# ATP flux through Creatine Kinase in Hypertrophic and Dilated Hearts: Altered Kinetics in Human Heart Failure

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**Introduction.** The creatine kinase (CK) reaction is important for mammalian energy metabolism, reversibly converting ADP and phosphocreatine (PCr) to ATP and creatine. In myocytes, the CK reaction may be central to the transport of high-energy phosphate from energy production sites in the mitochondria to where it is used in the myofibrils, as well as for providing a rapid temporal buffer to supply ATP during the varying energy demands of the cardiac cycle and with stress. For this purpose, a high ATP synthesis rate is critical for sustaining myocardial function, and it has been hypothesized that "energy starvation", an inadequate ATP supply, may play a key role in human heart failure (CHF) [1]. Noninvasive phosphorus ($^{31}$P ) and proton ($^{1}$H) MRS reveal reductions in CK metabolite levels and ratios in human CHF [2], but not whether the supply of ATP via CK-CK flux is impaired.

Measurements of cardiac CK flux by saturation transfer $^{31}$P MRS have in the past been limited to animal studies due to the long time required for the standard method. Recently, the Four Angle Saturation Transfer (FAST) method has enabled measurements of the pseudo-first-order CK rate constant, *k*, about an order-of-magnitude faster than the standard method [3]. By combining FAST with metabolite quantification, the first measures of both *k* and the forward CK flux, {*k.[PCr]*} in human heart have been reported [4]. A 40-50% reduction in *k* and CK flux was found last year in 9 patients with mild-to-moderate CHF and non-ischemic cardiomyopathy[4]. These results raise new questions. Are the findings associated with CHF in general, or are they limited to non-ischemic cardiomyopathy? If the reduction is linked to CHF, does the reduction in CK flux correlate with the severity of CHF?

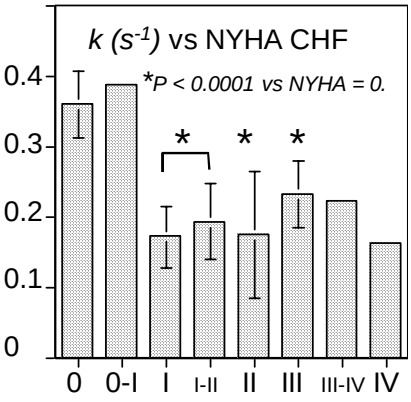
To address these questions, we applied quantitative localized FAST to measure CK rate constants, metabolite concentrations and CK flux in patients with left ventricular (LV) hypertrophy (LVH) with and without CHF, and to patients with non-ischemic dilated cardiomyopathy (DCM) and CHF of varying clinical severity.

**Methods.** The DCM+CHF group comprised 17 patients (age 46±10) with New York Heart Association (NYHA) CHF classifications I-IV, LV ejection fractions (EF) less than 40%. Significant coronary disease was excluded by x-ray angiography. The LVH group comprised 20 patients with hypertensive LVH defined by a septal and posterior echocardiographic wall thickness >1.2 cm, but no significant coronary disease by x-ray angiography or stress testing. Of these, 10 had no CHF symptoms (LVH; LV mass 181 ±51 g/m$^2$, EF 61 ±8.5%), while 10 had CHF with NYHA class II-III (LVH+CHF; LV mass 161 ±30 g/m$^2$, EF 48 ±19%; *P* = ns vs LVH). A further 13 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 6.5 cm receive and 25 cm surface transmitter coils. The protocol comprised: (i) scout $^{1}$H MRI to position subjects prone with the heart over the coil and auto-shimming; (ii) localized $^{31}$P FAST [3], involving four 1D CSI sequences with a pair of adiabatic 15° and 60° pulses applied during saturation of γ-ATP and during control saturation at -2.7 ppm; (iii) acquisition of a (5$^{th}$) 60° $^{31}$P 1DCSI set without saturation to enable metabolite quantification and a correction for saturation spillover; and (iv) acquisition of a (6$^{th}$) $^{1}$H 1DCSI data set with the 6.5-cm coil to provide a water concentration reference (TR~1s throughout; total exam time 60-70 min). After the patient exam: (v) steps #iii and #iv were repeated on a reference phantom to measure the fully-relaxed ratio of phosphate to proton signals [5]. The forward CK rate constant, *k*, was calculated from the spillover-corrected equations in ref [3] using the data from steps (ii)-(iii). [PCr] and [ATP] were calculated with the data from steps (iii)-(v) using both water and phosphate reference methods[5], and the values from both methods averaged. CK flux is {*k.[PCr]*}.

**Myocardial CK rate constant and CK flux rates**

| Group | *k*, s$^{-1}$ | [PCr], µmol/g | PCr/ATP | Flux, µmol/g/s |
|---|---|---|---|---|
| Normal (n=13) | 0.32 ±0.06 | 9.4 ±1.1 | 1.83 ±0.28 | 3.2±0.7 |
| DCM+CHF (n=17) | 0.21 ±0.08§ | 7.8 ±2.6† | 1.67 ±0.54 | 1.5 ±0.8§ |
| LVH (n=10) | 0.36 ±0.05 | 6.1 ±2.0§ | 1.26 ±0.29# | 2.2 ±0.7† |
| LVH+CHF (n=10) | 0.17 ±0.06* | 7.2 ±3.7† | 1.33 ±0.49# | 1.1 ±0.4* |

** P<0.0000005, ** P<0.000005, † P<0.05, #P<0.005, §P<0.0001 vs controls*




**Results and Discussion.** [PCr] is significantly reduced in DCM and LVH with or without CHF, compared to healthy subjects (Table). However, the forward CK rate constant, *k*, was reduced by 1/3 to 1/2 only in patients with CHF. Consequently, the forward CK flux in CHF was also 1/2 to 1/3 of that in normal subjects. Pooling all patients (DCM+LVH ±CHF) suggests that reduced *k* coincides with the presence of at least mild (Class I) CHF symptoms, with little evidence that *k* declines further with CHF severity (II-IV; Figure).

Although reduced [PCr] occurs in patients with and without CHF, reduced k is observed only in patients with CHF, independent of the underlying cause in LVH and DCM. That reduced k is observed in mild CHF, suggests that altered CK kinetics is an *early* response in the disease process. The resultant reduction in energy supply by CK is so large that it may well impair function in the failing human heart.

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**References:**

1. Lenfant C (NHLBI). Circulation 1994; 90: 1118-1123.
2. Neubauer S, et al. Circulation 1992; 86: 1810.
3. Bottomley PA, et al. Magn Reson Med 2002; 47: 850-863.
4. Bottomley PA, et al. Proc ISMRM 2004; 12: 2360.
5. Bottomley PA, Atalar E, Weiss RG. Magn Reson Med 1996; 35: 664-670.