Associated Risk of Cardiovascular Disease with Elevated Uric Acid

Evidence-based support for an association between increased xanthine oxidase activity and hyperuricemia with risk of cardiovascular disease

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Disclosures

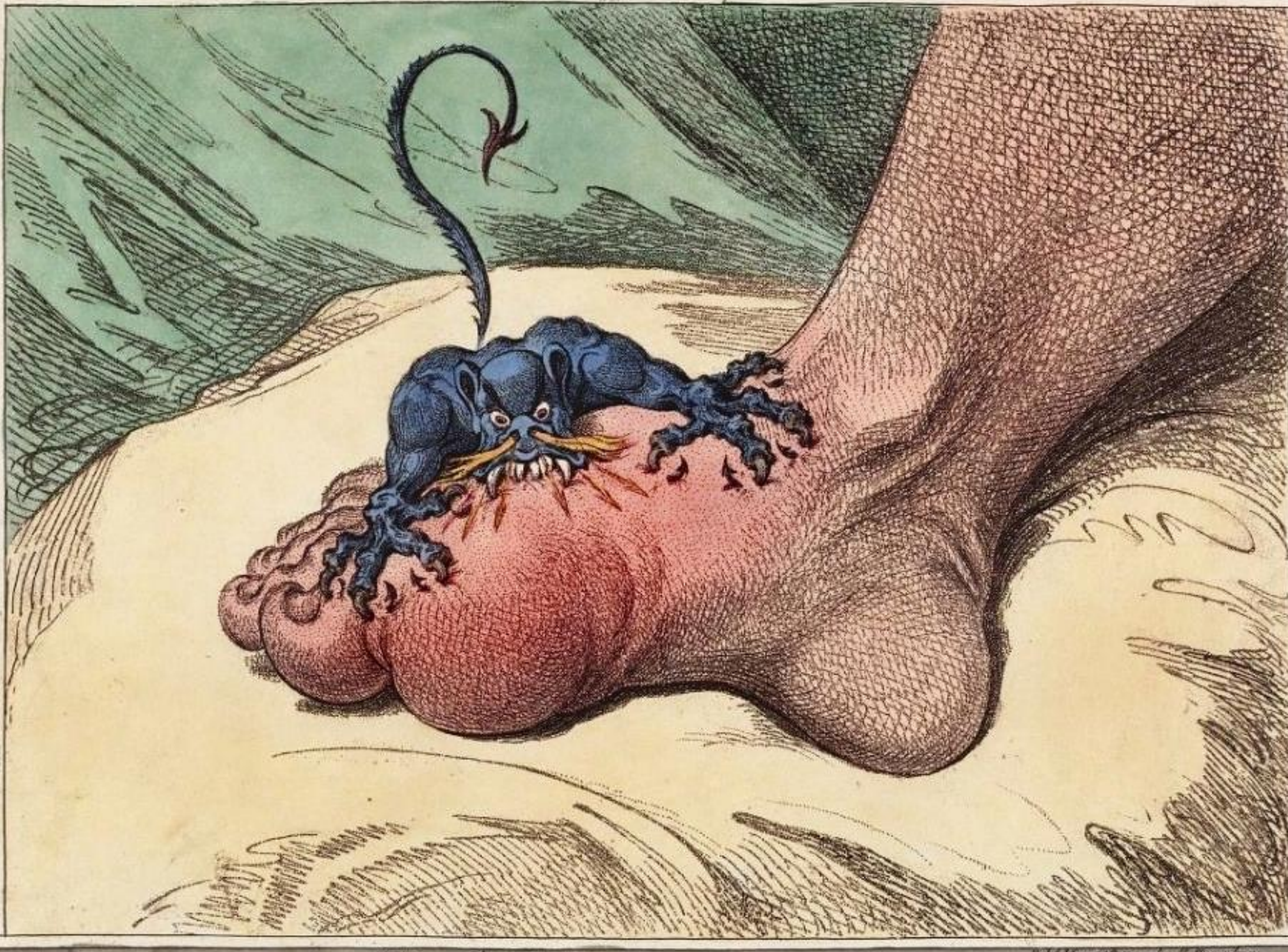
There are no conflicts of interest with this lecture.

My disclaimers are that I serve on advisory or speaker bureaus for the following:

- Abbvie, Genentech, Celgene, Crescendo, Sonosite

Objectives

- Review the body of evidence regarding Uric Acid’s place in regard to cardiovascular disease states
- Gain an understanding of inflammatory effects of Uric Acid via understood and proposed mechanisms
- Discuss a proposed mechanism of Uric Acid’s ability to promote cardiovascular disease.
- Discuss current findings and practices regarding the treatment of hyperuricemia



The GOUT.

Pub.d May 14th 1799. by H. Humphrey
27 St James's Street

- A 54-year-old male presents for a routine evaluation for hypertension. He currently has no complaints.
- BP: 142/90 Pulse 72
- Laboratory studies reveal normal kidney function but an elevated uric acid of 8.9 mg/DL

- Does the elevated uric acid affect your evaluation and treatment?

- The relationship of gout with hypertension, diabetes, kidney disease and CVD known since 19^{th} century

- In 1897, in his presidential address to the American Medical Association, Dr. Davis wrote, "High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increase the tonus of the [renal] arterioles."19

Hyperuricemia as a Predictor of Hypertension

- Hyperuricemia turns out to be a fairly good predictor of hypetertension[20,77, 19]
  - Hyperuricemia typically defined in studies as >7.0mg/dL
  - This has multiple proposed mechanisms

Treating Hypertension with Urate Lowering Therapy

- Feig et al.(2008) Small randomized control trial giving adolescents with newly diagnosed HTN 200 mg BID Allopurinol vs. Placebo [20]
  - There was a small, but statistically significant reduction of systolic blood pressure in the Allopurinol group

Hyperuricemia's Relation to Cardiovascular Disease

Combined retrospective and prospective analyses show mixed data on other outcomes:

- Coronary Heart Disease
- Congestive Heart Failure
- Cardiovascular Mortality Outcomes

- Cardiovascular Disease is a heterogeneous group of diseases, making it difficult to establish a clear link to hyperuricemia

- Is hyperuricemia a bystander, or is there a role of possible pathogenesis?

Other Facets of Cardiovascular Disease and Hyperuricemia- A Complicated Question

- Cardiovascular Disease, including CHD, CHF and Mortality have multiple confounding variables

- Comorbidities are often present as well
  - Hyperinsulinuemia results in sodium retention, as well as elevated Uric Acid
    - This complicates the picture of incident hypertension in hyperuricemic patients
  - Hyperuricemia may be a consequence of multiple disease states in various studies, rather than the cause[23,77]
    - Hypertension, for instance is a known risk factor for CHD

Coronary Heart Disease and Hyperuricemia

- Weak association is present with CV mortality in patients with hyperuricemia (>7.0mg/dL) without taking into account gout attacks[46,77]

- After MI, increased serum UA was shown to have an increased 30 day and long-term mortality
  - Associated with worsening Killip class, a classification predicting mortality[45,77]

Coronary Heart Disease and Hyperuricemia

- On First Look- Hyperuricemia has no association with CHD
  - Framingham
    - Adjusted for other cardiovascular risk factors
  - British Regional Heart Study
    - Adjusted for other cardiovascular risk factors as well in men with prior MI [9,77]
    - It does not appear that hyperuricemia is an independent risk factor for CHD

- Severity and adverse outcomes may have association with hyperuricemia[54,77]
  - CHD Related Death- HR of 1.26 risk (95% CI 1.15-1.38) for every 1mg/dL increase in UA in a Cleveland Clinic based study [35,77]
  - Gout flares may be a predictor of CHD related death
    - MRFIT trial showed that gout patients had an increased risk of CHD death and death from any cause vs. those without gout over 17 year period[77]

