Challenges with the Diagnosis of Iron Deficiency in Heart Failure

Iron deficiency (ID) is a very common comorbidity in patients with heart failure (both acute and chronic), but overall awareness is low and the diagnosis of ID is challenging in this patient population. The diagnostic criteria for ID in HF patients remains an area of active research and disagreement, as shown by the different criteria used to define ID across HF trials.1,2 Awareness about ID in HF also remains low, even among specialists, as highlighted by a recent survey during our own symposium on this topic at the 2020 American Heart Association (AHA) Scientific sessions; during this symposium, 52% of participants indicated that they rarely assess iron status in HF patients, 14% responded that they have never assessed iron status, and only 10%-24% do so frequently or all the time.3 As such, these results seem to support prior reports of delayed diagnosis and missed opportunities to address ID in HF.1

DIAGNOSING IRON DEFICIENCY IN HEART FAILURE

Iron is an essential component of body homeostasis and a key component for erythropoiesis in the bone marrow, and as such ID is naturally linked with anemia. This condition, often referred to as iron deficiency anemia often accompanies chronic diseases with an increased inflammatory burden (e.g., chronic kidney disease, heart failure, inflammatory bowel disease, rheumatoid diseases), however, the pathophysiological impact of ID regardless of anemia is consequential.4 One of the main challenges in diagnosing ID is the distinction between functional and absolute iron deficiency.1,4,5 Iron deficiency can be absolute, when total body iron is decreased, or functional, when total body iron is normal or even increased, but iron is not available or not sufficient because it has been trapped in the iron storage pool.5 This interplay between the iron storage pool (consisting of liver, spleen, and lymph nodes) and functional pool (consisting of red blood cells, bone marrow, and cardiac and skeletal muscle) makes it very challenging to diagnose ID.1,5 In diseases like heart failure, due to complex pathophysiological mechanisms, the body often does not have enough iron to utilize for homeostasis despite normal iron levels within the storage pools, and more often ID in HF is functional rather than absolute.5,6 Furthermore, although ID can decrease hemoglobin synthesis, it is only classified as anemia once hemoglobin levels fall below a certain level.6 As such, screening for anemia is not enough, and the diagnosis of iron deficiency without anemia is a critical one to make, particularly in HF patients.6
The gold standard for ID diagnosis is bone marrow aspiration with Prussian Blue staining, but this approach is not well-suited for everyday practice. Several biomarkers which are detected in the blood and secreted by tissues that utilize or store iron have been proposed to measure ID. Two commonly-used markers for ID are serum ferritin, an intracellular protein that stores iron, and transferrin saturation (TSAT), a marker of how much serum iron is bound to transferrin, which is a molecule that carries iron to the storage and functional pools. However, serum ferritin is a poor measure of iron deficiency in patients with heart failure, and many patients with normal serum ferritin (defined by many as greater than 100 µg/L) have iron deficiency. Inflammation or oxidative stress may also artificially increase ferritin concentrations, regardless of actual iron status. In contrast to other clinical settings, the ferritin threshold defining deficient iron storage is increased to 100 µg/L in heart failure patients to take account of the chronic inflammatory state. As such, it is recommended that in chronic inflammatory conditions, including HF, when ferritin levels may be elevated, that TSAT levels must be used. These two markers, serum ferritin and TSAT make up the current definition of ID that is used in most heart failure trials: ferritin <100 µg/L or 100-299 µg/L with TSAT <20%. This forms the basis for the diagnostic algorithm for ID in HF and for the potential initiation of iron repletion treatment to correct ID regardless of anemia status (Figure 1).

**Symptomatic HF Patient (NYHA II-IV)**

Check Hemoglobin levels

**YES**

Check Ferritin and TSAT levels, if:
- Ferritin <100 µg/L or
- Ferritin 100-299 µg/L with TSAT <20%

Consider iron deficiency treatment with intravenous iron**

**NO**

Investigate for anemia accordingly

No Iron Deficiency Treatment

*Normal levels of hemoglobin are ≥130 g/L for males, ≥120 g/L for females, and ≥110 g/L for pregnant females

**Re-evaluate iron status after 3-6 months

Figure 1. The diagnostic algorithm for ID in HF.

**PERSPECTIVES AND FUTURE DIRECTIONS**

As mentioned above, the definition of ID in HF remains controversial. The diagnosis based on ferritin and TSAT may be inadequate in advanced disease or acute heart failure when ferritin becomes an unreliable marker. Iron deficiency can therefore be underdiagnosed in these types of patients, and there is a need to identify additional and more reliable biomarkers. Recently, the World Health Organization updated it's recommended cut-off values to define ID and risk of iron overload by measuring serum ferritin, indicating that in adults or older persons with infection or inflammation (which can encompass also HF patients), a serum ferritin level of <70 µg/L should be used to define ID, with levels of >500 µg/L used to define the risk of iron overload. However, for the reasons indicated above, this might not be relevant so much for defining ID in HF patients, but more likely to reduce the risk of iron overload, since it has been suggested that ferritin levels could be more relevant for monitoring iron overload rather than diagnose ID in this setting.

Additional markers of ID in HF are currently being investigated. The soluble transferrin receptor (sTfR) levels are increased in ID and are not affected by inflammation, and studies have shown that among serum parameters, sTfR and TSAT may have the strongest correlation with bone marrow iron depletion. Another emerging biomarker is serum hepcidin, which may correlate with iron stores more precisely than ferritin. However, they remain investigational at this stage and are not available in clinical practice, and improving the diagnostic accuracy of non-invasive markers for ID in HF remains an active area of research.

www.cardiometabolichealth.org
REFERENCES: