Intravenous iron administration in patients with heart failure alters endothelial homeostasis with early release of endothelial microvesicles and subsequent mobilization of endothelial progenitor cell

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Background: Intravenous iron supplementation is an established therapy for patients with heart failure (HF) with reduced ejection fraction (LV-EF<50%) and iron deficiency, resulting in reduced risk of HF hospitalization. Since iron may induce oxidative stress, inflammation and apoptosis in endothelial cells, concerns persist regarding potential adverse vascular effects of iron therapy. To evaluate endothelial health following ferric carboxymaltose (FCM) administration, we assessed the profile of circulating endothelial microvesicles (EMVs) and endothelial progenitor cells (EPCs) in a cohort of 23 HF patients using flow cytometry.

Results: Compared to healthy control subjects (HC; n=15), baseline levels of CD31+/CD41- EMVs were significantly higher and EMVs featured a more apoptotic phenotype in HF patients. Following administration of 1000mg FCM, EMV levels showed an early but transient increase (Fig. 1) and displayed an altered phenotype profile with dominant augmentation of EMVs expressing the inducible markers CD62E and CD54, indicating endothelial activation and injury. Levels of circulating vasoregenerative CD45lowCD34+KDR+ EPCs were lower in HF patients and FCM application resulted in an early decrease of EPCs followed by substantial mobilization into the circulation after one week (Fig. 2). Levels of EMVs and EPCs returned to baseline values within two and four weeks, respectively. Compared to HF patients with preserved renal function, the EMV/EPC ratio was higher in HF patients whereas EPC mobilization was diminished with additional chronic kidney disease, suggesting impaired vascular repair capacity. In vitro experiments with cultured endothelial cells revealed that FCM at therapeutic concentrations dose-dependently promotes endothelial apoptosis, increases expression of adhesion molecules and CXCL12, and triggers the generation of EMVs.

Conclusion: Intravenous iron supplementation with FCM in HF patients provokes a biphasic response with early release of CD62E+ and CD54+ enriched EMVs and subsequent mobilization of EPCs, suggesting temporary aggravation of endothelial dysfunction upon FCM supplementation and consecutive engagement of a vascular defense program.