Creatine Kinase-Overexpression Improves Adriamycin-induced Dysfunction and in vivo ATP kinetics in Murine Hearts
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SYNOPSIS: Adriamycin (ADR) is a commonly used life-saving antineoplastic agent that also causes dose-dependent cardiotoxicity. Impaired energy metabolism may contribute to contractile dysfunction in a human heart failure and may play a role in ADR-induced cardiotoxicity. We overexpressed the myofibrillar isoform of creatine kinase (CK-M), the primary energy reserve of the heart. Improving CK metabolism in ADR-induced cardiotoxicity by increasing CK expression is a logical means to test this hypothesis because reduced CK metabolism has been linked to human and experimental HF. We created mice conditionally and cardiac-specifically overexpressing the myofibrillar isoform of CK (CK-M-OE), the most abundant isoform, and administered ADR to them and non-transgenic littermates in a regimen previously shown to induce cardiotoxicity and contractile dysfunction. We quantified the in vivo metabolic and contractile consequences of CK-M-OE in ADR hearts with ³¹P MRS.

MATERIALS AND METHODS: Experiments were carried out on a Bruker Biospec MRI/MRS spectrometer equipped with a 4.7T/40cm Oxford magnet, as previously described. Intra-peritoneal injection of ADR (5mg/kg) was administered once a week for 5 weeks as described previously. In vivo ³¹P MRS was performed at 6 and 8 weeks, and ³¹P MRS was performed at 7 weeks after ADR or placebo administration, on placebo-treated (n=6), ADR-treated (n=10 at 6wk; n=8 at 8wk), and CK-M-OE placebo-treated (n=6) and CK-M-OE ADR-treated (n=7) mice. Multi-slice cine MR images were acquired of the entire left ventricle (LV) to assess LV mass, ventricular volumes and ejection fraction (EF). The TRiST method was used to measure CK flux from [PCr(γ−)] and [ATP(γ−)]. ³¹P MR cardiac voxel denoted by white lines (B) Control ADR (7wk) (C) Control ADR overexp (D) Control ADR 8wk

RESULTS: A representative T2 image and spatially-localized TRiST ³¹P spectra are shown in Fig.1. CK-M overexpression did not alter baseline contractile function. However at 7 wk of ADR the mean PCr/ATP ratio, kᵣ and CK flux were significantly reduced in ADR-treated hearts and this was also associated with contractile dysfunction with significant reductions in EF and SV (Table 1).

DISCUSSION: First, we observe that not only is cardiac PCr/ATP reduced after ADR, as previously reported, but that for the first time, kᵣ and CK flux are significantly reduced during ADR administration. Second, CK-M overexpression increases the rate of ATP synthesis through CK (CK flux) in placebo hearts but has no effect on PCr/ATP, [PCr] and [ATP] (Table 2) or on contractile function (Table 1). Third, critically, CK-M overexpression improves cardiac energetics in ADR hearts and improves ADR-induced contractile dysfunction (Tables 1 & 2). Metabolic strategies, in particular those targeted at improving CK energy metabolism, promise a new avenue for treating or preventing cardiac dysfunction associated with ADR and thereby may allow continued or higher dose administration of this life-saving drug for some patients with malignancy.