Impaired creatine kinase ATP supply in the failing human heart

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Synopsis

Because chemical energy fuels myocardial contractile function, inadequate myofibrillar supply of high-energy phosphate could underly contractile dysfunction in human heart failure. The creatine kinase (CK) reaction is a vital source of ATP. ^{31}P MRS reveals modest reductions in CK metabolite levels in patients with moderate to severe heart failure, but CK levels do not directly index the ATP flux supplied by CK. We have quantified ATP production via CK in the failing human heart using *in vivo* ^{31}P MRS. We report that the ATP synthesis rate and flux through CK are reduced by 40% to 50%, which may be limiting.

Introduction

The CK reaction is central to mammalian energy metabolism, reversibly converting ADP and phosphocreatine (PCr) to ATP and creatine. In myocytes, the CK reaction may also play a role in transporting high-energy phosphate between the energy production sites at the mitochondria, and the myofibrils. In any case, high ATP synthesis rates are needed to sustain myocardial function, and it has been hypothesized that "energy starvation"-inadequate ATP supply-plays a central role in human heart failure (1). Phosphorus (^{31}P) and proton (^{1}H) MRS has revealed some reductions in CK metabolite levels in the failing heart (2,3), but not whether the actual supply of ATP-the CK flux-is impaired.

CK flux has been measured by saturation transfer ^{31}P MRS in animal models, but to date, noninvasive localized saturation transfer studies of myocardial CK flux in normal subjects and patients with heart disease have been precluded by inefficiencies in the standard methods. Recently, the Four Angle Saturation Transfer (FAST) method was introduced for measuring the pseudo-first-order rate constant, *k*, providing about an order-of-magnitude speed-up in scan-time in muscle studies (4). The technique enables for the first time, direct quantitative measurement of the forward CK flux or ATP supply in the normal and ailing human heart, when used in combination with metabolite concentration measurements in the same exam (5). Here we report the first measurements of CK energy supply in the failing heart.

Methods

Nine patients with New York Heart Association (NYHA) congestive heart failure classifications I-IV, left ventricular ejection fractions less than 40%, but no significant coronary disease by x-ray angiography, were recruited for the study. Fourteen subjects (<50 yr old) with no history of heart disease served as controls. Subjects were studied at rest on a GE 1.5T MRI/MRS system with a 6.5cm cm ^{31}P receive coil, and a 25 cm transmitter to provide a uniform excitation. The protocol comprised: (i) conventional ^{1}H MRI to position subjects prone with anterior myocardium over the coil and 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 with control saturation (-2.7 ppm); (iii) acquisition of a 5th ^{31}P 1DCSI set with saturation turned-off (60° excitation) for metabolite quantification and saturation spillover correction; and (iv) acquisition of a 6th ^{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). (v)After the patient exam, steps (iii) and (iv) were repeated, fully-relaxed, on a reference phantom to calibrate the ratio of phosphate to proton signals (5). The forward CK rate constant, *k*, was calculated from the spillover-corrected equations of Ref (4) based on the data from steps (ii)-(iii), [PCr] and [ATP] was calculated from the data acquired in steps (iii)-(v) per Ref (5). The CK flux is given by {*k.[PCr]*}.

Results

The *k* , [PCr], and flux measurements are summarized in the Table. Myocardial [PCr] was mildly reduced vs controls consistent with prior data (2). However, the resting CK reaction rate is reduced by 38% and the CK flux by 50% in patients with heart failure.

Table: Myocardial CK rates and fluxes in normal and CHF patients

Group	*k*, s^{-1}	[PCr], µmol/gwet	Flux, µmol/gwet/s
Normal (n=14)	0.32 ±0.07	10.1 ±1.3	3.2±0.9
CHF (n=9)	0.20 ±0.06*	8.3 ±2.1†	1.6 ±0.7*

P<0.0005 vs heart in same subjects †p<0.02 vs controls

Discussion

The efficiency advantage of the FAST method enables noninvasive measurements of myocardial CK energy flux in normal and disease states that were not previously obtainable from patients due to scan time limitations. Application of FAST and metabolite quantification to patients with heart failure reveals, for the first time, that the myocardial ATP-energy supplied by the CK reaction is significantly impaired in the failing heart. Our measurements of the myocardial CK ATP supply in heart failure still appear to be several-fold greater than prior invasive estimates of the rate of ATP utilization at rest, but energy delivery could be limiting during exercise, especially in the more severe cases of CK flux reductions. These findings support the use of intervention strategies that improve energy supply to the failing heart.

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References

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