

How Should Serum Uric Acid Concentrations be Interpreted in Patients with Hypertension?

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Abstract: A large number of epidemiological studies have identified an association between high serum uric acid (SUA) concentrations and increased cardiovascular risk. However, the significance of this relationship has been difficult to interpret due to the co-existence of other cardiovascular risk factors. The relationship between SUA concentrations and morbidity appears particularly strong in patients with hypertension, and a number of recent studies have found that this relationship persists after adjusting for potential confounders. This paper reviews the potential mechanisms by which SUA might be causally related to cardiovascular disease in patients with hypertension. We critically appraise the evidence in favour of a causal, coincidental or compensatory relationship, and consider the potential outcomes of lowering SUA in patients with hypertension. The potential consequences of high SUA concentrations are discussed and, based on existing evidence, consideration is given to the potential therapeutic value of strategies to lower SUA as a means of cardiovascular risk reduction in patients with hypertension.

RELATIONSHIP BETWEEN SERUM URIC ACID CONCENTRATION AND CARDIOVASCULAR RISK

An association between SUA concentrations and cardiovascular risk has been recognised for more than 50 years [1]. However, this has been difficult to interpret because high SUA concentrations are associated with a number of conditions that increase cardiovascular risk, including hypertension, obesity, hyperlipidaemia and diabetes mellitus [2] (Table 1). Several large population studies, including the British Regional Heart Study, the Social Insurance Institution of Finland Study and the Framingham Heart Study, have indicated that the relationship is co-incidental, and based on confounding associations between SUA and other risk factors [3, 4]. However, a number of epidemiological studies, including the MONICA project and Gothenburg prospective study indicate that there is an association between SUA concentrations and cardiovascular risk even after taking account of potential confounding factors [5, 6]. Epidemiological studies have also shown that a relationship exists between SUA and cardiovascular risk in specific patient groups. For example, in patients with hypertension, age-adjusted myocardial infarction and stroke risk increases across SUA quartiles, in both men and women [7]. And in patients with diabetes, high SUA concentrations confer an almost 2-fold increased risk of stroke [8]. In patients with established coronary artery disease, high SUA concentrations confer a 2-3 fold increased mortality risk [9]. These findings have raised the possibility that SUA might contribute to cardiovascular disease as an independent, causal risk factor. However, there is continued uncertainty over the significance of the association between SUA and cardiovascular risk.

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SERUM URIC ACID AND CARDIOVASCULAR RISK IN HYPERTENSION

A number of studies have found that asymptomatic hyperuricaemia predicts the development of hypertension in apparently healthy adults [10-12]. Furthermore, in unselected populations high SUA concentrations are associated with widened pulse pressure [13], suggesting a possible mechanistic link between hyperuricaemia and isolated systolic hypertension.

Amongst patients with established hypertension, the US National Health and Nutrition Survey (NHANES) III found that age-adjusted rates of myocardial infarction and stroke were significantly higher across increasing SUA quartiles in both men and women [14]. During a mean 6.6 year follow-up, the proportional hazard ratio associated with a standard deviation increase in SUA (29 $\mu\text{mol/l}$) was 1.22 (95% confidence interval 1.11-1.35), and higher than that associated with comparable increases in blood glucose, serum cholesterol or systolic blood pressure [14]. The Hypertension Detection and Follow-up Program Co-operative Research group showed a significant correlation between SUA concentrations and 5-year cardiovascular risk, which was independent of potential confounding variables [15]. A number of large epidemiological studies have confirmed a strong association between high SUA and increased cardiovascular risk. In most of these reports, but not all, the association persisted after correcting for potential confounding risk factors (Table 2).