Congestive Heart Failure in Relation to Hyperuricemia

- There is an increased risk of new-onset HF and Hyperuricemia in specific populations
  - Patients with normal insulin levels [11,77,17]
  - Subgroup analysis: [17]
    - Those without thiazide diuretic use
    - Those without hypertension
    - Patients without hyperinsulinemia
    - Patients with normal kidney function
- Increased mortality risk in patients with existing systolic HF with hyperuricemia [2,76]

Poor Clinical Indicators in Heart Failure Patients Associated with Hyperuricemia

- Diastolic dysfunction by echocardiogram [7,77]
- Increased right atrial pressures [77]
- High pulmonary vascular resistance indices [77]
- Endothelial dysfunction [1,77]
- Lower cardiac index [42]
- Cachexia [12]

Mortality Outcomes Associated with Hyperuricemia Show Positive Association

- Increased attention is being given to uric acid as a prognostic factor

- After MI, increased serum UA was shown to have an increased 30 day and long-term mortality[45,77]

- There is an association between Hyperuricemia and Cardiovascular Mortality[6,17,21,43,46,55]
  - The Framingham Studies and British Regional Health Studies did not show a positive association
    - As we previously discussed, this is likely negating the effect of hyperuricemia in the pathogenesis of CVD risk factors

    - NHANES-1 Study:
      - HR 1.09 in Men per approximately 1mg/dL increase[17]
      - HR 1.26 Women per approximately 1mg/dL increase[17]

Mechanism of Injury, Inflammation, and Vascular Response to Uric Acid and Xanthine Oxidase Activity

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Mechanism of Gouty Inflammation

- Monosodium Urate (MSU) Crystal induced inflammation
  - MSU crystals trigger the innate immune system, acting as Danger Associated Molecular Patterns (DAMPs)
  - NLRP3 Inflammasome is activated in response to the presence of DAMPs
    - conversion of pro-IL1 to IL1[67]

Gout Link to CV Disease?

- There is a confusing body of evidence that Uric Acid may be related to Cardiovascular Disease
- MSU crystals have been identified within human aortic atherosclerotic plaques[59]
- Little evidence exists for MSU having direct cardiovascular consequence through its effect on the NLRP3 Inflammasome in vascular endothelial cells

- The NLRP3 Inflammasome is, however, active within atherosclerotic plaque
  - This is triggered by Cholesterol Crystals, acting as DAMPs to stimulate the inflammatory cascade necessary to propagate the inflammatory process of atherogenesis[10,52,62]
  - Reactive Oxygen Species (ROS) are also involved in the stimulation of the NLRP3 Inflammasome[10,73,79]

- Uric Acid in its soluble form may not be involved in directly activating the NLRP3 Inflammasome to result in cardiovascular disease
  - What other mechanisms may exist for uric acid to mediate a role in CV Disease?

