Myocardial iron homeostasis and hepcidin expression in a rat model of chronic heart failure at different levels of dietary iron intake

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Background:
Systemic iron deficiency is present in up to 50% of patients with chronic heart failure (HF) and it is associated with impaired exercise tolerance and poor prognosis. Myocardial iron deficiency (MID) in HF patients has recently been described; however, its causes and consequences remain unknown.

Purpose:
We examined impact of HF and dietary iron content on systemic iron status, myocardial iron content, cardiac structure, function, expression of iron regulator hepcidin and other iron-related genes and survival in well-defined rat HF model induced by volume overload due to aorto-caval fistula (ACF).

Methods:
8-week old male Sprague Dawley rats fed defined synthetic diets with low, normal or high iron content underwent needle ACF/sham operation (HF/controls, n=28/30). After 21 weeks, we performed echocardiography and laboratory analyses. Separate animal cohort served for survival analysis.

Results:
MID developed in HF animals (myocardial iron content was 10% to 20% lower compared to healthy controls, p<0.05 for normal and high iron diet group). In pooled data, there was positive relation of left ventricular (LV) function (fractional shortening, r=0.40, p=0.002) and inverse relation of pulmonary congestion (lung/body weight, r=-0.47, p=0.003) to myocardial iron content. Iron supplementation did not normalize myocardial iron content; however, it improved survival (nearly 70% at 26th week in high iron diet group vs. 30% in normal iron diet group, p<0.05). Cardiac hepcidin was markedly upregulated in HF animals compared to controls (>3-fold, p<0.05). It was not related to systemic or cardiac iron levels, but strongly correlated with markers and parameters of heart injury (natriuretic peptide A, r=0.82; LV fractional shortening, r=-0.66; heart/body weight, r=-0.74, p<0.0001 for all). Identical iron-independent pattern was observed for several iron-related gene expression.

Conclusions:
In rat HF model, MID is not caused by defective iron absorption or decreased systemic iron levels, but rather by intrinsic myocardial iron deregulation. Altered cardiac hepcidin and other iron-related gene expression is
driven by iron-independent stimuli. Although the mechanisms of MID development remain incompletely understood, myocardial iron content enhancement may improve cardiac function and survival.