conversion of XDH to XO [35] or due to reduced renal excretion. Also hyperuricemia in HF may result from the reduced renal tubular secretion and the clearance of UA [36]. CHF is an insulin resistant, hyperinsulinaemic state [37, 38] in which there is an accelerated rate of glycolytic metabolism. Insulin regulates the activity of the enzyme glyceraldehydes 3-phosphate dehydrogenase (the only oxidative step in glycolytic pathway) [39, 40]. In the presence of insulin resistance and hypoxia the activity of this enzyme is affected and leads to diversion of early glycolytic intermediates toward ribose-5-phosphate and phosphoribosyl pyrophosphate, which would favour UA production [41]. Also, low salt diets and insulin-resistance may increase the reabsorption of UA in the proximal tubules of kidney [42].

Diuretics used in the treatment of HF can also contribute to elevated UA concentrations [43]. Overproduction of UA in advanced HF could be related to tissue hypoxia which is known to increase adenosine triphosphate degradation [44].

Uric acid as a prognostic marker in heart failure

Serum UA has a prognostic value in patients with CHF [21, 45]. Sakai et al. have suggested that the prognostic significance of UA measurement is independent of B-type natriuretic peptide (BNP) levels and monitoring a combination of UA and BNP may be useful for the management of patients with CHF [46]. The assessment of UA provides even better information independent of other well-established parameters, like the clinical status, exercise capacity, parameters of renal function, and the computer-based 7-parameter heart failure survival score (HFSS). High UA level can predict mortality and indicate the need for transplantation in patients with CHF [45].

Also in patients hospitalized for acute heart failure and left ventricular dysfunction, hyperuricemia has been shown to be associated with a higher risk of death and/or new hospitalizations in the long term [24]. In patients with acute myocardial infarction (AMI), Kojima et al. have shown a close relation between serum UA concentrations and Killip's classification suggestive of left ventricular failure. The combination of Killip's classification and serum UA level after AMI may be a good predictor of mortality in patients with AMI [47].

Uric acid as a measure of altered oxidative metabolism

An accelerated utilization of adenosine triphosphate (ATP) in excess of synthetic capacity promotes degradation of adenosine nucleotides to inosine, hypoxanthine, xanthine, and UA [48]. Hence UA levels are high in hypoxic conditions such as obstructive pulmonary disease, cyanotic heart disease, acute heart failure and neonatal hypoxia [49-53]. It is also increased in states of regional ischemia such as during coronary angioplasty [54] and coronary artery bypass operations [55]. In patients with CHF, there is an inverse relationship between serum UA and maximum oxygen uptake during treadmill exercise test [6] and to maximal leg blood flow [56].

Histologically in CHF there is a shift in skeletal muscle fiber distribution and derangements in mitochondrial structure, so during exercise there is an early depletion of ATP which promotes anaerobic metabolism. Also during exercise in patients with CHF, the perfusion of skeletal muscles is markedly reduced which further promotes early anaerobic skeletal muscle metabolism [57]. The anaerobic threshold (AT) is a measure of the balance between aerobic and anaerobic cellular metabolism. In CHF measurement of UA may provide the basis of surrogate measure of AT [58].

Antioxidant property of uric acid

UA possess antioxidant property by its ability to scavenge carbon-centered and peroxyl radicals and its inhibitory effect on lipid peroxidation [59-61].

Systemic administration of UA (100 mg intravenously) was found to raise serum free radical scavenging capacity to an extent greater than vitamin C (1000 mg) in healthy volunteers [20 of 1] and high concentrations of serum UA are associated reduced exercise-induced oxidative stress in healthy adults [62]. UA as an anti-oxidant may have a protective effect on endothelial function. However even though UA is an antioxidant, *in vitro* study have shown that it may accelerate the peroxidation of human Low density lipoprotein (LDL) trigger by copper, even in the presence of endogenous antioxidants [63]. As oxidized LDL can inhibit endothelial-derived relaxing factor – induced vasorelaxation [64], hyperuricemia may cause endothelial dysfunction.

Rationale for the use of xanthine oxidase inhibitor in heart failure

CHF is now being considered as a state of endothelial dysfunction [65] and increased oxidative stress [66, 67]. XO activity may contribute to abnormal energy metabolism in human cardiomyopathy by interfering with myocardial energitics [68] and myofilament calcium sensitivity [69]. In HF, the oxygen cost of ventricular contraction remains relatively unchanged despite markedly impaired left ventricular work, leading to decrease in mechanical efficiency of contraction [70]. This has been described as Mechanoenergetic uncoupling.

Allopurinol inhibits XO and thus reduces the formation of xanthine, of UA and of reactive oxygen species [71]. Allopurinol and its major active metabolite Oxypurinol are hydroxyl radical scavengers [72]. Favorable effect of serum UA lowering treatment with allopurinol on the rate of cardiovascular complications has been reported in patients with congestive heart failure [73]. A serum level of UA has inverse relation with nitric oxide activity. Nitric oxide modulates the production of UA by interfering with the activity of XO [74]. In the failing heart the activity of XO is upregulated relative to nitric oxide synthase (NOS) activity and contributes to the mechanoenergetic uncoupling. The energy-sparing effects of XO inhibitor (allopurinol) is seen only when NOS signaling is intact. Further the improvement in myocardial contractility and efficiency seen with allopurinol can be blocked by NOS inhibitor, N^G-monomethyl-L-arginine (L-NMMA). This points towards the role of XO and NOS cross-talk in HF and mediating mechanoenergetic uncoupling [75].