Proposed Mechanisms for Uric Acid to Affect the Cardiovascular System

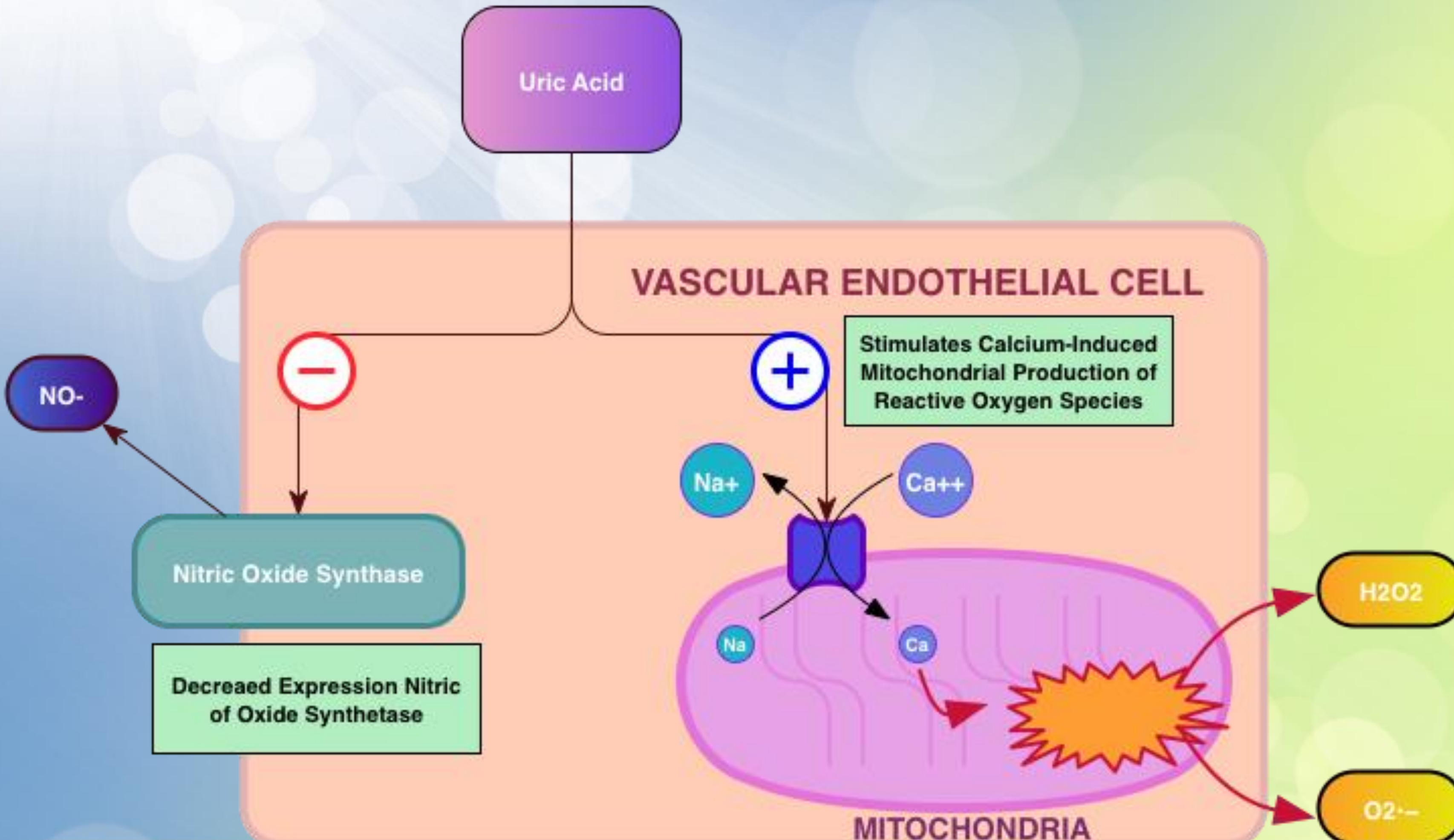
- Four major models exist:
  - Decrease in Nitric Oxide (NO) Production
    - NO facilitates vascular relaxation while inhibiting platelet and leukocyte adhesion to vascular endothelium
      - Also prevents smooth muscle proliferation[8]
  - Generation of Reactive Oxygen Species[72]
    - Resulting in Vascular Damage and decreased NO levels
  - Increased Renin Production
    - Ultimately leading to hypertensive mechanisms
  - Vascular Remodeling via Production of CRP
    - Smooth muscle proliferation results in increased arterial tone

Uric Acid Results in Decreased Nitric Oxide Production

- Uric Acid results in decreased Nitric Oxide (NO) and decreased Vascular Endothelial Nitric Oxide (eNOS) levels[25,34,38, 41]