THIAZIDE DIURETIC TREATMENT AND CARDIOVASCULAR RISK

Thiazide diuretics confer unequivocal benefits in patients with hypertension, and significantly reduce cardiovascular morbidity and mortality [22]. Despite this, thiazide treatment is known to increase SUA, and an association between SUA concentration and cardiovascular risk was found among patients in The Hypertension Detection and Follow-up

Table 1. Major Cardiovascular Risk Factors Associated with High SUA Concentrations, Which Confound Interpretation of the Relationship Between SUA and Cardiovascular Risk

Risk factor	Mechanism of association
<i>Congestive heart failure</i>	xanthine oxidase activity & UA production renal blood flow
<i>Thiazide diuretics</i>	renal clearance
<i>Loop diuretics</i>	Haemoconcentration Hypovolaemia causing tubular reabsorption
<i>Obesity & type 2 diabetes</i>	Hyperinsulinaemia insulin-mediated renal tubular UA reabsorption
<i>Hypertriglyceridaemia</i>	Selective insulin resistance: insulin-mediated glucose and FFA uptake but retained renal sensitivity to insulin-mediated UA reabsorption
<i>Renal impairment</i>	May be manifestation of cardiovascular disease. renal UA clearance
<i>Peripheral vascular disease</i>	Ischaemia: adenosine release, metabolised to UA

Table 2. Prospective Epidemiological Studies Examining the Association Between SUA Concentration and Cardiovascular Risk in Patients with Hypertension, Using Univariate and Multivariate Analyses. *Thiazide-Treated Patient Subgroup

Study	n	Duration (y)	Univariate correlation	Independent correlation	Year	Ref.
Hypertension Detection & Follow-up Cooperative Research Group	10940 3693*	5	Y	Y	1985	[15]
		5	Y	Y (women)	1987	[16]
European Working Party	822	3	Y	N	1991	[17]
Work Site Study	7978	6.6	Y	Y	1999	[14]
PIUMA Study	1720	4	Y	Y	2000	[18]
SHEP Study	4327	5	Y	Y	2001	[19]
Syst-China	1873	3	Y	Y	2001	[20]
Syst-Eur	4522	2	N	N	2002	[21]

Program Co-operative Research group who were receiving a thiazide diuretic [16]. Persistence of the relationship between SUA and risk in thiazide-treated patients has prompted speculation that treatment-mediated elevation of SUA might attenuate some of their potential benefits [23]. This might, at least in part, be explained by the apparently lower response to antihypertensive treatment in patients with high SUA concentrations [24].

Notwithstanding the potential concerns about thiazide-mediated increases in SUA concentration, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study recently showed that thiazide treatment reduces cardiovascular risk to a similar or even greater extent than other antihypertensive agents that caused comparable reductions in blood pressure [25]. These latter findings have raised interest in the possibility that the benefits of thiazide diuretics over other antihypertensive agents might be attributable to increased SUA concentrations

[26]. Mechanisms through which raised SUA could possibly have a protective effect on the cardiovascular system remain unclear, and this hypothesis has not been examined directly in patients with hypertension.

HYPERURICAEMIA AND IMPAIRED RENAL FUNCTION

Renal function is a major determinant of uric acid clearance and, therefore, SUA concentration. Around one quarter of patients with hypertension have co-existent hyperuricaemia due to impaired renal clearance of uric acid [27]. Therefore, impaired renal function is a major confounding factor in examining the relationship between SUA concentrations and cardiovascular risk. Notwithstanding, there appears to be a significant relationship between SUA concentration and cardiovascular mortality in patients with isolated systolic hypertension even after adjusting for renal function in multivariate analysis [20].

ANIMAL MODELS OF HYPERURICAEMIA AND HYPERTENSION

Oxonic acid inhibits urate oxidase activity in mammalian species, and thereby increases SUA concentrations in animal models of hyperuricaemia. Dietary supplementation of 2% oxonic acid causes a significant increase in blood pressure in rats from 125 ± 15 to 143 ± 13 mmHg (mean \pm SEM) at 4 weeks, and a close correlation was found between the resultant increase in SUA concentration and rise in blood pressure [28]. This effect persisted until death or euthanasia at 7 weeks, and could be prevented by concurrent administration of allopurinol or a uricosuric agent [28]. A characteristic form of microscopic renal injury and increased plasma renin concentrations were noted, suggesting a possible renal mechanism for elevated blood pressure in the setting of hyperuricaemia.

