The ATP flux generated by creatine kinase in the human heart at rest and during stress

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Synopsis

Although the creatine kinase (CK) reaction plays a central role in cardiac energy supply, direct measures of the ATP flux supplied by CK have not been possible in the beating human heart. We have now quantified energy flux through CK in the human heart using ^{31}P MRS with the Four Angle Saturation Transfer (FAST) method in combination with water-referenced metabolite concentration measurements in a single exam. We report that myocardial ATP synthesis through CK is less than that in skeletal muscle, and that cardiac CK flux in normal humans is largely unchanged by a pharmacologically-induced doubling of cardiac workload.

Introduction

The heart consumes the most energy per gram of any body organ and the CK reaction serves as its prime source of ATP-energy-during ischemia. It is hypothesized that the CK reaction serves as an intracellular spatial energy shuttle in myocytes, facilitating the transfer of high-energy phosphate from the mitochondria, where ATP is produced, to the cytosol where it is used (1). If the CK system is an obligate spatial energy shuttle for the human heart, then net CK flux must exceed net ATP production through oxidative phosphorylation (Ox-Phos). Measurements of the CK flux would provide an important test for the "shuttle" hypothesis.

Although standard ^{31}P MRS saturation transfer methods can measure the CK first-order forward rate constant, *k*, and CK flux in animal studies, they are inefficient, and localized measurements in humans have proved impractical due to intolerance of long exam times. Recently, the Four Angle Saturation Transfer (*FAST*) method was introduced to enable rapid measurement of CK-rates with localized ^{31}P MRS (2). FAST yielded CK-rate measurements in human skeletal muscle that agreed with conventional measurements in about 1/7 the time. CK-flux is the product of the *k*, and phosphocreatine content, [PCr]. We report the first measurements of CK pseudo-first-order rates and CK flux at rest and during dobutamine stress at 200% heart-rate blood pressure product (HRxBP) in the normal human heart. These were obtained using FAST in combination with water-referenced [PCr] metabolite quantification (3).

Methods

All experiments were done on a broadband GE 1.5T MRI/MRS system with a 25/6.5 cm diameter ^{31}P transmit/receive pair. Six normal subjects were positioned prone on the ^{31}P coil set under MRI guidance. FAST 1D CSI was performed at rest (baseline), acquiring four ^{31}P MRS data sets using both adiabatic 15° and 60° excitation pulses, with saturation of γ-ATP at +2.7 ppm and with control saturation at –2.7 ppm. This was followed by a ^{31}P and a ^{1}H MRS acquisition using a 60° pulse and no saturation, with the same ^{31}P detect coil for water-referenced [PCr] quantitation (3). Dobutamine was then infused *i.v.* until HRxBP was double that at baseline. Two further 60° acquisitions were made with γ-ATP and control saturation per the "FASTest" protocol (2). After the exam, the ratio of ^{31}P to ^{1}H signals for the coil set was measured with fully-relaxed 60° 1D CSI measurements of a calibration phantom. *k*, [PCr], and fluxes were calculated for chest and heart muscle from the data sets per Equations in (2,3).

Table: ***CK rates and fluxes in chest and heart muscle***

Muscle	*k*, s^{-1}	[PCr], μmol/gwet	Flux, μmol/gwet/s
Skeletal	0.22 ±0.07*	27 ±8	5.7±2.2*
Heart, rest	0.28 ±0.06	9.9 ±1.2	2.8 ±0.7
Heart, stress	0.33 ±0.09	9.9	3.3 ±1.2

P<0.003 vs heart in same subjects

Results

The *k* and flux measurements are tabulated above. Surprisingly, CK flux in the working beating heart is about 50% that of resting skeletal muscle. Dobutamine infusion doubled HRxBP from 7820±521 to 16,300±1260 mmHg/min, which should increase myocardial oxygen consumption and ATP synthesis through oxidative phosphorylation (Ox-Phos) by the same proportion. Yet cardiac *k* and CK flux were not significantly changed during stress: certainly not doubled.

Discussion

FAST enables, for the first time, quantitative localized measurements of CK ATP flux in the living human heart under rest and stress conditions. Prior indirect estimates of resting myocardial ATP produced by Ox-Phos are in the range 0.3-0.4 μmol/g wet wt/s (4). Thus, the rate of myocardial ATP production through CK at rest (Table 1) is still 7-10 times estimates of ATP production through Ox-Phos. Our data do not refute the CK shuttle hypothesis, but the lack of change during stress indicates that the CK-energy supply is not unlimited. *Supported by NIH grants 2RO1 HL56882, 2R01-HL61912*

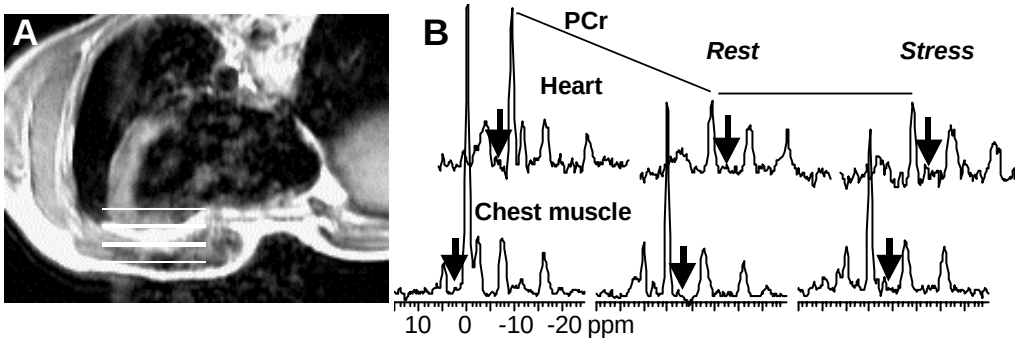

Figure: MRI showing chest muscle and heart section (A), and corresponding 6 min spectra with control and γ-ATP irradiation (arrows) at rest and dobutamine stress. The decrease in PCr is proportional to *k*.

References

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