Journal of the American College of Cardiology Vol. 59, No. 9, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.895

Allopurinol Acutely Increases Adenosine Triphospate Energy Delivery in Failing Human Hearts

Glenn A. Hirsch, MD, MHS,* Paul A. Bottomley, PhD,† Gary Gerstenblith, MD,* Robert G. Weiss, MD*

Baltimore, Maryland

Objectives This study tested the hypothesis that acute administration of the xanthine oxidase (XO) inhibitor allopurinol improves cardiac high-energy phosphate concentrations in human heart failure (HF) and increases the rate of adenosine triphosphate (ATP) synthesis through creatine kinase (CK), the primary myocardial energy reserve.

Background Studies of patients and animal models implicate impaired myocardial high-energy phosphate availability in HF. The XO reaction is a critical terminal step in ATP and purine degradation and an important source of reactive oxygen species. Thus, XO inhibition is a potentially attractive means to improve energy metabolism in the failing human heart.

Methods We randomized 16 patients with nonischemic cardiomyopathy in a double-blind fashion to allopurinol (300 mg intravenously) or placebo infusion, 4-to-1, the latter for purposes of blinding only. The myocardial concentrations of ATP and creatine phosphate (PCr) and the rate of ATP synthesis through CK (CK flux) were determined by ^{31}P magnetic resonance spectroscopy.

Results Allopurinol infusion increased mean cardiac PCr/ATP and PCr concentration by ~11% ($p < 0.02$), and mean CK flux by 39% (2.07 ± 1.27 μmol/g/s to 2.87 ± 1.82 μmol/g/s, $p < 0.007$). Calculated cytosolic adenosine diphosphate concentration decreased, whereas the free energy of ATP hydrolysis ($\Delta G_{\sim ATP}$) increased with allopurinol. The increased CK flux was disproportionate to substrate changes, indicating increased CK enzyme activity.

Conclusions Intravenous administration of the XO inhibitor allopurinol acutely improves the relative and absolute concentrations of myocardial high-energy phosphates and ATP flux through CK in the failing human heart, offering direct evidence that myofibrillar CK energy delivery can be pharmaceutically augmented in the failing human heart. (Intravenous Allopurinol in Heart Failure; NCT00181155) (J Am Coll Cardiol 2012;59:802–8) © 2012 by the American College of Cardiology Foundation

Because adenosine triphosphate (ATP) is required for normal cardiac contractile function, it has long been hypothesized that inadequate ATP availability may contribute to the contractile dysfunction observed in nonischemic chronic heart failure (HF) (1–3). Indirect support for the hypothesis that the failing heart is "energy starved" arises from studies showing that abnormalities in myocardial energy metabolism are observed in nearly every experimental model of HF and in patients with HF. It is additionally supported by observations that common HF medications including beta-blockers and angiotensin-converting enzyme inhibitors that improve HF outcomes and survival (1,3) coincidentally also reduce energetic demand. Nevertheless, there are currently no approved HF treatment strategies designed to improve energy delivery or the coupling between energy delivery and mechanical function (mechanoenergetic coupling) in the failing heart.

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Xanthine oxidase (XO) inhibition is a potentially attractive strategy for improving energy metabolism and mechanoenergetic coupling in HF (4,5). XO is a critical, terminal reaction in ATP and purine degradation and also an important source of reactive oxygen species (ROS). There is evidence of increased myocardial XO activity and ROS in

From the *Department of Medicine, Division of Cardiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and the †Department of Radiology, Division of Magnetic Resonance Research, The Johns Hopkins University School of Medicine, Baltimore, Maryland. This work was supported by NIH RO1-HL61912 and R01-HL056332; D.W. Reynolds Clinical Cardiovascular Center at Johns Hopkins, and the Clarence Doodeman Endowment. All authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Hirsch and Bottomley contributed equally to this work.

Manuscript received June 6, 2011; revised manuscript received October 3, 2011, accepted October 19, 2011.