Similarly, in Sprague-Dawley rats maintained on a low salt diet, oxonic acid supplementation increased blood pressure at 5 weeks compared to controls, 143 ± 4 versus 126 ± 2 mmHg (mean \pm SEM) [29]. Histopathology and immunostaining showed pre-glomerular arteriolar hypertrophy, suggesting a renal mechanism. Both renal injury and elevation of blood pressure were prevented by administration of allopurinol [29]. Findings from these animal models of hyperuricaemia have tempted speculation that high SUA concentrations might play a causal role in the development of hypertension in humans.

DOES URIC ACID INFLUENCE CARDIOVASCULAR FUNCTION?

Potential biological mechanisms through which high SUA concentrations might impair cardiovascular function have been suggested, as outlined in (Fig. 1). Many of these

pathways have been proposed on the basis of *in vitro* or *ex vivo* experimental findings, and their biological importance has not yet been clearly established.

Impaired Vascular Function and Atherosclerosis

The endothelium is a non-thrombogenic monocellular lining that maintains vascular integrity by regulating active transport of macromolecules, and providing a semi-permeable barrier. In addition to its structural role, the endothelium regulates cardiovascular function through the generation and release of a number of autocrine and paracrine factors, including nitric oxide (NO), adenosine, endothelin, and prostaglandins. In health, NO is liberated from the endothelium, formed by NO synthase, and has a number of important effects on local cardiovascular function, including relaxation of vascular smooth muscle and vasodilatation, inhibition of platelet and leukocyte adhesion to endothelium, and inhibition of myointimal hyperplasia. Loss of endothelium-derived NO bioavailability, so-called 'endothelial dysfunction', is believed to be a key early step in the development of atherosclerosis, and is a characteristic finding in patients with any one of several major cardiovascular risk factors [30, 31]. Endothelial dysfunction is thought to arise from excessive free radical activity, which disrupts NO formation and accelerates its degradation [32]. Furthermore, oxidative stress is believed to play a central role in the development and progression of atherosclerosis, through disruption of endothelial function, and oxidation of low density lipoprotein. Oxidative stress is a characteristic finding in a number of major risk factors, such as diabetes mellitus, hypertension, hypercholesterolaemia and smoking [33], and provides a biologically plausible link between seemingly diverse major risk factors, endothelial dysfunction, and the development of atherosclerosis. The