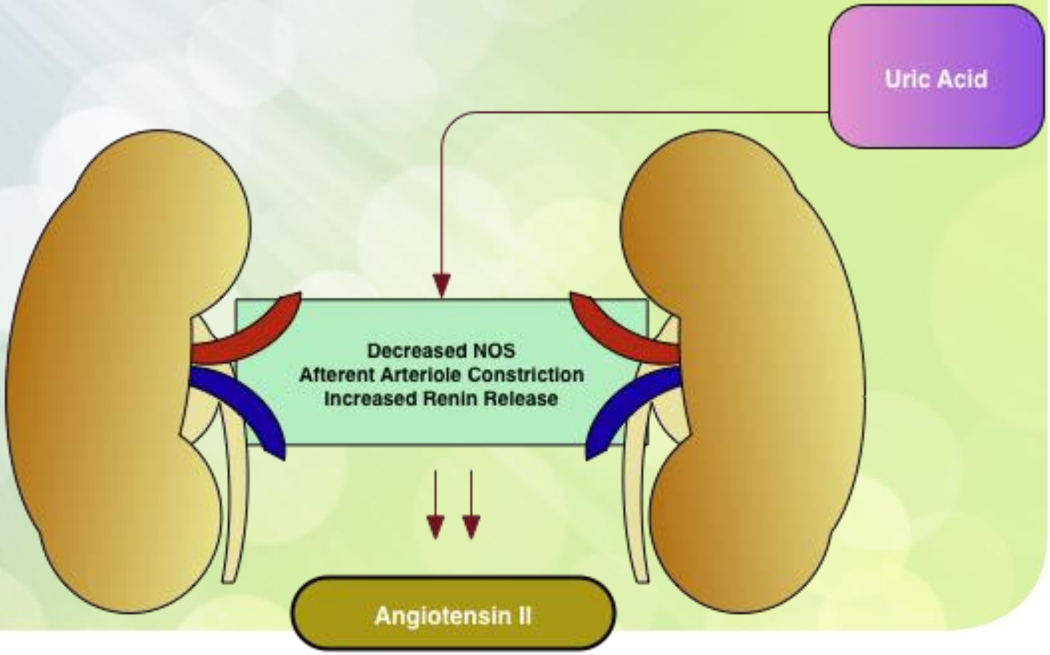
- Uric Acid's effect also seems to be due to it's ability to generate mitochondrial reactive oxygen species[34]

Vascular Endothelial Stimulation by UA Leads to ROS and Decreased NO via eNOS Suppression