In the rat model hyperuricemia induced by uricase inhibitor have shown to induce hypertension by downregulation of neuronal nitric oxide synthase (NOS1) expression in macula densa and can be partially reversed by L-arginine (a substrate of NOS) [76]. In terms of cardiac effects, neuronal NOS have a facilitative effect on cardiac contractility by releasing calcium from sarcoplasmic reticulum [77]. Neuronal NOS directly interact with XO to regulate cardiac

contraction. Deficiency of neuronal NOS can lead to profound increases in XOR-mediated superoxide production, which can depresses myocardial excitation-contraction coupling. This can be reverse by XOR inhibitor, allopurinol [78].

In the study by Ekelund et al. on dogs with HF, XO activity was 4-fold increased in failing dog hearts but was not detectable in plasma. Allopurinol decreased myocardial oxygen consumption and significantly increased mechanical efficiency (stroke work/myocardial oxygen consumption). Allopurinol possessed unique ionotropic action with an increased myocardial contractility and simultaneously reduces cardiac energy requirements [33]. In addition to improving left ventricular function at rest in dogs with HF [33], allopurinol also decreases oxygen consumption and increases myocardial contractility in response to exercise- and dobutamine-induced β-adrenergic stimulation [79].

In patients with idiopathic dilated cardiomyopathy, Cappola et al. reported an increased XDH/XO protein abundance in failing heart compared with normal myocardium. In their study, infusion of allopurinol into the coronary circulation in HF patients improved myocardial efficiency by diminishing oxygen consumption. But the ionotropic action was not noted in human model; however the contractility did not decrease despite the fall in energy consumption [68].

In patients with HF, intake of 600 mg/day Oxypurinol (another XO inhibitor) for 1 month can decrease serum UA and improves left ventricular ejection fraction (LVEF) in patients with LVEF ≤40% [80]. Oxypurinol can increase the rat myofilament twitch tension and this effect is much more marked in failing myocardium, where total XO activity is elevated. Thus, the inotropic action of oxypurinol is in atleast relatively selective for HF. Oxypurinol does not affect resting tension, thus there is no impairment of diastolic myocardial function [81].

Myocardial infarction (MI) frequently produces left ventricular (LV) dilatation and hypertrophy of the noninfarcted myocardium, phenomenon of remodeling. This contributes to the development of depressed cardiac performance and increase the risk of development of HF. Increased myocardial reactive oxygen species production plays a critical role in cellular signaling pathways leading to hypertrophy, dilation, and dysfunction of the ventricle after MI [82]. In the study on animal model with HF by Engberding et al., treatment with allopurinol showed a marked attenuation of left ventricular remodeling processes and dysfunction after experimental MI [83].

Similarly in another animal model Mellin et al. reported that long-term treatment with allopurinol can improve cardiac haemodynamics, reduce left ventricular dilation, hypertrophy and collagen accumulation, and thus ameliorates cardiac systolic and diastolic function [84]. Also in a study on mouse

model of postischemic cardiomyopathy chronic treatment with allopurinol improved survival and restored contractile function [85].

Thus, XO inhibition may offer a novel therapeutic strategy for the treatment of congestive heart failure as shown by studies on animals [33, 69] and humans [68]. Randomized trials have shown that allopurinol can improve peripheral vasodilator capacity and peak blood flow [86] and can improve endothelial dysfunction in CHF [87]. But in the study of Farquharson et al. [87] vast majority of study subjects had normal range of serum UA levels, suggesting that blocking XO even in the absence of hyperuricemia may still improve endothelial dysfunction. Investigators speculated that allopurinol blocks the production of reactive oxygen species mediated by XO as there was a significant reduction of plasma malondialdehyde (MDA) with allopurinol and as oxidative stress caused by oxidized LDL is a major determinant of endothelial dysfunction and MDA is released from oxidized LDL itself.

Later George et al. reported 44% reduction of UA with 300 mg allopurinol and 46% reduction of UA with 1000 mg probenecid. Allopurinol improved endothelial-dependent vasodilatation by 53% compared to placebo, whereas probenecid did not alter endothelial-dependent vasodilatation at all. This suggests that allopurinol can improve endothelial function by its ability to reduce vascular oxidative stress and not by lowering UA [88].

In a recent study 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), where 405 patients with class III-IV HF were randomly assigned to treatment with either oxypurinol (600 mg/day) or placebo, for 24 weeks. Oxypurinol failed to show benefit compared to placebo for the treatment of heart failure. However in the post-hoc analysis of patients with elevated serum UA levels at baseline, there was an indication of a beneficial effect for oxypurinol [89]. Treatment of hyperuricemia is not included in the American College of Cardiology (ACC)/American Heart Association (AHA) updated guidelines on Heart failure. Thus, more prospective, double-blind, placebo-controlled studies should be conducted to show that treatment of hyperuricemia can reduce cardiovascular events, mortality and hospitalization before recommending treatment of hyperuricemia for chronic heart failure. Newer agents that lower UA directly for example, recombinanat urate oxidase-Rasburicase may cause rapid and substantial reductions in circulating UA concentrations [90] and future randomized studies should be conducted to validate this agent in CHF patients.

In conclusion, traditionally viewed as an inert end-product of purine metabolism, elevated levels of UA and its enzyme XO are now being considered as one

of the major metabolic abnormality in patients with chronic heart failure. So the measurement of this readily available cheaper marker may be considered a routine protocol in the assessment and follow-up for patients with HF and every effort should be taken to correct it by XO inhibitor which not only correct hyperuricemia but also improve the vascular function and oxidative stress in patients with chronic heart failure.

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