Resurrection of Uric Acid as a Causal Risk Factor in Essential Hypertension

Richard J. Johnson, Dan I. Feig, Jaime Herrera-Acosta, Duk-Hee Kang

In his landmark paper describing the entity of essential hypertension, Frederick Akbar Mahomed observed that many hypertensive subjects came from gouty families, leading him to suggest uric acid as a causal factor in the blood pressure response. Ten years later this hypothesis was championed by Haig, who proposed low purine diets as a means to prevent hypertension and vascular disease. During the same period the French academician, Henri Huchard, noted that renal arteriolosclerosis (the histological lesion of hypertension) was primarily observed in 3 groups: those with gout or lead poisoning or those with a diet enriched in fatty meat, all conditions associated with hyperuricemia.

During the early 1900s there continued to be reports linking uric acid with hypertension. In the 1960s and 1970s, at a time when hyperuricemia was present in ~5% of the US population, an elevated uric acid level was observed in 40% to 60% of hypertensive subjects; similarly, hypertension was observed in 50% to 65% of subjects with gout. Cannon et al reported that hyperuricemia was observed in 25% of untreated hypertensive subjects, 50% of those on treatment, and 75% to 100% of those with malignant hypertension or renal dysfunction. Population-based studies also found an increased frequency of hypertension with stepwise increases in serum uric acid levels in both blacks and whites.

Whereas these studies confirmed initial impressions of a close association of uric acid with hypertension, the studies did not address causality. Indeed, most authorities proposed that the presence of hyperuricemia in the hypertensive subject likely reflected the fact that an elevated renal vascular resistance (which is present in hypertension) may favor increased reabsorption of urate and because the hypertensive phenotype often carries similar characteristics as the patient with gout (with increased frequency of obesity, alcohol use, renal dysfunction, male gender, black race, and diuretic use). As a consequence, uric acid levels are largely ignored in medical practice, the uric acid measurement was removed from the routine laboratory (SMAC-20) panel, uric acid is not considered a risk factor for hypertension by either the American Heart Association or the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and asymptomatic hyperuricemia is currently considered benign and not requiring treatment.

A key experiment that had not been performed was to determine the effect of mild hyperuricemia on blood pressure in animals. In this regard, most mammals have a low serum uric acid level because of the presence of uricase, a hepatic enzyme that degrades uric acid to allantoin. However, in humans the uricase gene is mutated, resulting in uric acid levels that are both higher and less regulatable than in other mammals. Interestingly, when mild hyperuricemia was induced in rats by the administration of a uricase inhibitor, they became hypertensive. Further studies showed that the hypertension in this model was mediated by 2 mechanisms. The first mechanism resulted from uric acid–induced renal vasoconstriction mediated by endothelial dysfunction with reduced NO levels and by activation of the renin-angiotensin system. This hypertension type is salt-resistant in that it occurs even in the presence of a low-salt diet, and it responds to lowering of uric acid. Later, however, the hyperuricemia causes progressive renal microvascular disease (a lesion resembling arteriolosclerosis), and once sufficient narrowing of the arteriolar lumen occurs, a component of the hypertension becomes salt-driven, renal-dependent, and independent of uric acid levels. Finally, further studies demonstrated that this microvascular disease resulted from direct effects of uric acid, in that the urate was shown to enter into the vascular smooth muscle cell where it caused cell proliferation, activated the local renin-angiotensin system, and stimulated the production of various inflammatory mediators including CRP and monocyte chemoattractant protein-1 (reviewed in Reference 17).

The identification of a biological mechanism by which uric acid could cause hypertension in humans has led to a renewed interest in the role of uric acid in hypertension. Indeed, there are now 9 studies that have examined whether an elevated uric acid level predicts the development of hypertension, and all found uric acid predictive (Table 1). In all studies the risk for the development of hypertension was consistent and dose-dependent, and in the 8 studies in which multivariate analysis was performed to control for variables such as obesity, uric acid was always found to be an independent predictor (Table 1). Two of these studies are published in this issue. The first study, the Bogalusa Heart Study, found that uric acid levels in childhood predict the development of diastolic hypertension 10 years later. The second study, from the Framingham group, also found uric acid to predict...
the development of hypertension.26 This latter study is all the more remarkable as it was performed in an older population (mean age 50) in which they first eliminated 25% of their subjects because they already had hypertension or gout, thereby removing a large proportion of their target population.