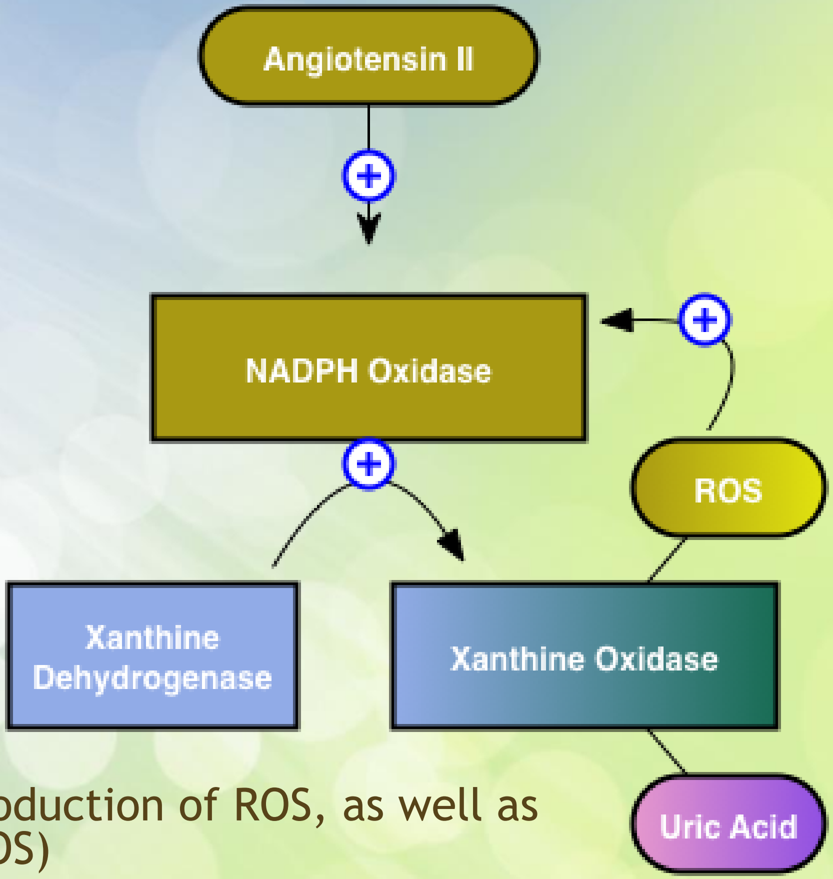


Uric Acid Results in Increased Renin Levels

- Inducing Hyperuricemia appears to result in hypertension
- Uric Acid increases juxtaglomerular renin release
- Decreased levels of neuronal NO in the macula densa
  - Juxtaglomerular NOS1 expression was decreased
  - Renal biopsies were characteristic of ischemic injury
    - Allopurinol blocked this effect!!!



Increased Uric Acid Results in increased renin activity, thereby increasing Xanthine Oxidase (XO) levels, creating more Uric Acid as well as Reactive Oxygen Species



- Xanthine oxidase is involved in the production of ROS, as well as inhibition of Nitric Oxide Synthase (NOS)
  - XO can have this effect without the presence of xanthine or hypoxanthine[4,29]

Uric Acid Induces Vascular Remodeling

- Uric Acid induces vascular remodeling
  - Stimulated smooth muscle cells show an increase in migration, with a decrease in the epithelial cell migration.
  - Neutralizing CRP negated the effect of Uric Acid's Vascular Remodeling[39]
- Induction of hyperuricemia results in arteriolar thickening and hypertension
  - This was also prevented with Allopurinol

A Closer Look at Atherosclerotic Plaques

- Atherosclerotic plaques have uric acid in the plaque burden, as well as increased activity of xanthine oxidase[58,59]

- What happens to plaque when allopurinol is added?

Major Effects of Endothelial Xanthine Oxidase Activity

- Increased production of Uric Acid
- Decreased capacity for vasodilation
- Oxidative stress in the vasculature
  - Reactive Oxygen Species (ROS) are of primary concern[68]

Scenarios with Increased Xanthine Oxidase Up-regulation

- Hypoxemia
  - Subsequent activation of NADPH
  - Increased conversion of xanthine dehydrogenase to XO
    - XO Seems to play a part in reperfusion injury[71]
- Hypertension
  - Particularly in setting of increased Angiotensin II levels[4]
  - When induced by salt heavy diets
- Suboptimal cardiac rhythms and ventricular dysfunction[14]
- Congestive Heart Failure[29,30,48]