HF (4,5). ROS have many potentially adverse effects that include inactivation of sulfhydryl (SH)-containing enzymes. The creatine kinase (CK) reaction is the prime energy reserve of the heart (6,7). It reversibly and rapidly transfers a high-energy phosphoryl group between creatine phosphate (PCr) and ATP, and the myofibrillar isoform of the CK enzyme is particularly sensitive to ROS (8). Thus, a XO inhibitor (XOI) could enhance the energetic profile of the failing heart (9) by limiting the degradation of ATP and loss of adenine nucleosides and/or by attenuating the decrease in CK capacity and thereby increasing the rate of ATP generation through myofibrillar CK.

Allopurinol is an XOI approved for the clinical treatment of gout. However, it also improved mechanoenergetic coupling in a canine paced tachycardia model of HF (10) and acutely reduced myocardial oxygen consumption without impairing contractile function in patients with dilated cardiomyopathy (11). There are, however, few direct studies of the effects of XO inhibition on myocardial energy metabolism and none in the human heart.

^{31}P magnetic resonance spectroscopy (MRS) is the only method capable of noninvasively measuring myocardial high-energy phosphate metabolites in the human heart. ^{31}P MRS studies have identified significant reductions in cardiac PCr/ATP in HF patients (12–14). Furthermore, recent magnetization transfer MRS techniques capable of measuring the rate of ATP production through CK in the human heart have documented 50% to 70% reductions in the rate of ATP synthesis through CK in several common forms of HF (15–17). In animal models, chronic XO inhibition improved cardiac PCr/ATP in murine myocardial infarction (18), and acute XO inhibition increased PCr/ATP and total PCr content in pacing-induced canine HF (9); however, the energetic effects of XOI have never been documented in human HF. Moreover, there have been no direct studies of the effects of XO inhibition or any other intervention on the rate of ATP synthesis through CK in the failing human heart.

Therefore, the purpose of this study was to measure directly both the myocardial concentrations of high-energy phosphates and the rate of ATP synthesis through CK in patients with HF using noninvasive ^{31}P MRS. We tested the hypothesis that acute administration of allopurinol improves cardiac high-energy phosphate metabolism in the failing human heart by increasing the rate of ATP production through CK (CK flux).

Methods

Study patients. The study was approved by the Johns Hopkins Institutional Review Board for Human Investigation. All subjects gave informed consent after receiving an explanation of the study and protocol. Sixteen patients with New York Heart Association functional class II or higher HF symptoms, a left ventricular ejection fraction <40%, and nonischemic cardiomyopathy diagnosed by either a cardiac catheterization demonstrating no significant coronary artery disease (n = 13), a negative stress perfusion study in low-risk patients (n = 2), or onset of cardiomyopathy during pregnancy at age younger than 25 years (n = 1) were enrolled. Cardiac magnetic resonance imaging/MRS was performed using a General Electric 1.5-T magnetic resonance imaging/MRS system (General Electric Healthcare Technologies, Waukesha, Wisconsin) in subjects before and 15 min after completion of intravenous infusion of the study drug, either allopurinol (Aloprim 300 mg) or placebo (equivalent 50 ml dose of 5% dextrose). The study drug allocation was randomized in a 4-to-1 ratio by the research pharmacy with all investigators and subjects blinded to the randomization. Because the critical comparison was the metabolic effect of allopurinol compared with baseline in the same patient, equal randomization was not required and a smaller placebo group was used for purposes of blinding only.

Abbreviations and Acronyms

ADP = adenosine diphosphate
ATP = adenosine triphosphate
CK = creatine kinase
$\Delta G_{\sim ATP}$ = free energy of adenosine triphosphate hydrolysis
HF = heart failure
k_f = pseudo first-order creatine kinase rate constant
MRS = magnetic resonance spectroscopy
PCr = creatine phosphate
ROS = reactive oxygen species
SH = sulfhydryl
V_{max} = maximum velocity of the creatine kinase reaction
XO = xanthine oxidase
XOI = xanthine oxidase inhibitor

Study protocol. MRS studies were performed with subjects oriented prone on a 6.5-cm ^{31}P receive/25-cm ^{31}P transmit surface coil set, as previously described (15,17,19). The complete patient cardiac MRS protocol is described in the Online Appendix but includes the following steps:

1. Conventional scout magnetic resonance imaging for positioning
2. Acquisition of the 4 ^{31}P 4-angle saturation transfer method datasets localized by 1-dimensional chemical shift imaging to measure CK flux
3. Acquisition of a fifth ^{31}P 1-dimensional chemical shift imaging set with saturation turned off for phosphate metabolite quantification
4. Acquisition of a sixth ^{1}H 1-dimensional chemical shift imaging data set for metabolite quantification
5. Infusion of allopurinol or placebo
6. Repetition of step 2 to obtain a second measurement of CK flux (15), followed by removal of the patient from the magnet
7. Repetition of steps 3 and 4 with a 0.15-mol/l inorganic phosphate reference phantom to measure the metabolite concentrations

Data analysis. MRS DATA. MRS data were analyzed in blinded fashion by one of the authors (P.A.B.), without knowledge of the group assignment or the number of

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Table 1 Clinical Characteristics of the Allopurinol Group (n = 13)

Age, yrs	47.8 ± 12.9
Male	9 (69.2)
LV ejection fraction, %	18.1 ± 6.0
NYHA functional class	
II	10 (76.9)
III	3 (23.1)
Hypertension	4 (30.8)
Diabetes mellitus	0 (0)
Medications	
ACE inhibitor or ARB	13 (100)
Beta-blocker	9 (69.2)
Loop diuretic	9 (69.2)
Aldosterone blocker	7 (53.9)
Digitalis	3 (23.1)
Statin	5 (38.5)
Aspirin	6 (46.2)

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LV = left ventricular; NYHA = New York Heart Association.

subjects in each group, with the results declared before the code was broken. The pseudo first-order CK reaction rate constant (k_f) and the myocardial PCr and ATP concentrations (PCr and ATP concentrations) were calculated as previously described (15–17,20). The forward CK flux or rate of ATP synthesis through CK is given by the product (k_f.PCr concentration), in μmol/g wet weight/s (15–17). Intracellular-free ADP concentration and the free-energy change of ATP hydrolysis ($\Delta G_{\sim ATP}$ [kJ/mol]) were determined as previously described (15,21). The theoretically predicted rate of the CK equation was calculated as previously reported (15,22) and detailed in the Online Appendix.

Statistical analyses. Data analyses were performed using STATA version 11.0 (StataCorp, College Station, Texas). Data are displayed as mean ± SD. Two-sided paired *t* tests were used to compare each subject's pre- and post-infusion variables. A p value <0.05 was considered statistically significant.

Results

The characteristics of the patient cohort are summarized in Table 1. Intravenous infusion of allopurinol (300 mg) had no significant hemodynamic effects (heart rate pre-infusion, 75.8 ± 12 beats/min vs. 74.7 ± 13 beats/min post-infusion, p = 0.49; systolic blood pressure pre-infusion, 131.7 ± 28 mm Hg vs. 134.6 ± 24 mm Hg post-infusion, p = 0.68; rate pressure product pre-infusion 9,817 ± 2,484 beats-mm Hg/min vs. 10,358 ± 3,380 beats-mm Hg/min post-infusion, p = 0.35).

Representative myocardial ^{31}P magnetic resonance spectra are shown in Figure 1. Before allopurinol or placebo

