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Novel Therapeutic Strategy for Ventricular Dysfunction?

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Myocardial dysfunction and heart failure perturb cardiovascular homeostatic signaling pathways as well as initiate a program of molecular, biochemical, and structural modifications to remodel the failing ventricle. Accumulating evidence suggests that the cardiovascular redox state plays an integral role in these processes. In fact, in the failing heart, elevated levels of reactive oxygen species (ROS) and cardiomyocyte oxidant stress are associated with maladaptive ventricular remodeling and a progressive decline in cardiovascular function.

The association between ROS and heart failure has been established. Increased indices of oxidant stress have been measured in patients with congestive heart failure. In clinical studies, patients with heart failure were found to have evidence of lipid peroxidation and elevated 8-iso-prostaglandin $F_{2\alpha}$ levels[1–4] whereas in experimental models of heart failure, investigators have been able to directly measure increased ROS production from cardiomyocytes.[5,6] These findings have been corroborated in studies that measured ROS levels in explanted human hearts at the time of transplant.[7] Furthermore, a number of neurohormonal and mechanical stressors that are associated with the heart failure phenotype augment ROS generation.[8,9] Prolonged exposure to ROS, in turn, results in cardiomyocyte dysfunction.[10]

At a cellular level, elevated levels of ROS impair cardiomyocyte function by damaging ion channels as well as inhibiting contractility. ROS disrupt the structural integrity of ion channels via membrane lipid peroxidation.[2,11] ROS also decrease expression and activity of the sarcoplasmic reticulum Ca^{2+} ATPase SERCA2,[12] which is critical for effective cardiac calcium handling. Interestingly, ROS have also been shown to decrease myofilament calcium sensitivity by activation of ASK-1, a redox-sensitive kinase. ASK-1 phosphorylates troponin T and thereby decreases contractility and regulates calcium handling.[13]

Concomitant with these adverse effects on cardiomyocyte function, ROS stimulates a number of responses associated with the ventricular remodeling processes. These include ROS-mediated activation of matrix metalloproteinases to alter the architecture of the extracellular matrix,[14] modulation of signal transduction pathways that initiate cardiomyocyte hypertrophy,[15] and apoptosis or cell death.[16]

Taken together, these observations suggest that one mechanism to halt deleterious ventricular remodeling and abnormal cardiomyocyte functional responses is to decrease oxidant stress by limiting ROS production. ROS are derived from the superoxide anion, a one-electron reduction product of oxygen. In the myocardium, superoxide anion may be generated by both metabolic and enzymatic sources including mitochondrial respiration, xanthine oxidase (XO), NAD(P)H oxidases, and, when substrate or cofactors are not replete, uncoupled nitric oxide synthase(s).[17,18] In the failing heart, activation of these ROS-generating systems leads to the accumulation of superoxide anions and the formation of a number of pathophysiologically relevant reactive species including hydrogen and lipid peroxides, peroxynitrites, and peroxynitrous acids.

In the failing heart, there is experimental evidence to suggest that xanthine oxidoreductase (XOR), comprised of the isoenzymes XO and xanthine dehydrogenase (XDH), is an important source of ROS. Xanthine oxidase catalyzes the terminal steps in the catabolism of purines to uric acid in a series of reactions that reduce molecular oxygen to yield superoxide.[18] Studies have shown that XO expression, as well as activity, are increased in cardiomyocytes isolated from failing hearts.[19–22] In contrast, inhibition of XO activity with allopurinol or oxypurinol in rodent or canine heart failure models improved myocardial function, decreased myocardial oxygen consumption, and ameliorated myocardial contractility.[19] Although it was not shown conclusively that these effects resulted from inhibition of XO-generated ROS, other studies done with antioxidant agents suggest that this may be the case. Here it was found that treatment with high doses of the antioxidant ascorbate resulted in the same benefits that were seen with allopurinol.[20] Prolonged inhibition of XO with allopurinol in rodent models of post-infarction heart failure has also been shown to prolong survival, improve contractile function, and prevent ventricular remodeling.[21,23] These effects are believed to result from allopurinol-mediated XO inhibition and a resultant decrease in ROS levels.