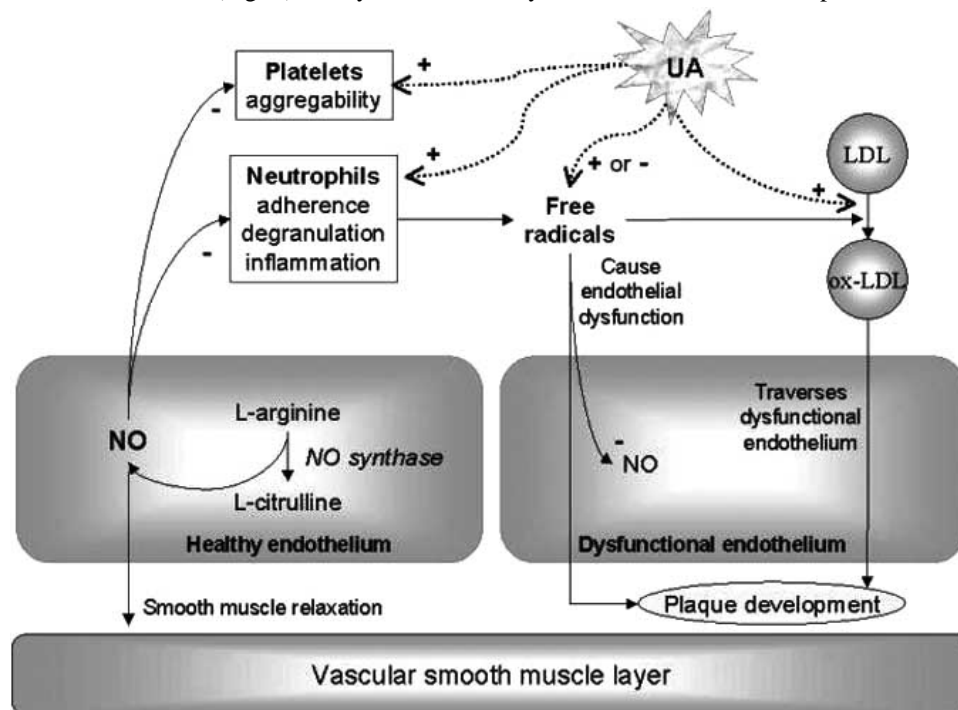


Fig. (1). Schematic representation of potential mechanisms through which high SUA could impair vascular function, and thereby promote development of atherosclerosis or increase cardiovascular risk.

importance of endothelial dysfunction in cardiovascular disease is underpinned by experimental models of atherosclerosis, in which pharmacological inhibition of NO synthase activity and consequent reduction of NO bioavailability cause more rapid and extensive plaque development *in vivo* [34]. Alleviation of any one of several major cardiovascular risk factors, including blood pressure lowering, cholesterol reduction, smoking cessation or correction of hyperglycaemia, is capable of improving vascular NO bioavailability [35]. Consequently, endothelial function is gaining increasing acceptance as a surrogate marker for future cardiovascular risk, and offers an opportunity to evaluate the vascular effects of potential risk factors, and treatments that ameliorate them.

Uric Acid and Endothelial Dysfunction

The potential effects of SUA on vascular function are of interest, because other established cardiovascular risk factors mediate risk, at least in part, through impairment of endothelial function and attenuation of NO bioavailability. If SUA acts in a similar way, then the influence of high concentrations on endothelial function might indicate a link between SUA and mechanisms of atherosclerosis, thereby allowing its role as an independent causal risk factor to be more clearly defined. A number of observations have highlighted associations between raised SUA concentrations and endothelial dysfunction. For example, an inverse relationship has been identified between SUA concentration and flow-mediated vasodilatation in the forearm vascular bed, which is an endothelium and NO dependent response [36]. In patients with congestive heart failure, who typically have hyperuricaemia and vascular dysfunction, there is an inverse relationship between SUA concentrations and lower limb flow-mediated, endothelium-dependent blood flow responses. Furthermore, administration of allopurinol, a xanthine oxidase inhibitor, to lower SUA concentrations allows restoration of endothelial function in patients with heart failure [37]. Some difficulty may be encountered in interpreting these findings because allopurinol is capable of exerting a number of potentially beneficial cardiovascular effects, for example those resulting from its ability to act direct as an antioxidant. However, in patients with heart failure, the improvement in endothelial function due to allopurinol correlated closely with the extent by which SUA was lowered, suggesting that this may have been the responsible mechanism [37].

Uric Acid and Oxidative Stress

Xanthine oxidase activity is increased in the setting of ischaemia or oxidative stress. The consequences are an increase in uric acid production and raised SUA concentrations, and increased hydrogen peroxide synthesis, which stimulates further liberation of free radicals. Peroxynitrite is a pro-oxidant that is capable of promoting oxidative vascular damage. Uric acid reacts with peroxynitrite to form a stable nitric oxide donor and thereby lowers the risk of peroxynitrite-mediated oxidative injury [38]. Raised SUA concentrations could therefore be expected to have a favourable influence on vascular redox state. However, the situation is complex because peroxynitrite is capable of inactivating xanthine oxidase [39], an effect that is inhibited by uric acid. Therefore, in certain situations SUA

might act to conserve xanthine oxidase activity, through its interaction with peroxynitrite, and facilitate hydrogen peroxide and free radical liberation. The beneficial or detrimental effects of raised SUA concentrations are likely to depend on the degree of xanthine oxidase activity, which is ordinarily quiescent in health but up-regulated in high risk groups. Overall, the significance of interactions between uric acid and peroxynitrite *in vivo* remains unclear, but might be more likely to have detrimental effects in high risk groups in whom vascular xanthine oxidase activity is characteristically increased.