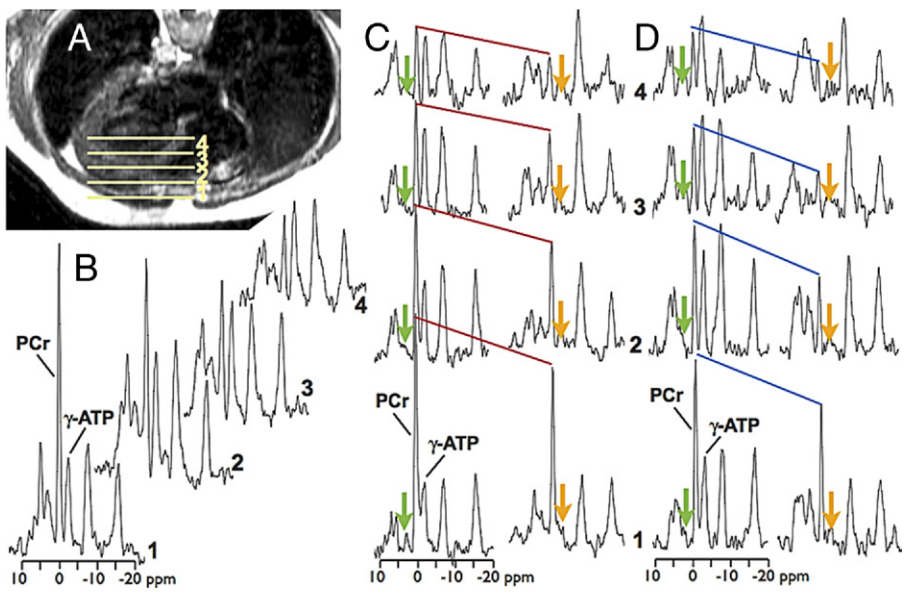

Figure 1 MRS Study With Corresponding Spectra

Annotated scout magnetic resonance image **(A)** showing 4 locations (no. 1 to 4) of ^{31}P spectra acquired from the chest wall (no. 1) and anterior myocardium (nos. 2 to 4) of a 45-year-old man with dilated cardiomyopathy and New York Heart Association functional class III heart failure **(B to D)**. **(B)** Spectra acquired in step 3 of the MRS protocol without chemical selective irradiation for quantification of metabolite concentrations. **(C)** Spectra acquired in step 2 with chemical selective irradiation applied to the γ-ATP resonance **(orange arrow)**, and at the control location **(green arrow)**. The change in height in PCr **(red line)** is a measure of the forward CK flux. **(D)** Spectra from step 6 of the MRS protocol following, in this case, allopurinol infusion. An increase in CK flux from 0.7 μmol/g/s to 1.7 μmol/g/s is evidenced, in part, by a greater decrease in the PCr signal with saturation **(blue line)**. All spectra are scaled identically. γ-ATP = γ-adenosine triphosphate; CK = creatine kinase; MRS = magnetic resonance spectroscopy; PCr = creatine phosphate; ppm = parts per million.

infusion, the mean cardiac PCr/ATP was 1.59 ± 0.40, and PCr and ATP concentrations were 7.6 ± 1.8 μmol/g and 4.9 ± 1.3 μmol/g, respectively, for all 16 HF subjects. Likewise, mean k_f and CK flux at baseline for all subjects before administration of study drug were 0.25 ± 0.13 s^{-1} and 1.91 ± 1.19 μmol/g/s, respectively, both consistent with previously reported values in patients with nonischemic dilated cardiomyopathy (15).

Allopurinol infusion in 13 patients increased the mean cardiac PCr/ATP and PCr concentration by ~11%, from 1.58 ± 0.41 to 1.75 ± 0.59 ($p < 0.02$) and from 7.31 ± 1.79 μmol/g to 8.06 ± 2.40 μmol/g ($p < 0.02$), respectively. Mean k_f trended higher by ~20% (0.28 ± 0.13 vs. 0.34 ± 0.14, $p = 0.054$). Importantly, the rate of ATP synthesis through CK increased significantly by 39% during allopurinol infusion, from 2.07 ± 1.27 μmol/g/s to 2.87 ± 1.82 μmol/g/s ($p < 0.007$) (Table 2, Fig. 2).

There were no changes in cardiac PCr/ATP, PCr concentration, or CK flux in the small group who received placebo.

The observed increases in PCr/ATP and PCr concentration during allopurinol infusion are associated with energetically favorable changes in free cytosolic [ADP] and the free energy of ATP hydrolysis ($\Delta G_{\sim ATP}$). Cytosolic free [ADP] decreased with allopurinol infusion, from 60 ± 24 μM to 53 ± 28 μM ($p < 0.05$), and mean $\Delta G_{\sim ATP}$ decreased from −60.4 ± 1.2 kJ/mol to −61.0 ± 1.7 kJ/mol ($p < 0.05$). Note that the more negative $\Delta G_{\sim ATP}$ reflects a greater energy release for each molecule of ATP hydrolyzed (21) with allopurinol infusion.

To test whether the increase in CK flux elicited by allopurinol is due to differences in the substrates and reactants driving the CK reaction and/or a change in activity of the CK enzyme itself (maximum velocity [V_{max}]), the predicted rate of ATP synthesis through CK was calculated (ν_f pred in Equation 5 in the Online Appendix). The predicted effect of the observed 11% increase in myocardial PCr/ATP and 13% decrease in [ADP] is to actually decrease the rate of ATP synthesis through CK by 2%. Therefore, the observed 39% increase in the rate of ATP synthesis through CK with allopurinol in these HF patients is attributable to a significant (~40%) increase in CK enzyme activity (V_{max}).

Table 2 In Vivo Myocardial Energetics Including Cardiac PCr/ATP, Creatine Phosphate Concentration, Cytosolic ADP, $\Delta G_{\sim ATP}$, and ATP Flux Through CK

	Baseline	After Allopurinol Infusion
Cardiac PCr/ATP	1.58 ± 0.41	1.75 ± 0.59*
PCr concentration, μmol/g wet weight	7.3 ± 1.8	8.1 ± 2.4*
ADP concentration, μM	60 ± 24	53 ± 28†
$\Delta G_{\sim ATP}$, kJ/mol	−60.4 ± 1.2	−61.0 ± 1.7†
CK flux, μmol/g/s	2.07 ± 1.27	2.87 ± 1.82‡

Values are mean ± SD. Allopurinol n = 13 for all endpoints. *$p < 0.02$ vs baseline. †$p < 0.05$. ‡$p < 0.007$ vs. baseline.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; CK = creatine kinase; $\Delta G_{\sim ATP}$ = free energy of adenosine triphosphate hydrolysis; PCr = creatine phosphate.

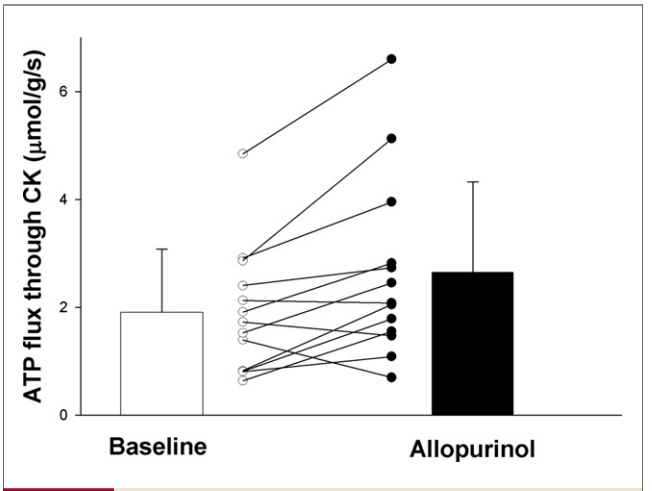

Figure 2 Effect of Allopurinol on ATP Synthesis via CK

The rate of ATP synthesis through cardiac CK (μmol/g/s) under baseline and allopurinol conditions (summary bars represent mean ± SD). Abbreviations as in Figure 1.

Discussion

There are at least 4 novel observations in this randomized, double-blind, uncontrolled study of the acute energetic effects of intravenous allopurinol infusion in HF patients. First, the myocardial high-energy phosphate, PCr, is increased significantly, in both absolute (PCr concentration) and relative (PCr/ATP) terms, by allopurinol infusion in the failing human heart. Second, in terms of ATP utilization, allopurinol acutely results in favorable energetic changes that include a reduction in cytosolic free ADP concentration and an increase in the amount of energy released with each ATP molecule hydrolyzed ($\Delta G_{\sim ATP}$). Indeed, both would significantly reduce the energetic cost of contraction. Third, allopurinol increases ATP availability, the amount of ATP synthesized through CK, the major myocardial energy reservoir, by almost 40% in the failing human heart. This demonstrates that a pharmacologic intervention can acutely increase ATP synthesis through CK in the human heart. Fourth, the increase in ATP flux through CK cannot be explained by the changes in PCr and other energy metabolite pools and is best explained by an acute allopurinol-induced increase in CK enzyme activity (V_{max}). It is interesting to note that the predicted rate of ATP flux through CK increases by 35% if the V_{max} measured in failing human hearts is substituted by values from normal human hearts (7). This suggests that the observed allopurinol-induced increase in CK flux in failing hearts is due to near-normalization of CK enzyme activity. We speculate that allopurinol nearly normalizes CK activity by attenuating ROS-induced CK inhibition because ROS is increased in HF and because myofibrillar CK activity is decreased by ROS in in vitro models (8).

