Creatine kinase flux and metabolite concentrations in the dysfunctional human heart following infarction

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Introduction

The primary myocardial energy reserve during periods of ischemia, hypoxia and stress is the creatine kinase (CK) reaction. The CK reaction reversibly transfers high-energy phosphate from phosphocreatine (PCr) to adenosine diphosphate (ADP) to generate ATP, the chemical energy currency essential for viability, muscular contraction and other cell functions: *PCr + ADP <-> Cr + ATP*. The pseudo-first order forward reaction rate constant is *k* (s^{-1}), and the product, {*k*.[PCr]}, is the flux for generating ATP, in µmol/g wet wt/s. *k* has long been measured by ^{31}P MRS saturation transfer methods in animals. In pigs, for example, these reveal normal *k* after myocardial infarction (MI), significant reductions in *k* in those hearts that progress to heart failure (CHF), and reduced CK flux post-MI with or without CHF [1]. Until now however, such studies have proved impractical in humans because of the inefficiency of the saturation transfer protocol and the need for spatial localization. Recently, the Four Angle Saturation Transfer (FAST) method was introduced for measuring *k* [2]. The method requires only four acquisitions that can be combined with chemical shift image (CSI) localization at short repetition periods (TR) to provide about an order-of-magnitude speed-up in scan-time compared to the classic saturation transfer method. This enables, for the first time, direct quantitative measurement of the forward myocardial CK rate constant, k, as well as the rate of ATP production via CK (flux), when combined with metabolite concentration measurements in the same exam [3, 4]. Here we report the first measurements of CK energy supply in human MI. We test the hypothesis that cardiac CK metabolites and net flux are reduced in the presence of contractile dysfunction following MI in humans.

Methods

Eleven patients (age 57 ±18 yr; 4 women) with chronic anterior MI, anterior wall motion abnormalities, and echocardiographic ejection fractions of 10-40%, were studied at rest on a GE 1.5T MRI/MRS system 6 wk-17 yr post-MI. Thirteen subjects less than 50 years old with no history of heart disease served as controls. Subjects were oriented prone on a 6.5 cm ^{31}P surface receive coil and a 25 cm transmitter coil, to provide a uniform excitation. The MRI/MRS protocol was comprised of: (i) conventional ^{1}H MRI to position subjects with the anterior myocardium over the coil and for auto-shimming; (ii) application of the localized ^{31}P FAST method involving four 1D CSI sequences with adiabatic 15° and 60° pulses, one pair acquired with saturation of γ-ATP (2.7 ppm) and another pair with control saturation (-2.7 ppm) [2]; (iii) acquisition of a fifth ^{31}P 1DCSI set with saturation turned-off (60° excitation) to provide data for metabolite quantification and correction of saturation spillover effects [3, 4]; and (iv) acquisition of a sixth ^{1}H 1DCSI data set with the ^{31}P coil to provide a water concentration reference (TR ~ 1s throughout; total exam time 60-70 min)[3]. (v) After the patient exam, steps (iii) and (iv) were repeated, fully-relaxed, on a phosphate reference phantom to calibrate the ratio of phosphate to proton signals [3]. The forward CK rate constant, *k*, was calculated from the spillover-corrected equations in ref [2] based on the data from steps (ii)-(iii). [PCr] and [ATP] (in µmol/g wet wt) were calculated from the data acquired in steps (iii)-(v) using both the water-reference method [3] and a phosphate reference method [4]: the values from both methods were averaged for each depth and patient. Contrast-enhanced MRI data was recorded from every subject in a separate exam.

Results

Myocardial CK rate constant and CK flux rates

Group	*k*, s^{-1}	[PCr], µmol/g	[ATP]	PCr/ATP	Flux, µmol/g/s
Normal (n=13)	0.32 ±0.06	9.4 ±1.1	5.6 ±1.3	1.83 ±0.28	3.2±0.7
MI (n=11)	0.33 ±0.07	5.8 ±1.6*	3.5 ±1.2†	1.70 ±0.26	1.9 ±0.5*

** P<0.00005 vs controls † P<0.0005*

[PCr] and [ATP] were both significantly reduced by 37% in anterior MI compared to healthy subjects (see Table). Consequently, the forward flux given by the product {*k*.[PCr]} was also significantly reduced by 40% in MI. The forward CK rate constant, *k*, was unchanged.

Discussion

In the dysfunctional human heart following MI, there was a significant reduction in net ATP synthesis or flux through CK that is entirely attributable to metabolite depletion. Importantly, the CK rate constant, *k*, which reflects the fraction of the PCr pool that exchanges with ATP, is normal and consistent with the porcine MI findings for animals not in CHF, and with the flux measurements [1]. That both *k* and PCr/ATP are normal, suggests that CK metabolism may also be normal in the surviving myocytes, whereas the observed bulk tissue metabolite concentrations and net CK flux are depressed by cell loss. The findings support therapies that primarily ameliorate the effects of tissue loss post-MI, as distinct from those that affect energy transfer. It is now possible to directly measure ATP turnover through CK in the human heart and to characterize ATP kinetics in the post-MI dysfunctional heart.

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References

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