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Xanthine Oxidase Inhibitors in Heart Failure: Where Do We Go From Here?

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Despite its public health impact, there are relatively few classes of drugs in use for the treatment of heart failure (HF) and left ventricular dysfunction.[1] HF pharmacology is based upon relatively few signal transduction pathways – most prominently the sympathetic nervous system and the renin angiotensin aldosterone system.[1] As such the quest for additional therapeutic targets remains critically important, and in this regard oxidative stress/ nitroso-redox imbalance is a potential target of long standing interest.[2]

Several lines of evidence support that this pathway may be of pathophysiologic relevance. First, serum uric acid (SUA) is a biomarker of oxidative stress in several cardiovascular diseases including heart failure.[3–5] This elevation of SUA is primarily due to the increased amounts of available xanthine and hypoxanthine after cellular damage, which is then catalyzed into uric acid via xanthine oxidase (XO).[6] XO uses oxygen as a potential electron acceptor, thus forming reactive oxygen species (ROS) resulting in oxidative stress.[6]

Several observational studies and meta-analysis have identified elevations of SUA as an independent marker of poor cardiac function, mortality, poor functional capacity as well as the development of atrial arrhythmias in heart failure.[7–10] Thus an active hypothesis is that SUA may not only represent a prognostic biomarker of heart failure but may also represent a potential target for intervention.

A second line of evidence emerges from experimental studies exploring the role of XO in heart failure, showing first and foremost an upregulation of this enzyme in the cardiovascular system.[6] Furthermore, preclinical animal data supported the use of XO inhibitors in heart failure showing greater survival, improved left ventricular function, enhanced mechanoenergetic coupling, attenuation of ventricular remodeling, decrease in

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myocardial oxygen consumption, reduced afterload and improved ventricular vascular coupling.[11,12] In humans, intracoronary and intravenous allopurinol improved myocardial efficiency and increased the concentration of high-energy phosphates within the heart.[3,13] Therefore, XO inhibitors in animals and humans improve cardiac function enhancing mechanoenergetic coupling while reducing myocardial oxygen consumption and improving afterload. An important insight however is that the enhancement of mechanoenergetic coupling depends on the degree XO overexpression in heart failure animal models.[6]

A third line of evidence is supported by nested case-control and retrospective cohort studies showing a decrease in heart failure readmissions as well as all-cause mortality in patients with gout who receive allopurinol.[14,15]

Together these findings have prompted a series of clinical trials examining XO inhibition in patients with HF. In this issue of *Circulation*, Givertz and colleagues[16] report the results of the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) trial, a double blind, multicenter randomized trial that compared guideline adherent therapy plus allopurinol to guideline adherent therapy alone in a high risk HF population with elevated SUA. In this study XO inhibition with allopurinol did not improve functional capacity, clinical status or left ventricular ejection fraction. Other randomized studies have reached similar conclusions and are summarized in Table 1.[17–21] The randomized studies of XO inhibition in HF consistently fail to show improvement in clinical composite outcomes. It is important to note however that two studies, including the EXACT-HF trial, do show trends toward improvement of secondary outcomes like hospitalizations and ejection fraction.[16,21] The results seem to be independent of the severity of the HF, patients enrolled, the use of active metabolites of XO inhibitors and dosages to decrease uric acid, as well as the use of different clinical composite outcomes. Another potential caveat from the randomized trials is that long-term effects of these medications remain unknown since the trials had relatively short-term follow-up.

The study by Givertz is based in part on the Oxypurinol Therapy for Congestive Heart Failure (OPT-CHF) trial results which compared xanthine oxidase inhibitors to guideline therapy. In post-hoc analysis of this study oxypurinol showed a potential benefit in HF patients with elevated SUA and this benefit correlated to the degree of SUA reduction. This study contributed to the rationale for the present study, which employed elevated SUA as an enrollment criteria in order to select for a group of patients with elevated XO.

Potential epidemiological explanations for the negative findings reported by Givertz[16] and others include the possibility that SUA might be just a marker of disease severity and prognosis and not a target for therapy. Also, a combination of sample size, low event rates and short follow-up time could have limited the ability to detect a real long-term effect shown as a trend towards lower hospitalizations in the allopurinol group reported in this study. Another potential but unlikely explanation could lie in the use of oral medications subject to first pass effect metabolism of the liver since the available experimental results in humans used parental allopurinol.[3,13] This is an unlikely theory because there was a significant decrease in SUA.

The non-significant findings of EXACT-HF and other studies prompt an examination of the pathophysiological mechanisms that are the basis for this novel therapeutic strategy. A leading possibility explaining the lack of response to XO inhibition could be the fact that this pharmacologic strategy only addressed one of two limbs underlying nitroso-redox imbalance (Figure 1). In HF, not only are ROS generating pathways upregulated but important aspects of reactive nitrogen species (RNS) production are downregulated.[2]

Three important factors related to the nitroso-redox balance might have bearing on the findings by Givertz and colleagues.[16] First, other enzymes and metabolic pathways contribute to nitroso-redox imbalance, including other enzymes that produce ROS (NADPH oxidase enzymes and the respiratory chain in the mitochondria), superoxide dismutase that neutralizes superoxide, and the family of nitric oxide synthases (NOSs) which produces nitric oxide (NO). Selective XO inhibition might be inadequate to curtail the cascade of ROS accumulated in HF and, very importantly, this is supported by the present study because myeloperoxidase levels did not change. Second, we now know that the nitroso-redox balance is intimately interconnected. This is supported by a series of experiments that found that NO binds superoxide to produce peroxynitrite, NO modulates the expression of XO, NOS inhibitors abolish the contractile effect of XO inhibitors and XO inhibition can actually decrease NO production.[6,22] NOS1 deficient animal models have proven an increase in mortality, left ventricular remodeling, and ventricular arrhythmias after myocardial infarction.[23,24] Thus, inhibition of XO in the failing circulation may fail to have beneficial effects if NOS activity and/or signaling is also depressed; XO inhibition may affect only one limb of the nitroso-redox imbalance.

Thus, the results of EXACT-HF add another important data point in the quest to unravel whether aspects of nitroso-redox imbalance have potential as a therapeutic target. The trial suggests that XO inhibition even in high SUA heart failure patients alone is inadequate to improve clinical outcomes. As this field progresses it will be crucial to examine other limbs of this balance and to ask whether augmenting NO production concomitantly with inhibition ROS production will have clinical benefits in HF.

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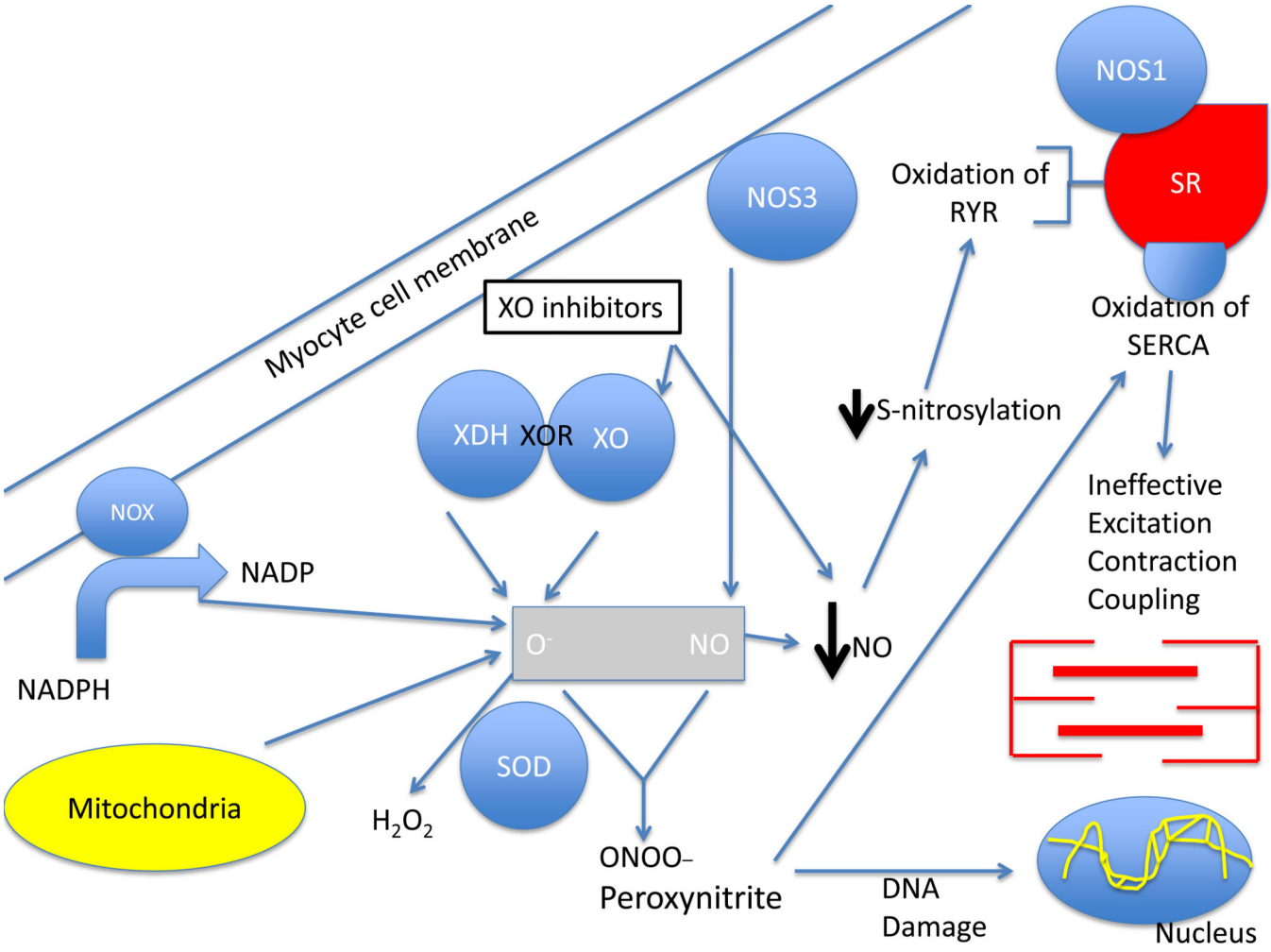

Figure 1.

Effect of XO inhibition on the nitroso-redox balance. The underlying mechanistic basis for the use of xanthine oxidase inhibitors in the failing heart. As depicted xanthine oxidase inhibitors (XOI) act on one key enzyme – XO/XDH – to inhibit ROS production but has other actions that might detract from full restoration of nitroso-redox balance. XOI decrease serum uric acid and superoxide production by inhibiting xanthine oxidase. Importantly, however, there are other sources of ROS production in the failing heart, including mitochonrdrial respiration and NADPH oxidases, that are not affected by XOI. In addition, NOS activity may be impaired in heart failure, or further disrupted by XOI. In states of inadequate NO production, oxidation or diminished S-nitrosylation of the RYR receptor and other key proteins involved in excitation-contraction coupling impairs calcium cycling which drives optimal myocardial performance. Persistent ROS production also consumes NO and leads to peroxynitrite formation which can cause DNA, protein and lipid damage. Peroxynitrite oxidizes the calcium ATPase SERCA (responsible for calcium reuptake into the SR). Thus, NO continues to be depleted by XO inhibition perpetuating nitroso-redox imbalance and causing ineffective excitation-contraction coupling. Abbreviations: XOR: xanthine oxidoreductase, XO: xanthine oxidase, XDH: xanthine dehydrogenase, O^{-}:

Superoxide, NO: nitric oxide, NADPH: nicotine adenine dinucleotide phosphate, NOX: NADPH oxidases, ^{2}NOS: nitric oxide synthase, SOD: superoxide dismutase, SR: sarcoplasmic reticulum, SERCA: sarcoplasmic reticulum calcium ATPase, RyR: ryanodine receptor.

Table 1

Comparison of randomized studies using xanthine oxidase inhibition in heart failure.

Author	**Heart failure Population**	**Xanthine oxidase inhibitor**	**Follow-up in weeks**	**Primary Outcome definition**	**Primary outcome result**
Givertz et al. 2015	253 with SUA >9.5 mg/dl with one more high risk marker	Allopurinol 300–600 mg/day	24	Clinical status: Outcomes, medication change and patient global assessment.	13% improved in both allopurinol and placebo arms.
Greig et al. 2011	32 NYHA II–III	Allopurinol 300 mg/day	4	6-minute walk test and oxidative stress markers	No difference in 6-minute walk test and improved oxidative markers
Nasr et al. 2010	59 NYHA III–IV	Allopurinol 300 mg/day	36	Composite endpoint: Global cardiac function and mortality/morbidity	Allopurinol did not improve composite endpoint
Hare et al. 2008	405 with a median SUA of 7.8 mg/dl and NYHA III–IV	Oxypurinol 600 mg/day	24	Clinical status: Outcomes, medication change, patient global assessment or NYHA	43% improved in the oxypurinol arm compared to 45% in the placebo arm. Improved primary outcome in patients with higher uric acid levels
Cingolani et al. 2006	60 NYHA II–III	Oxypurinol 600 mg/day	4	Ejection fraction	4.7+/− 2.6 % higher EF between oxypurinol and placebo arms
Gavin et al. 2005	50 NYHA II–III	Allopurinol 300 mg/day	12	Exercise stress test and 6 minute walk test	No difference in exercise performance with a decrease in plasma BNP.

SUA: Serum uric acid, NYHA: New York Heart Association, EF: ejection fraction, BNP: Brain natriuretic peptide