Uric acid possesses powerful chain-breaking antioxidant properties and, given its comparative abundance in both the intracellular and extracellular compartments, is believed to have significant free radical scavenging activity *in vivo* [40]. Increased oxygen-derived free radical activity can be provoked by intense physical exercise, leading to a temporary state of oxidative stress and raised concentrations of circulating lipid peroxidation products. Endothelial release of adenosine is increased during ischaemia, and rapidly metabolised to uric acid, so that circulating SUA concentrations rise during and after acute exercise [41]. In exercising skeletal muscle, SUA is actively taken up from the circulation and oxidised to allantoin [42]. Therefore, SUA appears to counter intracellular increases in free radical activity during acute exercise and thereby protect against local oxidative stress. Administration of uric acid to healthy people, so as to temporarily increase SUA concentrations, is associated with increased circulating antioxidant activity and attenuates the rise in plasma 8-iso-prostaglandin F₂ alpha, a marker of vascular oxidative damage, during acute aerobic exercise [43]. These findings suggest that high SUA concentrations might confer protection against oxidative stress *in vivo*, as a consequence of antioxidant properties. An unresolved issue, which may be of greater importance, is whether raised SUA concentrations offer protection against free radical activity in the setting of chronic oxidative stress as observed, for example, in hypercholesterolaemia, regular smoking, or diabetes mellitus.

Perhaps somewhat paradoxically uric acid possesses pro-oxidant properties and, under certain circumstances, can promote oxidation of low-density lipoprotein [44]. This effect can be inhibited by ascorbic acid [45], indicating that the redox potential of SUA may depend on interactions with other aqueous antioxidants. If uric acid enhances oxidation of low density lipoprotein *in vivo*, then raised SUA concentrations could be expected to promote the development of atherosclerosis. Therefore, despite the widely held view that uric acid is an important antioxidant *in vivo*, there is a lack of data to clearly support its physiological relevance, or potentially beneficial effects of high circulating concentrations.

Uric Acid and Leukocyte Activation

Uric acid can stimulate vascular adherence of neutrophils and their subsequent degranulation, so that peroxide and superoxide free radicals are liberated in close proximity to the endothelium [46]. SUA is able to traverse dysfunctional endothelial cells, and can accumulate within developing atherosclerotic plaques [47], and urate crystals are found within atherosclerotic lesions, which may contribute to

further plaque progression by stimulating local vascular inflammation. This mechanism is underpinned by strong associations between SUA concentrations and systemic markers of inflammation, such as C-reactive protein [48], and suggests that high SUA concentrations could impair vascular endothelial function through leukocyte activation.

Uric Acid and Platelet Activation

Some, but not all studies have found that individuals with high SUA concentrations have excess platelet aggregability *ex vivo* in response to a variety of agonists, and urate within atherosclerotic plaques is known to stimulate platelet degranulation. Therefore, high SUA concentrations could promote cardiovascular risk through excessive platelet aggregability, which might predispose to thrombosis and atherosclerotic plaque progression. In health, endothelium-derived NO inhibits platelet aggregability and platelet adhesion to the endothelium. Therefore, an apparent association between high SUA concentrations and increased platelet aggregability may simply reflect a relationship between SUA and loss of NO bioavailability [49], particularly in patients with established cardiovascular risk factors.

