Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure. (Ironout-Hf Trial)

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Hypothesis: In patients with iron deficiency and symptomatic HFrEF, oral iron replacement improves exercise capacity. An inter atrial shunt device (IASD, Corvia Medical, Qp:Qs 1.2 to 1.3), can unload the LA in the setting of increased LA pressure (LAP), transferring the excess LA blood volume to the larger reservoir of the right atrium (RA) and systemic veins, leading to decrease in LAP, pulmonary venous pressures (PVP), pulmonary capillary wedge pressure (PCWP). This mechanistic effect should improve quality of life and exercise capacity in HFmEF / HFpEF patients.

Background: Iron plays an important role in oxygen delivery. It is crucial for the production of red blood cells. It is also a cofactor for enzymes needed for cellular respiration and vascular homeostasis. About 50% of patients with symptomatic HFrEF have an iron deficiency which has been linked with reduced exercise capacity, quality of life, and increased mortality. In the 2009 Ferinject Assessment in Patients with Iron Deficiency and Chronic HF (FAIR-HF) trial, patients with symptomatic HFrEF and iron deficiency (with or without anemia) given IV iron replacement had improvements in functional capacity, HF symptoms, and quality of life. Iron Repletion Effects on Oxygen Uptake in HF (IRONOUT-HF) trial was conducted to see if inexpensive and readily available oral iron replacement would confer similar benefits. HFmEF / HFpEF patients have increased LAP, PCWP & LVEDP during rest as well as exercise. This trial evaluated the safety and functionality of the IASD System II in the treatment of HFmEF / HFpEF patients with elevated LAP, who remain symptomatic despite optimal guideline directed medical therapy (GDMT). Theoretically an artificial shunt created across the IAS with an IASD should attenuate the LAP and its surrogates PVP, PCWP & LVEDP during rest/exertion.

Methods: The 2017 IRONOUT-HF trial investigators randomized 225 patients with symptomatic HFrEF (LVEF <40% with NYHA II–IV symptoms) and iron deficiency (either ferritin 15–100 ng/mL or 100–299 ng/ML with TS at <20%) to either oral iron polysaccharide (150 mg twice daily) or placebo. The primary endpoint was increase in peak oxygen uptake (VO2 max) on cardiopulmonary exercise testing (CPET). Out of 68 patients 64 met the inclusion / exclusion criteria and underwent the IASD implantation. The primary safety endpoint was major adverse cardiac, cerebrovascular events (MACCE) at 1 month. PCWP during rest / exercise was compared between treatment groups. Safety and robust performance of the IASD at 6 months, functional capacity as well as clinical status constituted the co-primary endpoints.

Results: There was no significant improvement in the primary endpoints (VO2 max on CPET) or the secondary outcomes (6-min walk distance, NT pro-B-type natriuretic peptide [BNP] levels, quality of life). Iron markers were only modestly improved with oral iron therapy. This points out to the fact that route of administration is very important in increasing iron stores. The REDUCE LAP-HF phase I study was a multicenter, open-label, single-arm study designed to assess the performance and safety of a transcatheter IASD in patients > 40 years of age with symptoms of HFpEF despite GDMT, LVEF≥40%, and an increased PCWP at rest (>15 mmHg) or during exercise (>25 mmHg). IASD implant proved to be safe and well tolerated and was accompanied by a reduction in PCWP. The primary outcomes were encouraging as shown in Table 3. During subsequent 6 months of follow-up there was no peri-procedural or major adverse cardiac, cerebro vascular event (MACCE) or need for IASD related cardiac surgical intervention. IASD patency was confirmed by left-to-right shunting at 6 months.

Conclusion: In patients with iron deficiency (ferritin 15–100 or 100–299 with transferrin saturation <20%) and symptomatic HFrEF (LVEF ≤40% with NYHA II–IV), oral iron replacement had no significant positive effect on primary endpoints (VO2 max on CPET). Implantation of an IASD is feasible, seems to be safe, reduces LAP during exercise, and could be a new strategy for the management of HFPEF. The efficacy of IASD compared with existing treatments for patients with HFPEF requires validation in a RCT.

Clinical Perspective

IRONOUT-HF trial results suggest that there is currently no role for routine oral iron supplementation iron deficient HFrEF patients. However, FAIR-HF trial randomized 459 patients with symptomatic HFrEF (defined as LVEF ≤40% with NYHA II–III symptoms or LVEF ≤45% with NYHA III symptoms) and concomitant iron deficiency (ferritin <100 g/L or ferritin 100–299 g/L with iron saturation <20%) with mild or no anemia (hemoglobin 9.5–13.5 g/dL) and assessed the effects of administration of IV ferric carboxymaltose versus placebo on functional status. FAIR-HF showed that the use of IV iron repletion resulted in a 20% absolute increase moderate improvement in HF symptoms, 17% absolute increase in the number of patients with improvement to NHYA Class I or II, a mean 35 m increase in 6-min walk distance at 24 weeks and lower rate of first cardiac hospitalization. However, there was no significant difference in adverse event rate between the IV iron and placebo groups. One may conclude that IV iron therapy better replenishes the iron stores of the body than the oral route iron therapy. This probably explains why FAIR-HF trial is a positive and IRONOUT-HF trial is negative.

In severe mitral stenosis LA is dilated due to pressure and volume overload. However in Lutembachers syndrome where severe mitral stenosis is associated with congenital atrial septal defect (ASD), the pulmonary arteries, veins and the LA appear to acquire partial protection from the deleterious effects of pressure / volume overload. This observation has lead to the logical conclusion that IASD can transfer excess LA pressure / volume load to the RA and systemic veins during rest as well as exertion without significant increase in RV pressure / volume load.

In this non-randomized, open-label, single-arm study it is evident that IASD implant significantly lowers PCWP a surrogate of LAP, pulmonary venous pressure, PCWP and LVEDP during rest / exercise in HFmEF / HFpEF patients. The trial also proved that IASD was safe and associated with fewer symptoms. It also improved quality of life, and exercise capacity, without the occurrence of right-sided HF or pulmonary hypertension. Gerd et al have made a commendable and fairly successful attempt to cut the Gordian knot of HFpEF by circumventing the pathophysiology and trying to partially equate the atrial pressures (LA unloading) leading to attenuation of the LAP and its surrogates PVP, PCWP and LVEDP. The IASD is designed to dynamically (at rest and during exercise) decompress LA in HFmEF / HFpEF patients. However since this a non-randomized, open-label, single arm study with its associated bias and confounding factors, a larger RCT is warranted to prove the effectiveness of the IASD.

Reference: Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-27.

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