Noninvasive assessment of cardiac work and CK energy supply in healthy and failing human hearts

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Target audience: Physiologists, cardiologists and heart failure scientists.

Purpose: One theory about heart failure (HF) is that the failing heart is "energy starved" [1,2]. This hypothesis is supported, in part, by studies showing reduced high-energy phosphate metabolite ratios and flux through the creatine kinase reaction (CK), the heart's primary energy reserve. The reduction in CK energy supply might be limiting during periods of high energy demand. Because cardiac work and energy use are not uniform during the cardiac cycle, any supply/demand imbalance is most likely to occur during periods of peak demand. We propose a comprehensive MRI/MRS protocol for noninvasive assessment of CK energy supply and mechanical work in the human heart. Measurements of the rate of adenosine triphosphate (ATP) produced via CK (CK flux) by ^{31}P-MRS are paired with temporal MRI measurements of cardiac work to provide a picture of the myocardial energy balance in normal and failing human hearts.

Methods: Ten healthy subjects (6 men, age=42±13) and 16 patients (7 men, age=44±9) with mild-to-moderate HF (NYHA class I-III) were enrolled in this IRB-approved study. Experiments were performed on a *Philips* 3.0T *Achieva* MRI system. Absolute concentrations of phosphocreatine, [PCr], and [ATP] were obtained using a 31P-MRS external referencing method, correcting for coil loading, relaxation, heart motion, tissue volume, and coil sensitivity variations within voxels. The CK reaction forward rate constant, *k*, was measured using the triple-TR saturation transfer (TRiST) method [4], localized by cardiac-triggered 1D chemical shift imaging with adiabatic excitation. The CK flux in W/kg is given by the product $\{k\cdot[PCr]\cdot\Delta G_{ATP}\}$, where the free energy of hydrolysis of ATP, $\Delta G_{ATP} \approx 60$ kJ/mol in human heart [3].

The time course of cardiac work is described by the pressure-volume (PV) loop (Fig. 1) [5]. PV loops are typically measured by pressure-conductance catheters but the procedures are invasive and unsuitable for healthy subjects. As MRI is better at measuring absolute volumes [6], we replaced catheter left ventricular (LV) volumes by noninvasive cine MRI measures, and catheter pressures by blood pressure (BP) cuff measurements from the upper arm at the level of the heart. Because pressure variations are much smaller than those in LV volume during ejection, the PV-loop can be approximated by a rectangle, with the pressure in the ejection period (Pm) taken as the average of systolic and diastolic BP, and zero during the filling period (Fig. 1: grey rectangle). The work rate, or power per kg of LV mass (LVM) is given by: $p(t)=-P(t).\{dV(t)/dt\}/LVM$ [7]. MRI was performed using a double-oblique short-axis breath-held balanced SSFP protocol with 8-12 slices from the apex to the base. The average (p_{av}) and peak (p_p) power, stroke work (SW), the pressure-volume area (PVA; a measure of the total mechanical energy [5]), and the mechanical efficiency (SW/PVA), were calculated.

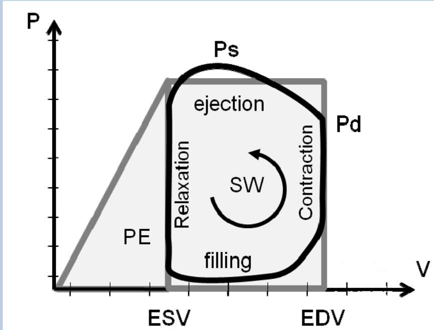

Fig 1: Pressure-volume (PV) loop (solid black) approximated by rectangular loop (grey). Stroke work (SW) and potential energy (PE) are approximated by the shaded areas. PVA=SW+PE.

Results and Discussion Table 1 reports the mechanical work and CK energy supply in absolute units (Watts) and W/kg. PVA measures are consistent with prior invasive measures [8]. When normalized by LVM, both p_{av} and p_p are significantly reduced (by 30-40%, p<0.01) in HF patients compared to healthy subjects. Also, the mechanical efficiency and the CK flux are significantly reduced in HF patients by 35% and 40%, respectively.

The reduction in the mass-normalized p_{av} and p_p, but not absolute power in HF, is consistent with LV remodeling being an adaptive response that raises total cardiac work to near normal levels at rest, while reducing mechanical work per gram of tissue. Importantly, the reduction in CK flux in HF patients (40%) is similar to that in the normalized p_{av} or p_p. This is consistent with the hypothesis that the reduction in mechanical energy per gram of tissue may be related to the reduction in ATP supplied to the myocardium by CK.

Table 1: Work and CK energy supply.
**P-value<0.01;* mM/kg=*milli-mol/kg wet wt.*

(means ±SD)	**Healthy subjects**	**HF patients**
p_{av}, Watts	1.13 ±0.20	1.06 ±0.40
p_p, Watts	5.1 ± 1.0	5.2 ± 2.1
p_{av}, W/kg	10.0 ± 1.7	6.1 ± 2.5*
p_p, W/kg	45 ± 7	30 ± 11*
PVA, W/kg	14 ± 2	13 ± 4
SW/PVA (%)	78 ± 3	51 ± 16*
[PCr] mM/kg	10.3 ± 1.6	9.1 ± 3.0
[ATP],mM/kg	5.7 ± 1.1	4.2 ± 1.4
k, s^{-1}	0.32 ±0.10	0.24 ±0.11
CK flux, W/kg	201 ± 74	120 ± 49*

Conclusion: A comprehensive MRI/MRS approach is introduced to enable noninvasive measurements of ATP flux through CK and temporal variations in cardiac work. This provides valuable insights into the heart's energy balance, and how compromised CK energy supply could affect cardiac work in HF.

References: [1] Neubauer S, N Engl J Med 2007; 356:1140. [2] Ingwall JS, Weiss RG, Circ Res 2004; 95:135. [3] Weiss RG et al, Proc Natl Acad Sci 2005; 102: 808. [4] Schar M et al, MRM 2010; 63: 1493-1501. [5] Suga H, Clin Exp Pharmacol Physiol 2003; 30: 580. [6] Slart RH et al, J Nucl Med , 2004; 45: 176-182. [7] Westerhoff et al, Snapshots of Hemodynamics, Springer, 2005, 69-70. [8] Takaoka H et al, Eur Heart J (1992) 13 (suppl E): 85-90. *Grant support: NIH HL61912.*