Xanthine Oxidase Inhibitors Improve Energetics and Function In The Post-Infarction Remodeled Mouse Heart

A. V. Naumova[1], V. P. Chacko[1], R. Ouwerkerk[1], L. Stull[2], E. Marbán[3], R. G. Weiss[3]

[1]Radiology, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3]Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, United States

Introduction

Ventricular remodeling occurs after myocardial infarction (MI) in many species, including humans, and is typically characterized by progressive ventricular dilatation, eccentric hypertrophy, and contractile dysfunction [6, 8, 10]. In addition to the geometric and contractile abnormalities associated with post-MI remodeling, adverse changes in energy metabolism also occur [4, 5, 6]. In non-ischemic experimental and human heart failure, inhibition of xanthine oxidase (XO) improves mechano-energetic coupling by improving contractile performance relative to a reduced energetic demand [1, 2]. Targeted XO blockade impacts on the progression of postischemic cardiomyopathy in mice [9] and attenuates of LV remodeling processes after experimental MI [3]. However, the metabolic and contractile effects of XO inhibitors (XOIs) on post-infarction remodeling and the effects of XOIs on depressed energetics in failing hearts have not been characterized. We hypothesized that XOIs improve bioenergetics and contractile function in the failing heart.

Methods

MI in mice was induced by the ligation of the left main coronary artery (LAD). After MI surgery, XOI mice received either allopurinol (0.5 mM, n=7) or oxypurinol (1 mM, n=11) in the drinking water, while control animals had neither (n=11). ^{1}H magnetic resonance imaging (MRI) and image-guided, spatially localized ^{31}P magnetic resonance spectroscopy (MRS) used to quantify *in vivo* functional and metabolic changes in post-infarction remodeled mouse myocardium and the effects of XO inhibition on that process (Fig.1). Experiments were performed using a GE Omega NMR spectrometer and Bruker Medical BioSpec Spectrometer (Bruker BioSpin Corp) equipped with a 4.7T/40 cm Oxford magnet. Mice were anesthetized with 1% isoflurane in oxygen (1 liter/min) delivered through a nose cone, and placed in a custom-constructed 1H coil with the heart centered over the 31P coil on a flat Plexiglas platform with temperature control (37±1°C). Single-lead ECG was recorded from platinum electrodes attached to the extremities for ECG-triggered MRI. Spin-echo transverse MR images (echo time 11ms, recycle time 500ms, slice thickness 2mm, field of view 32mm) were obtained to define the regions of metabolic interest, and to quantify left ventricular (LV) function. Spatially localized ^{31}P MRS were acquired using 1D-chemical shift imaging sequence with 32 phase encode steps in direction perpendicular to the plane of the coil, field of view of 32mm, recycle delay of 1s, 64 averages per phase encode step and an adiabatic excitation pulse**.** With this protocol, well-resolved spectra from 1-mm slices parallel to the coil were obtained. The PCr/ATP was determined from the integrated peak areas of the creatine phosphate and [β-P]ATP resonances from voxels centered on skeletal muscle or on cardiac muscle as identified from the ^{1}H MR images [7].

Results

Four weeks following MI there is a significant two-fold increase in mean LV mass (80±11mg in control group, n=9, vs 162±29mg in MI injured hearts, n=11, $p<0.001$), more than six-fold increase in LV chamber dimensions (end systolic volume (ESV) of 13mm^3 vs 182mm^3; end diastolic volume (EDV) of 31mm^3 vs 203 mm^3, for control and MI respectively, $p<0.001$), and a significant reduction in ejection fraction (EF) from 59±8% to 14±9% ($p<0.001$). Together these demonstrate a marked degree of geometric remodeling and LV dysfunction that occurs in this mouse model of permanent LAD occlusion. The myocardial PCr/ATP ratio was also significantly decreased in MI remodeled hearts (1.4±0.6) as compared to control animals (2.1±0.5, $p<0.02$). XOIs in 18 mice did not change LV mass (162±29mg in MI mice vs 151±28 in XOIs animals), but significantly attenuated the marked degree of ventricular dilatation of infarct hearts by 50% (EDV was 203mm^3 in MI group and 122mm^3 in XOI mice), increased EF (from 14±9% to 23±9%, $p=0.01$), and normalized cardiac PCr/ATP ratio (2.0±0.5, $p<0.04$).