Myocardial energy metabolism is impaired in experimental and clinical HF and thus presents a compelling target for

therapeutic intervention. Abnormalities in cardiac energy metabolism and specifically in the CK reaction, the primary myocardial energy reserve, have been reported in experimental models across many species including mice, hamsters, rats, rabbits, pigs, and dogs (3). Reductions in the cardiac PCr/ATP ratio at rest in HF patients were first reported approximately 20 years ago (12–14,23) and may predict cardiovascular mortality (24).

More recently, measures of the rate of ATP transfer via the CK reaction have become possible in the human heart, with reductions of 50% to 70% below normal values reported in failing dilated hearts (15). This reported reduction in ATP flux through CK (15) was disproportionate to the more modest (10% to 20%) decrease in resting PCr/ATP and occurred before a significant reduction in ATP concentration could be detected in patients with mild to moderate HF symptoms (15). It was suggested that the magnitude of the reduction in CK ATP flux could be sufficient to temporally limit ATP energy delivery during periods of stress or peak demand in patients with HF (15). Thus, an intervention that significantly enhances ATP delivery to the myofibrils to better fuel myocardial contraction by improving high-energy phosphate stores (e.g., PCr/ATP, PCr concentration, or ATP concentration) and/or CK flux could well represent an important treatment option for human HF.

The current observations demonstrate that allopurinol acutely enhances the energetic profile of the failing human heart by improving both myofibrillar ATP delivery and use. The significant increase in PCr content with allopurinol observed here is similar to that observed with a nonpurine XOI in canine hearts (9). The CK reaction provides a rapid source of myofibrillar ATP and is believed to serve as a spatial ATP buffer, enhancing ATP delivery from the sites of mitochondrial production to the cytosolic sites of ATP utilization (6,25). The ~40% acute allopurinol-induced increase in the mean rate of ATP synthesized through the CK reaction should significantly augment both the temporal and spatial delivery of myofibrillar ATP. Indeed, the rate of ATP flux through CK with allopurinol here appears to increase to almost that of healthy human hearts (3.3 ± 0.8 μmol/g/s wet weight) (17).

The amount of free energy released from ATP utilization for contractile and other myocellular functions is also increased acutely by allopurinol in the failing heart. By maintaining low ADP concentration and inorganic phosphate concentration, the CK reaction supports a high phosphorylation potential that maximizes the amount of energy liberated from the hydrolysis of each ATP molecule ($\Delta G_{\sim ATP}$). Inhibition of CK in rat hearts lowers contractile reserve and free energy release, which, in turn, limits the Ca^{2+}-handling capacity of the sarcoplasmic reticular Ca^{2+} ATPase (26). An increase in cytosolic-free ADP concentration is also associated with diastolic dysfunction, possibly by slowing the rate of cross-bridge cycling (27,28). In the current study, calculated cytosolic-free ADP concentration decreased significantly by ~11% and the mean $\Delta G_{\sim ATP}$ changed by ~0.5 kJ/mol after acute allopurinol administration in failing human hearts, signifying an increase in the free energy generated from ATP utilization. Although these metabolic changes may seem modest, the changes in ATP flux through CK and $\Delta G_{\sim ATP}$, would together result in an additional 3.8 kJ of energy availability per gram of myocardium over the course of a day. This could explain the acute improvement in mechanoenergetic coupling in the failing human heart reported for allopurinol, whereby contractile function is maintained with a lower requirement for oxygen consumption (10,11).

