Can Xanthine Oxidase Inhibitors Improve Cardiac Function in Patients With Chronic Heart Failure?

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Chronic heart failure (CHF) is the terminal stage of heart disease caused by myocardial infarction (MI), hypertension, cardiomyopathy, and valvular heart disease. Despite guideline-recommended therapy (pharmacological treatment, implantable devices, mechanical circulatory support, and heart transplantation), the prognosis of patients with CHF remains very poor and another strategy is necessary.

Improper functioning of various signaling pathways, including the sympathetic nervous system and renin-angiotensin-aldosterone system leads to progression of heart failure (HF). In addition, several studies have reported that oxidative stress and change of myocardium metabolism is expected to pave the way for new treatments for CHF.

From the viewpoint of myocardium metabolism, Decherd, et al observed that in the setting of CHF, cardiomyocytes exist in a state of “energy starvation”. Their findings are supported by recent evidence that impaired activity of respiratory-chain enzymes and altered glycolipid metabolism could cause the decreased myocardial ATP production in CHF. Energy derived from free fatty acid (FFA) metabolism accounts for 70% of the myocardial supply of ATP in the healthy heart. However, myocardium metabolism transits from a fatty acid metabolism-dependent pathway to a glucose metabolism-dependent pathway in CHF. The amount of energy that may be derived from glucose is much less than the amount that may be derived from FFA. In addition, in heart failure, p-53-dependent chronic inflammation leads to insulin-resistance; which in turn leads to decreased glucose metabolism in the myocardium and reduced generation of energy in CHF.

Patients with CHF frequently present hyperuricemia. Several reports have indicated that a high level of uric acid (UA) is an independent prognostic factor or independent marker of CHF. Hyperuricemia in CHF is attributed to impaired renal urate excretion, while, on the other hand, overproduction of urates via activation of XO also could contribute to hyperuricemia in CHF.

Allopurinol, a specific XO inhibitor, is approved for the clinical treatment of hyperuricemia. Studies in animals and humans with HF have shown that allopurinol can improve myocardial energy efficiency and reduce oxygen consumption. Notably, usage of allopurinol was a marker of improved survival in the Seattle Heart Failure Model.

Several clinical trials addressed the question whether allopurinol might restore cardiac function in hyperuricemic patients with CHF. The OPT-CHF study (Oxyuricin compared with placebo for class with placebo with CHF; the Seattle) showed that a subgroup of patients with hyperuricemia (UA ≥ 9.5 mg/dL) responded favorably with improved clinical status and trends toward decreased all-cause and cardiovascular death. However, the EXACT-HF study (Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients) failed to show improved clinical status, exercise capacity, quality of life, or ventricular ejection fraction in patients treated with allopurinol. These results suggest there is still controversy with respect to the actions of allopurinol on cardiac function in hyper-
uricemic patients with CHF.

It has been reported that allopurinol has a protective effect against ischemia-reperfusion injury in humans. One of its mechanisms is the inhibition of ROS production and protection of mitochondria from oxidative damage. In addition, allopurinol could enhance the energetic metabolism of the failing heart by ATP salvage. ATP, adenosine diphosphate (ADP), adenosine monophosphate (AMP), and inosine monophosphate (IMP) significantly decrease, whereas UA precursors such as inosine, hypoxanthine, and xanthine significantly increase after ischemia. This means that ATP degradation occurs in the hearts during ischemia followed by accumulation of purine metabolites, which are sources of ROS generation, resulting in the reduction of cardiac adenine nucleotides, causing energy starvation of the heart. Allopurinol limits the degradation of ATP and increases the rate of ATP generation by blocking the conversion from hypoxanthine to xanthine. Several studies have shown that intravenous administration of allopurinol increased the concentration of high-energy phosphates in patients with CHF. However, the mechanism underlying the allopurinol-mediated improvement of energy metabolism in the failing heart associated with improved cardiac function remains unknown.

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Wang and colleagues investigated the effects of allopurinol on myocardial energy metabolism in a CHF model after MI. They found that allopurinol prevented damage to the cardiac structural tissue such as myofilament lysis and mitochondrial swelling. Simultaneously, allopurinol significantly improved parameters of cardiac function including left ventricular internal diastolic dimension, left ventricular internal systolic dimension, and ejection fraction (EF). Interestingly, allopurinol exhibited increased activity of respiratory-chain enzyme activity, as well as increased mRNA level and expression at the protein level of a regulator of mitochondrial energy metabolism and biogenesis, namely, of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and of the fatty acid oxidation marker carnitine palmitoyltransferase1 (CPT-1). On the other hand, oxidative stress marker malondialdehyde activity as well as expression at the mRNA and protein levels of XO and of the glucose oxidation marker GLUT4 were decreased. The authors concluded that allopurinol improved myocardial energy metabolism in rats with CHF, probably as a result of PGC-1α regulation during the stage of glycolipid metabolism, enhancing the production of ATP. Their study showed a novel mechanism for the allopurinol-induced restoration of cardiac function in a murine model of CHF from the aspect of cardiac energy metabolism. Yet, their study had a limitation in that they did not show the energy change of adenine nucleotides including ATP, ADP, AMP, and IMP. It is very important to clarify how energy metabolism changes with improvement of cardiac energy metabolism. In addition, it remains unknown whether this proposed mechanism for allopurinol-induced restoration of cardiac function in CHF would work in clinical settings. The recent EX-ACT-CHF study showed that treatment with allopurinol did not improve cardiac function in CHF patients with hyperuricemia, although the non-purinergic XO inhibitor febuxostat significantly improved EF in hyperuricemic patients with CHF compared with treatment with allopurinol. Further investigation, including clinical and basic research, is definitely necessary to address the question “Can xanthine oxidase inhibitors improve cardiac function in patients with chronic heart failure?”

References