In this issue of *Circulation Research*, Minhas et al extend these findings and demonstrate that XO inhibition initiates reverse remodeling in rats with established dilated cardiomyopathy.[24] In these studies, the authors used a rat model of heart failure, the spontaneously hypertensive/Heart Failure (SHHF) model and inhibited XO with oxypurinol. Treatment of SHHF rats with oxypurinol decreased ROS levels and improved hemodynamic and contractile parameters in vivo. In addition, oxypurinol abrogated (1) fetal gene activation,

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(2) alterations in calcium cycling proteins, (3) increased cardiomyocyte diameter, and (4) activation of ERK. These findings corroborate positive results seen in other studies that demonstrated improved contractile parameters in heart failure with XO inhibition.[19,21,22,25–27]

The positive inotropy induced by XO inhibition in the setting of heart failure differs significantly from standard clinically used pharmacological inotropes. Unlike cAMP-modulating inotropes, XO inhibition decreases myocardial oxygen consumption, thereby sparing energy expenditure in the energy-deprived failing heart.[22,25] In a more recent study, XO inhibition was also shown to restore high-energy phosphates to basal levels.[26]

The mechanisms of action of XO inhibition have not been fully elucidated. On a functional level, there is strong evidence that XO inhibition enhances the responsiveness of the myofilaments to calcium.[21] The study by Minhas et al additionally shows that XO inhibition enhanced SERCA2a levels while decreasing expression of the sodium–calcium exchanger to increase contractility.[24] It is important to note, however, that in all these experimental models of heart failure, the beneficial effects of XO inhibition were achieved because XO activities were increased within the myocardium; treatment with either allopurinol or oxypurinol restored XO activity to baseline levels and myocardial function was restored.[19,21,22,25–27] These findings, therefore, suggest that by limiting oxidant stress to maintain levels of ROS required for ambient signaling, XO inhibition abrogates the destructive effects of ROS on various intracellular mechanisms that maintain function and integrity in the working cardiomyocyte. In addition, it has also been suggested that decreases in uric acid levels seen with XO inhibition have an antiinflammatory effect on the cardiovascular system.

These promising results in experimental models have led to the evaluation of allopurinol as a therapeutic modality in patients with congestive heart failure. Acutely, intravenous allopurinol administration has been shown to improve left ventricular efficiency in patients with dilated cardiomyopathy[22] and ameliorate endothelial dysfunction in heart failure patients.[28] In contrast, a recent study of chronic administration of oral allopurinol failed to show any improvement in exercise capacity in patients with heart failure.[29] These contrasting results demonstrate clearly that large-scale clinical trials are needed with more surrogate end points to evaluate the effects of this treatment strategy. Furthermore, it will be important to elucidate whether targeted XO inhibition will benefit only select subsets of patients with congestive heart failure, specifically those who are hyperuricemic, or will be efficacious in a larger population. Although results such as those presented by Minhas et al imply that XO inhibition alone will decrease oxidant stress and improve functional and structural parameters in all patients with dilated cardiomyopathies, heart failure is a remarkably complex and multifactorial disease process. It therefore appears unlikely that XO inhibition will be used as a stand alone agent. At present, a large clinical trial is underway to evaluate the Efficacy and Safety of Oxypurinol Added to Standard Therapy in Patients with New York Heart Association (NYHA) class III–IV Congestive Heart Failure (OPT-CHF).[30] This randomized, double-blind, placebo-controlled trial will hopefully shed light on some of these questions and may determine the clinical utility of XO inhibition as a treatment strategy in clinical heart failure.

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KEY WORDS: xanthine oxidase ■ reactive oxygen species ■ heart failure ■ contractility