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EDITORIAL COMMENT

Allopurinol for Heart Failure

Novel Mechanisms*

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Oh, for oxygen is the cry that we could imagine coming from the famished cardiomyocytes in heart failure (HF). But how can energy in the form of adenosine triphosphate (ATP) be conserved? The principles are much like those of the economy: either cut the demand for dollars or increase the supply or do both. A simple way of energy conservation is to rest the heart, for example, by decreasing the heart rate by beta-blockade or ivabridine. Equally simple is reduction of the afterload by inhibition of the renin-angiotensin system or by nitrate/hydralazine. "Is the failing heart energy-starved," asked Joanne Ingwall and Robert Weiss (1) in 2004. In their view, yes, it is. "The failing heart—an engine out of fuel" is how Stefan Neubauer (2) saw it. This working hypothesis rests on many previous contributions from Harvey onward, including those of Osler, Hill, Meerson, and many others, who have all contributed to the varying concepts of HF, leading to the "modern" view as outlined by Arnold Katz (3). Many of the current research leaders have worked on basic biochemical aspects of models of HF, but the present article focuses our attention on chronic human HF and the proposal that allopurinol might confer benefit.

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The accompanying paper in this issue of the *Journal* (4) helps us to understand better the role of high-energy phosphate compounds in chronic human HF, a topic that goes back to Hermann and Decherd (5) in 1939 who described a significantly reduced creatine content in the failing heart. Defects in creatine led us right on to the fundamental advances made by the Johns Hopkins group, first defining the defects in energy metabolism in the human heart (6) and then providing a proposed therapeutic solution (4).

ATP in the failing heart: increased synthesis. Already in 2005, the Johns Hopkins group had studied the creatine kinase (CK) flux in human heart failure, finding that the flux through CK was reduced by 50% in mild to moderate HF (6). Their critical technological advance was the use of magnetic resonance imaging/magnetic resonance spectroscopy to detect the energy flux of CK in the human heart. The CK reaction is essential in 2 vital steps in energy production. First, in the mitochondria, mitochondrial CK converts the ATP produced by oxidative phosphorylation to phosphocreatine that then readily diffuses out of the mitochondria to become cytosolic phosphocreatine. Second, cytosolic CK then promotes the resynthesis of cytosolic ATP from cytosolic adenosine diphosphate, thus being an essential link in the overall sequence of transfer of energy from the mitochondria to the contractile mechanism (see Fig. 1 in Neubauer [2]). The creatine required for these reactions is not synthesized in the heart tissue, so that it must be taken up from the circulation by the creatine transporter (2).

An attractive hypothesis, strongly supported by the data presented, is that the forward flux of energy through cytosolic CK is reduced in human HF. Thus, the heart lacks cytosolic ATP, the immediate source of energy for cardiac contraction. The highly novel proposal of the current paper is that allopurinol helps to reverse these unfavorable trends in high-energy phosphate metabolism in those with chronic HF. Allopurinol is much better known for its capacity to inhibit the xanthine oxidase reaction, thereby lessening the formation of uric acid and providing benefit in gout. As this site of action is far down on the breakdown path of ATP, in fact as many as 5 reactions away from ATP (Fig. 1), it is more than likely that only a massive increase in hypoxanthine could help to preserve ATP in the failing heart. Thus, an alternate site of action of allopurinol should be considered.

By inhibiting xanthine oxidase, the proposal is that allopurinol also inhibits the formation of reactive oxygen species (ROS) (7,8). ROS, in turn, are inhibitors of the cytosolic CK reaction. As ROS falls under the influence of allopurinol, the CK reaction is enhanced and cytosolic ATP is synthesized. In fact, the acceleration of the CK ratio in the direction of ATP synthesis is exactly what their elegant technology could detect. Thus, the way is now paved for a larger study on the proposed benefits of allopurinol in those with chronic HF (the EXACT-HF study). Due attention might be given to the possible nephrotoxicity of allopurinol, previously established (9) but recently argued against (10). This possible safety issue might well warrant attention when renal impairment accompanies HF.

Increased ATP conservation. An entirely different approach to the energy problem in HF is not to enhance the ATP supply, but to make better use of the ATP that there is. Metabolic measures that reduce the oxygen wastage found in advanced HF will indirectly improve the energy supply. Here we need to revert to the consequences of excess delivery to the myocardium of oxygen-inefficient free fatty acids (FFAs) with subsequent preferential use of FFAs over

