Screening and Diagnosis of ID in HF

CHALLENGES WITH THE DIAGNOSIS OF IRON DEFICIENCY IN HEART FAILURE

Iron deficiency (ID) is a very common comorbidity in patients with heart failure (HF; 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 patients with HF remains an area of active research and disagreement, as shown by the different criteria used to define ID across HF trials.[1,2] ID has traditionally been associated with anemia in HF patients, despite the fact that iron status does not strongly correlate with red cell indices in this population. Awareness of ID in HF also remains low, even among specialists, as highlighted by a 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 to 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]

IRON DEFICIENCY VERSUS IRON DEFICIENCY ANEMIA

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 (IDA), can accompany chronic diseases with an increased inflammatory burden (e.g., chronic kidney disease, HF, inflammatory bowel disease, rheumatoid diseases). However, ID and IDA do not always coexist, and the pathophysiological impact of ID independent of anemia is consequential.[4]

In patients with HF, ID is much more prevalent than IDA. Approximately 25 to 45% of HF patients have ID without anemia.5 Up to 68% of chronic HF patients have ID,6 and in men and women with acute HF, rates are also high at 57% and 79%, respectively.[7] In HF with preserved ejection fraction (HFpEF), ID prevalence rates may be slightly higher than HF with mid-range (HFmrEF) or reduced EF (HFrEF).[8] Regardless of anemia status, ID negatively impacts exercise capacity, and is associated with increased acute care utilization, death, and reduced quality of life (QoL) in patients with HF.[9] In HFmrEF and HFrEF, ID is associated with higher rates of HF hospitalization, heart transplantation, and increased mortality.[9] In HFpEF, ID is also associated with decreased exercise capacity as well as lower QoL.[9] Regardless of hemoglobin levels, correction with IV iron reduces hospitalizations, improves QoL, exercise capacity, and patient symptoms.[10] A growing body of evidence also suggests that ID may not be a mere comorbidity of HF, but rather an important contributor to HF pathophysiology and disease progression.[9] This new data further underscores the importance of ID screening, diagnosis, and treatment in patients with HF, whether or not these patients present with anemia.

DIAGNOSING IRON DEFICIENCY IN HEART FAILURE

One of the main challenges in diagnosing ID is the distinction between functional and absolute iron deficiency.[1,4,11] 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.[11] 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.[1,11] In diseases like heart failure, due to complex pathophysiological mechanisms, the body often does not have enough iron to utilize for homeostasis despites normal iron levels within the storage pools, and more often ID in HF is functional rather than absolute.[11,12] Furthermore, although ID can decrease hemoglobin synthesis, it is only classified as anemia once hemoglobin levels fall below a certain level.[12] 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.[12] The gold standard for ID diagnosis is bone marrow aspiration with Prussian Blue staining, but this approach is not well-suited for everyday practice.[5] Several biomarkers which are detected in the blood and secreted by tissues that utilize or store iron have been proposed to measure ID.[11] 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.[11,12] 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.[11] 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%.[1] 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).[1] While acknowledging the limitations of this diagnostic approach and the need for an improved definition of ID, authors of the 2023 Scientific Statement on ID in HF from the Heart Failure Society of America endorsed it as a valid approach until optimal markers are identified.[5]

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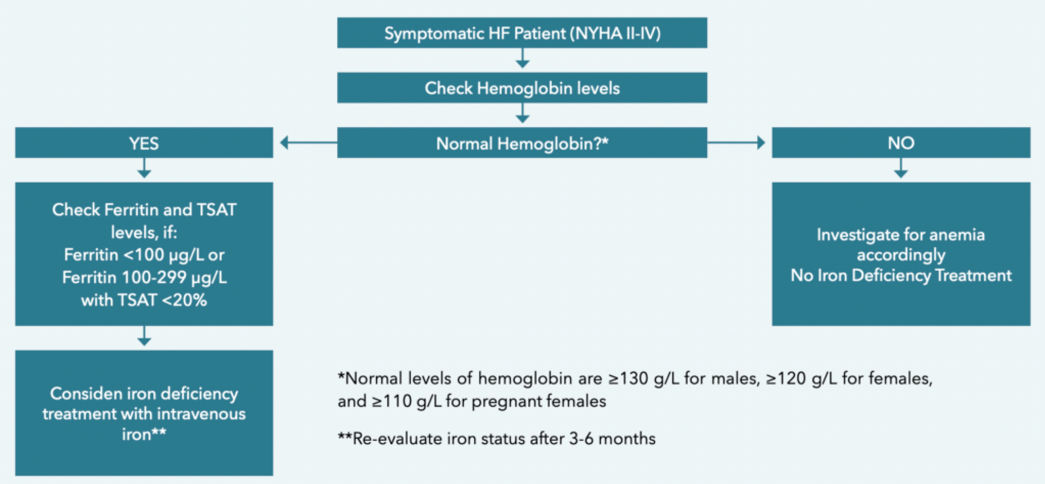

Figure 1. The diagnostic algorithm for ID in HF.1

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 HF 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.[1,4,11] Recently, the World Health Organization updated its 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 also encompass 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.[13] However, for the reasons indicated above, this cutoff might not be as relevant for defining ID in HF patients, but may help reduce the risk of iron overload, given that ferritin levels may be more relevant for monitoring iron overload rather than for diagnosing ID in this setting.[11] Additional markers of ID in HF are currently being investigated. Serum iron <13 µmol/L may be a more accurate predictor of bone marrow iron deficiency and has been found to correlate with low TSAT.[8] 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.[11,14] In multivariate prediction models of 3-year all-cause mortality in patients with HF, sTfR was found to eliminate the prognostic value of serum ferritin and TSAT after adjustment for other prediction factors.[9] Another emerging biomarker is the acute phase protein hepcidin, which may correlate with iron stores more precisely than ferritin. Hepcidin plays a key role in iron homeostasis, and it is now believed that decreased iron absorption related to chronic inflammation and increased hepcidin levels may be a cause of ID in HF.[10] However, these novel markers remain investigational at this stage and are not available in clinical practice. Improving the diagnostic accuracy of non-invasive markers for ID in HF remains an active area of research.

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