Xanthine Oxidase Activity in Relation to Hypertension

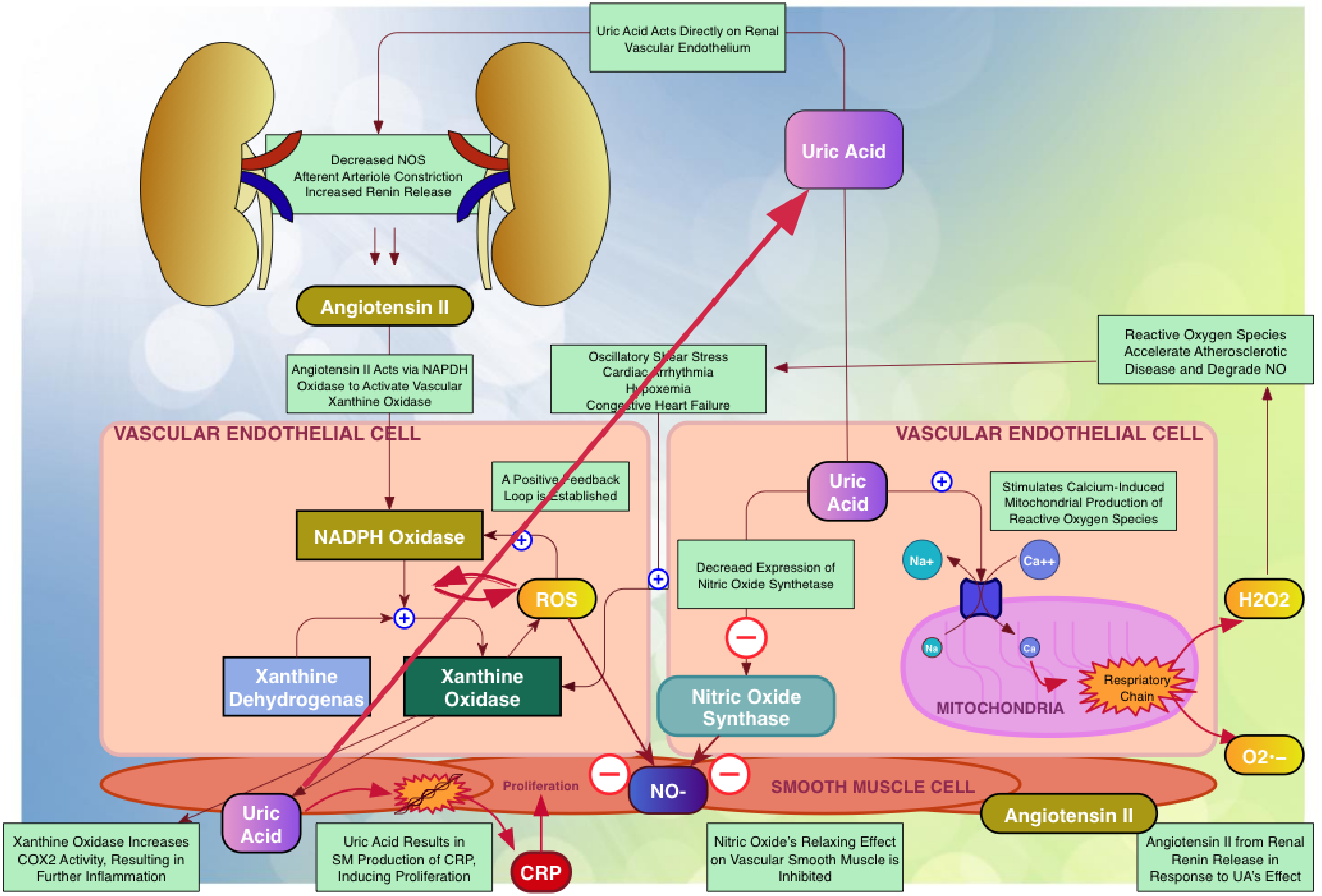
- Angiotensin II activity and hypoxemia[14,47,51] both result in increased NADPH Activity
- This results in activation of Xanthine Oxidase
  - This may in part explain some of the physiologic benefit derived from ACE-I therapy[4]
- Xanthine Oxidase produces reactive oxygen species in addition to uric acid[29,30,69]
- Reactive oxygen species result in further increase in NADPH Activity
- A Positive Feedback Loop may result:
  - Xanthine oxidase produces hydrogen peroxide, resulting in activation of NADPH oxidase.
  - NADPH oxidase produces ROS that increase the conversion of XO from XDH in endothelial cells.

How does increased Xanthine Oxidase activity lead to physiological changes?

- Increased Xanthine Oxidase results in:
  - Reactive Oxygen Species
    - Partly via Production of Uric Acid
    - Primarily Through its Generation of Reactive Oxygen Species (ROS) [29,30,69]
  - Decreased Nitric Oxide production
  - Activation of Cyclooxygenase 2
  - Increased uric acid production

XO expression and COX2

- XO transcription and activity results in increased COX-2 levels[4,29,57]
  - XO may regulate vascular COX-2 levels to some extent
  - Cells cultured with Hypoxanthine or UA show increased COX-2 expression



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What initiates the hyperuricemia and up-regulation of xanthine oxidase in patients with preclinical hyperuricemia?