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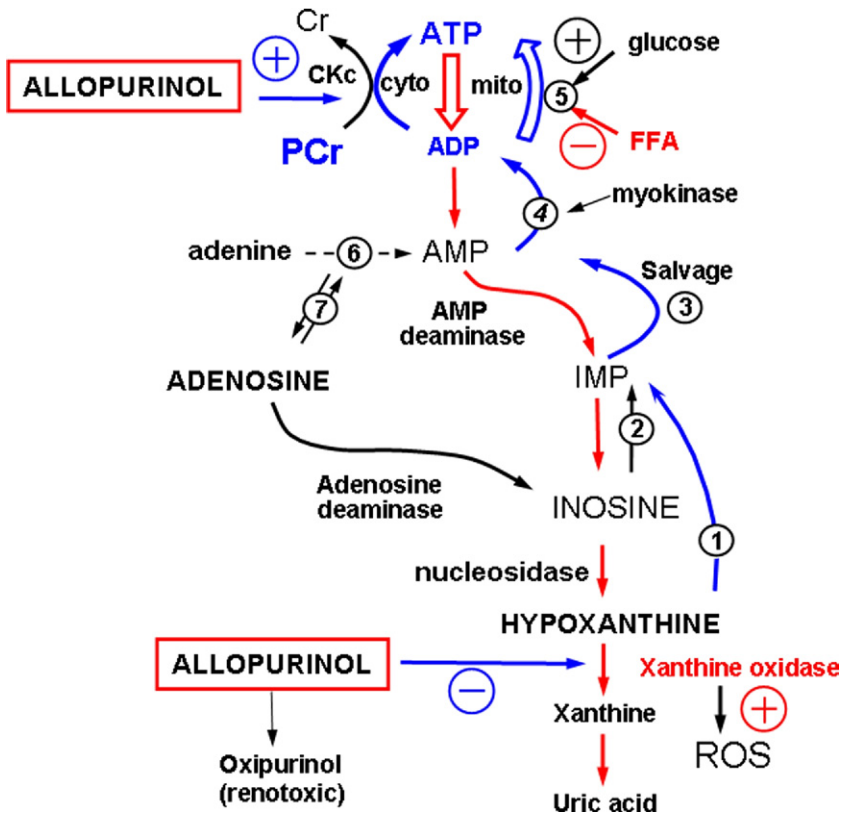

Figure 1 **Proposed Sites of Action of Allopurinol in HF**

Adenosine triphosphate (ATP) made in the mitochondria is converted to phosphocreatine (PCr) under the influence of mitochondrial creatine kinase. PCr is much more permeable and is exported to the cytosol where it converts adenosine diphosphate (ADP) to ATP through the activity of cytosolic creatine kinase (CKc). Cytosolic ATP is used by the contractile mechanism to reform ADP, which is resynthesized by oxidative phosphorylation in the mitochondria (mito). In states of ATP depletion such as heart failure (HF), the breakdown paths below ADP are shown, eventually reaching the theoretically possible breakdown endpoint of uric acid. Allopurinol, by inhibiting xanthine oxidase, could theoretically reverse these reactions. The path from hypoxanthine to ATP requires as many as 5 synthetic steps, making it a very unlikely mechanism to achieve the benefit of allopurinol in increasing cytosolic ATP. However, inhibition of xanthine oxidase by allopurinol brings with it decreased formation of cytosolic reactive oxygen species (ROS) **(bottom right)**, which are increased in HF. The proposal is that such allopurinol-induced decreased formation of ROS in turn lessens the inhibition imposed by ROS on the CKc that in turn simulates the formation of cytosolic ATP from cytosolic PCr **(top left)**, thereby providing energy for contraction in HF. Breakdown paths are shown in **red** and synthetic paths in **blue**. The 5 steps are: 1) hypoxanthine phosphoribosyl transferase; 2) inosine kinase activity; 3) low-activity salvage path; 4) myokinase activity; and 5) oxidative phosphorylation. Also shown are: 6) adenine phosphoribosyl transferase; and 7) adenosine kinase. AMP = adenosine monophosphate; FFA = free fatty acid; IMP = inosine monophosphate. Adapted from Opie LH. The Heart. Physiology and Metabolism. 2nd edition. New York, NY: Raven Press, 1991.

glucose (11) as also proposed in HF (12). The oversimplified concept of oxygen wastage is that glucose is "good" and FFAs are "bad," as can be explained by the differences in the ATP yield per oxygen atom (P/O ratio), the values being 3.17 glucose versus 2.83 for palmitate, with approximately an 11% saving of oxygen when moving from one extreme (only FFAs) to the other (only glucose). This brings us to the time-honored but still controversial concept of glucose-insulin-potassium, initially proposed and only now being tested to counter the FFA increase in early phase acute myocardial infarction in the ambulance. Administering glucose-insulin-potassium as soon as possible after the onset of chest pain is important because within 1 h in the baboon model there is already severe depletion of high-energy phosphate compounds (13), whereas overall data in patients suggest that interventions within the first 1 to 2 "golden" hours of onset of pain are most effective (14).

These concepts are relevant to HF. In optimally treated HF patients, there was a 10% reduction in FFA oxidation when inhibited by the drug trimetazidine, and the ejection fraction increased, but myocardial efficiency was unchanged (15). Although this finding supports the benefits of inhibition of myocardial FFA oxidation in HF, an intriguing possibility is that the fatty acid–glucose interaction also occurred in skeletal muscle as an additional site of action of trimetazidine (16). Another metabolic modulator, perhexiline, has improved energy deficiency in patients with hypertrophic cardiomyopathy (17).

However, oxygen wastage with FFAs can be considerably >10%, especially when there is vigorous catecholamine stimulation, as could occur in untreated HF (12). For