URIC ACID LOWERING AND BLOOD PRESSURE

In animal models, hyperuricaemia is associated with the development of hypertension after several weeks, and may contribute to the development of salt sensitivity [28, 50, 51]. Prolonged exposure to high SUA concentrations causes preglomerular vascular abnormalities that perpetuate salt-sensitivity [29, 52]. Allopurinol, a xanthine oxidase inhibitor, has been used to study the effects of SUA lowering on systemic blood pressure. For example, in rat models of hyperuricaemia, allopurinol reduced SUA concentrations and was found to lower systemic blood pressure [28, 29, 50]. Similarly, allopurinol significantly lowered xanthine oxidase activity in dexamethasone-treated hypertensive rats, which was accompanied by reduced mean arterial blood pressure [53]. In the spontaneously hypertensive rat (SHR) strain, vascular xanthine oxidase activity is substantially increased compared to wild type [54]. Previous studies have reported conflicting reports about the effects of xanthine oxidase inhibition on blood pressure in this animal model. For example, one study found that administration of allopurinol caused virtually complete inhibition of renal xanthine oxidase activity but had no effect on blood pressure or progression to hypertension [55]. Other studies have found that xanthine oxidase inhibition causes a transient or modest reduction in systemic blood pressure in the SHR strain [56, 57]. In a SHR strain maintained on a high-salt diet, allopurinol delays the progression of left ventricular hypertrophy [55], suggesting that high SUA concentrations might be important in the development of target-organ damage in hypertension.

Few studies have examined the blood pressure effects of lowering SUA in people. A recent pilot study in adolescents with essential hypertension showed that administration of allopurinol 400 mg daily, for one month, caused normalisation of blood pressure in four of five patients studies [58]. In contrast, allopurinol administration had no significant effect on systemic blood pressure in patients with

Type II diabetes and mild hypertension [59], and those with chronic heart failure [37, 60].

There are a number of important limitations associated with allopurinol as a means of SUA lowering. For example, in people it causes only a modest reduction in SUA concentration, up to around 30% [61]. Inhibition of xanthine oxidase also prevents formation of hydrogen peroxide, a free radical that is thought to contribute to vascular dysfunction. In addition, allopurinol possesses antioxidant properties that are independent of its effects on xanthine oxidase activity [62]. Therefore, the potential cardiovascular effects of allopurinol could arise through a number of mechanisms, and its SUA-lowering effects require cautious interpretation [63].

CONCLUSIONS

An association between raised SUA concentrations and cardiovascular risk has long been recognised, and a number of potential mechanisms through which SUA could impair cardiovascular function have been identified. A relationship between high SUA concentrations and increased risk could possibly be explained on the basis of its associations with established cardiovascular risk factors. Further basic and clinical research is required to establish whether SUA, as a potential causal risk factor, can cause vascular dysfunction *in vivo*. Examining the effects of raising or lowering SUA concentrations on endothelial function, or progression of atherosclerosis in experimental models, might address this question more directly than observational studies have previously allowed.

High SUA concentrations reliably indicate groups of patients at increased cardiovascular risk across both unselected populations and patients with hypertension. However, it is uncertain to what extent SUA measurements can be used to enable risk stratification for individual patients given that a large number of potential confounding factors are capable of influencing SUA concentrations. Risk evaluation in patients with hypertension should be strongly based on established causal risk factors, namely blood pressure, serum cholesterol concentrations, smoking status, presence of diabetes and family history of premature cardiovascular disease. Within the context of conventional risk assessment, high SUA values might, in certain patients, indicate additional cardiovascular risk that is not fully accounted by other factors alone. At present, there is no compelling evidence of benefit associated with SUA lowering therapy in the context of overall cardiovascular risk management. Animal models have suggested favourable effects of xanthine oxidase inhibition on blood pressure and complications of hypertension. Further clinical trials are required to explore the potential impact of lowering SUA on blood pressure and longterm cardiovascular risk. High SUA concentrations should be interpreted as an important marker of global cardiovascular risk, which appears heavily co-dependent on other established risk factors. At present, insufficient evidence exists to support the role of SUA as an independent causal factor.

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