- High Fructose Diets
  - This has been demonstrated to increase serum and urine urate concentrations since the 1970s[61]
  - Fructose induces hyperuricemia in hepatocytes[53]
- High sodium Loads
  - Inducing hypertension in rat models result in increased uric acid
- Smoking and chronic hypoxemia
- Oscillatory shear force of vessels

Current Trials and Outcomes of Urate Lowering Therapy

What effect does xanthine oxidase inhibition provide?

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Studies supporting xanthine oxidase inhibition

- LIFE study- Losartan was superior in reducing CV events compared to atenolol
  - Perhaps explained by losartan's uricosuric effect
  - Effect is possibly attributable to blockade of Angiotensin II, which is known to further increase xanthine oxidase activity levels[28,33,77]

Urate Lowering Therapy in Heart Failure

- EXACT-HF trial recently failed to show benefit of Allopurinol in patients with Heart Failure characterized by EF <40%
  - Outcomes were 6 minute walk test and Kansas City Cardiomyopathy Questionnaire[26,77]

Benefits of Urate Lowering Therapy in Heart Failure

- Patients treated with Allopurinol after TIA or ischemic stroke had reduced carotid intima-media thickness at 1 year, with lower central blood pressure when compared to placebo[27,77]
- High-dose Allopurinol regresses LVH, reduces LV end-systolic volume, and improves endothelial function in patients with IHD and LVH[63]
  - Patients with type 2 Dm and LVH randomized to 600mg Allopurinol daily vs. placebo showed regression of LVH[70,77]
- In canine models, Allopurinol prevents both structural and electrical remodeling of the myocardium, atrial fibrosis, and also prevented reduction in eNOS[64,77]
- IV Allopurinol in non-ischemic CM causes an increase in the myocardial ATP concentration, supporting the theory that XO inhibition prevents the breakdown of ATP[32]

Urate Lowering therapy in Heart Failure results in:

- Improved Peak Blood Flow[13,18,13,77]
- Increased Myocyte Efficiency[5, 74, 44]
- Decreased neutrophil chemotaxis during reperfusion with Allopurinol Therapy[37,71]
- Allopurinol enhances ventricular function in canine CHF induction models via pacing[15,64,77]

Why is the data unclear?

- The benefit for heart failure (a heterogeneous disease) is not homogenous
- Xanthine oxidase inhibition may not benefit every heart failure patient equally though.
  - OPT-CHF trial used 600mg oxypurinol vs. placebo[30,77]

- Xanthine Oxidase Inhibition Appears to Hold the Most Clinical Promise[44,56,77]
  - Uricosuric Agents seem to be ineffective
- In rat models, both uricosuric mechanisms and xanthine oxidase inhibition reverse hypertension caused by hyperuricemia[50]

Other potential routes of treatment: Febuxostat

- Little data exist for Febuxostat's capacity to improve CV outcomes
  - Some skepticism exists due to cardiovascular warning on package insert
    - Ongoing studies regarding CV safety non-inferiority
- Febuxostat is a non-purine derived drug, and may be able to target xanthine oxidase in a manner that causes more profound inhibition and ultimately better outcomes in the right population
  - In treating hyperuricemia, Febuxostat has proven to be quite potent in lowering serum urate levels

Current Guidelines for Urate Lowering Therapy

- US recommendations on Urate Lowering Therapy[40]
- Indications for Urate Lowering Therapy- Established Gouty Arthritis and:
  - Patients with tophus /tophi
  - Two or more attacks per year
  - Stage 2 or worse CKD
  - History of Urolithiasis

Conclusion

- There is significant evidence that Uric Acid and Xanthine Oxidase activity are involved in the development of vascular dysfunction
- Previous therapeutic trials have shown promise, although outcomes have not been consistent
- Many of the large retrospective studies do not show an effect of uric acid on cardiovascular outcomes when adjusted for factors such as hypertension
- In sub-populations of patients with CVD, uric acid and xanthine oxidase activity may play an important role, even if this does not relate to all-cause CVD
- Uric Acid mediates inflammation in its non-crystalline form, and likely has a direct role in production of ROS and endothelial dysfunction

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