Inhibition of XO, a terminal step in purine degradation, was proposed years ago as a means of preserving high-energy phosphates in ischemic hearts (29). Although the intracellular milieu during acute severe ischemia differs dramatically from that in the chronically failing heart, it is possible that some of the improvement in energetics observed here is related in part to allopurinol limiting purine breakdown. However, given the relatively short time course of this acute study and the relatively long time for adenine and other purine degradation in the failing heart (30), it seems unlikely that limiting purine degradation could explain all of the observed acute effects. On the other hand, XO activity and ROS are increased in HF (4,5), which could rapidly affect energy metabolism. ROS can directly inhibit CK by modulating its critical SH groups (31), as evidenced by studies of rat myocardium, suggesting that the main adverse effect of ROS in myofibrils is the oxidation of essential SH groups of CK, which inactivates the enzyme (8). This decreases the local ATP/ADP ratio and impairs Ca^{2+} handling with little or no change in magnesium-ATPase activity (8). The current observation of an acute increase in ATP flux through myofibrillar CK that cannot be explained by changes in the substrates driving the CK reaction is consistent with allopurinol acting to reverse such CK inhibition by limiting ROS inactivation of the essential SH groups on myofibrillar CK. The findings lend hope that treatments such as those limiting ROS or their consequences can acutely improve the impaired myocardial CK ATP supply in human HF (11).

The enthusiasm for long-term XOI therapy in human HF was initially diminished when the OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) trial failed to demonstrate a benefit based on the composite endpoint of HF morbidity, mortality, and quality-of-life assessment (31). That trial in symptomatic HF patients compared 600 mg oxypurinol, the active metabolite of allopurinol, with placebo over 24 weeks (31). However, the 600 mg oxypurinol may have been inadequate because it has a bioequivalence of only 81 mg allopurinol (32,33), which is often administered in doses of 300 to 600 mg. In addition, the decreases in serum uric acid reported in the OPT-CHF trial were less than would be expected for a

300-mg dose of allopurinol (31,32). In contrast, a recent, retrospective analysis of HF patients with gout demonstrated improved outcomes in those taking allopurinol, with a reduction in the risk of HF readmission (adjusted rate ratio: 0.69; 0.60 to 0.79; $p < 0.001$) and for all-cause mortality (adjusted rate ratio: 0.74; 0.61 to 0.90; $p < 0.001$) (34). The clinical trial EXACT-HF (Using Allopurinol to Relieve Symptoms in Patients With Heart Failure and High Uric Acid Levels) is currently enrolling 250 HF patients with an estimated completion date of May 2012 to compare allopurinol and placebo for combined clinical endpoints, quality of life, and submaximal exercise capacity (NCT00987415). Thus, the question of the clinical benefit of long-term allopurinol administration to patients with HF at therapeutic doses is currently unresolved and was not an aim of this acute study.

Metabolic strategies to treat heart disease were first proposed >50 years ago (35,36), and the literature has been recently reviewed (37,38). Another area where modest metabolic improvements may be clinically relevant in HF relates to the observation that fatty acid oxidation is increased in HF but is a less efficient carbon source than glucose, consuming 11% to 12% more oxygen per molecule of ATP synthesized (37,39). Thus, strategies to increase glucose use (40) or inhibit fatty acid oxidation have been pursued to limit "oxygen wastage" (37). One such inhibitor, trimetazidine, improved left ventricular ejection fraction and functional class in HF patients (41).

Study limitations. The limitations of the current study include the small placebo group sample size and the etiologic heterogeneity of the nonischemic cardiomyopathy group. It is unlikely, however, that these flaws are serious because the critical analysis relates to the before and after comparison in the larger allopurinol group and because etiologic heterogeneity in nonischemic cardiomyopathy occurs commonly in clinical practice.

Conclusions

In summary, this first study demonstrating that allopurinol acutely augments myocardial energy supply via CK and increases the free energy release from the hydrolysis of each ATP molecule in HF patients likely provides the mechanism by which allopurinol improves mechanoenergetic coupling, decreasing myocardial oxygen consumption while maintaining function in human HF (11). These observations are important for both evaluating allopurinol's potential as a therapeutic agent and demonstrating a role for noninvasive ^{31}P MRS in assessing the mechanistic consequences of treatments that target energy supply and use.

Acknowledgment

The authors thank Angela Steinberg, RN, for nursing assistance and the patients who volunteered for this study.

Reprint requests and correspondence: Dr. Robert G. Weiss, Carnegie 584, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21287-6568. E-mail: rweiss@jhmi.edu.

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Key Words: creatine kinase ■ energy metabolism ■ heart failure ■ magnetic resonance spectroscopy.

APPENDIX

For an expanded Methods section, please see the online version of this article.