Not only does uric acid predict the development of hypertension, but a recent study suggests that elevated uric acid is much more common in the new onset hypertensive patient than originally believed. In a study of new onset hypertension in adolescents, 89% of children with essential hypertension had a uric acid level >5.5 mg/dL versus 30% of secondary hypertension and 0% of white-coat hypertensive or control subjects. The relationship of uric acid to hypertension was independent of renal function or obesity and was strong and linear (r = 0.8).27 Finally, pilot studies suggest that lowering uric acid in the new onset hypertensive subject can normalize blood pressure,28 although one must be cautious because no placebo group was included. This has led to a National Institutes of Health double-blind placebo crossover trial, which is ongoing to determine the effect of lowering uric acid on blood pressure.

It has been 125 years since the original paper on essential hypertension and Mahomed’s hypothesis that uric acid may have a causal role, and still the controversy remains. However, studies such as those in this issue25,26 add to the increasing evidence that uric acid may have a true role in hypertension. Indeed, not only have Bradford Hill’s criteria for causation29 been satisfied (Table 2), but so have Koch’s postulates, if you are a rat (Table 3). However, not all of us are rats, and so we must await the careful clinical trials in humans to finally resolve these issues.

**Acknowledgments**

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**TABLE 2. Sir Bradford Hill’s Criteria**29 for Uric Acid as a Causal Factor in Hypertension

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Population</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan18 (1972)</td>
<td>10,000 males</td>
<td>2-fold relative risk at 5 years*</td>
</tr>
<tr>
<td>Selby19 (1990)</td>
<td>2062 subjects</td>
<td>3-fold relative risk at 6 years*</td>
</tr>
<tr>
<td>Hunt20 (1991)</td>
<td>1482 adults</td>
<td>2-fold relative risk at 7 years†</td>
</tr>
<tr>
<td>Jossa21 (1994)</td>
<td>619 males</td>
<td>1.2-fold relative risk at 12 years‡</td>
</tr>
<tr>
<td>Taniguchi22 (2001)</td>
<td>6356 males</td>
<td>2-fold relative risk at 10 years*</td>
</tr>
<tr>
<td>Masuo23 (2003)</td>
<td>433 males</td>
<td>A 1.0 mg/dL change in uric acid predicts a 27 mm Hg increase in systolic BP at 5 years</td>
</tr>
<tr>
<td>Nakanishi24 (2003)</td>
<td>2310 males</td>
<td>1.6-fold relative risk at 6 years*</td>
</tr>
<tr>
<td>Alper25 (2004)</td>
<td>577 children</td>
<td>Predicts diastolic hypertension at 11 years</td>
</tr>
<tr>
<td>Sundström26 (2004)</td>
<td>3119 adults</td>
<td>1.5-fold relative risk at 4 years*</td>
</tr>
</tbody>
</table>

*Highest tercile/quartile/percentile vs lowest tercile/quartile/percentile.
†Compared to 2 SD lower.
‡Per difference of 1 mg/dL.

**TABLE 3. Koch’s Postulates for Uric Acid as a Causal Factor of Hypertension**

<table>
<thead>
<tr>
<th>Postulate</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>An elevated uric acid predicts the development of hypertension (see Table 1).18-26</td>
</tr>
<tr>
<td>2.</td>
<td>An elevated uric acid is observed in 89% of new onset essential hypertension in adolescents and the level of uric acid correlates closely (r = 0.8) with the systolic BP.27</td>
</tr>
<tr>
<td>3.</td>
<td>Raising serum uric acid in rats results in the hemodynamic, pathological, and clinical characteristics of essential hypertension in humans.14-16</td>
</tr>
<tr>
<td>4.</td>
<td>A plausible biological mechanism has been shown in which uric acid induces a salt-resistant hypertension by inhibition of endothelial function and activation of the renin-angiotensin system, and a later salt-sensitive renal dependent hypertension by inducing microvascular disease; these changes are consistent with studies of hypertension in humans reviewed in Reference 17.</td>
</tr>
<tr>
<td>5.</td>
<td>Lowering uric acid in hyperuricemic rats prevents or treats new onset hypertension in rats:14,16 pilot studies in humans also suggest lowering uric acid may lower BP in new onset essential hypertension in adolescents.28</td>
</tr>
</tbody>
</table>
References

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