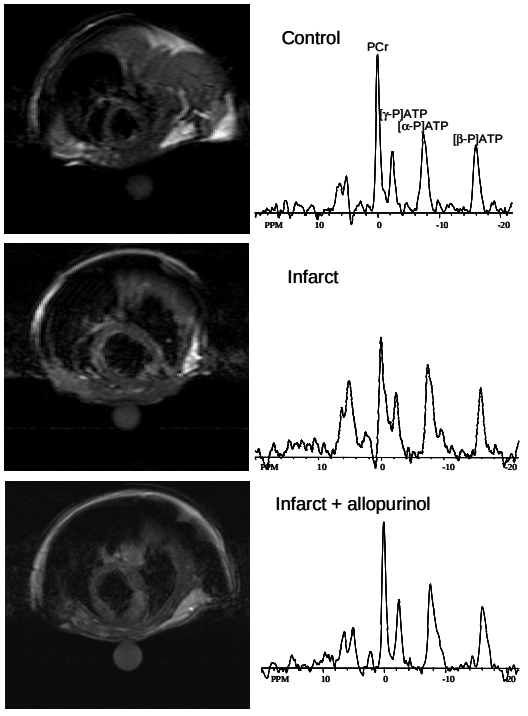

Figure 1.
Representative *in vivo* MR images (left column) and ^{31}P spectra (right column) in normal (upper) and infarct-remodeled (middle), and MI-remodeled with allopurinol mouse hearts. The cardiac PCr/ATP ratio is reduced in failing myocardium, as previously reported in larger animal infarct models [4, 5, 6], and normalized with chronic allopurinol administration.

Conclusion

Anatomic, functional, and metabolic remodeling occurs following infarction in mice to an extent grossly similar to that reported in larger animals. XO inhibitors improve ventricular function following infarction and are the first metabolic intervention to normalize high-energy phosphate ratios in heart failure. Thus XO inhibition offers a new and potentially complementary approach to limit the adverse contractile and metabolic consequences following infarction and is the first metabolic approach to improve energetics in the failing heart.

References

[1] Cappola T.P., Kass D.A., Nelson G.S., et al / Circulation 104(20): 2407-2411, 2001.
[2] Ekelund U.E., Harrison R.W., Shokek O., et al / Circ Res 85: 437–445, 1999.
[3] Engberding N., Spiekermann S., Schaefer A., et al / Circ 110: 2175-2179, 2004.
[4] Horn M., Remkes H., Strömer H., et al / Circulation 104: 1844, 2001.
[5] McDonald K.M., Yoshiyama M., et al / J Am Coll Cardiol 23 (3): 786-793, 1994.
[6] Murakami Y., Zhang J., et al/ Am J Physiol Heart Circ Physiol 276: H892-H900, 1999.
[7] Naumova A.V., Weiss R.G., Chacko V.P. / Am J Physiol Heart Circ Physiol 285(5): H1976-1979, 2003.
[8] Neubauer S., Krahe T., Schindler R., et al / Circulation 86: 1810-1818, 1992.
[9] Stull L.B., Leppo M.K., Gao W.D., and Marbán E. / Circ Res (in press).
[10] Wiesmann F., Ruff J., Engelhardt S., Hein L., et al / Circ Res 88 (6): 563-569, 2001.

Acknowledgements: NIH grant HL63030-04. We thank Michelle Leppo (Pathology Department, the Johns Hopkins University) for performing MI surgery for mice.