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Pathophysiology of Anemia in Heart Failure: Mechanisms and Clinical Implications

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SÚHRN

Anémia je častou komplikáciou srdcového zlyhávania (SZ) a jej prítomnosť je spojená s nepriaznivou prognózou nezávisle od ostatných rizikových faktorov. Postihuje až polovicu pacientov a často ju sprevádzajú zmeny erytrocytových indexov, ktoré odrážajú systémovú dysreguláciu. Patofyziológia anémie pri SZ je multifaktoriálna a zahŕňa hemodilúciu v dôsledku kongescie, poruchu produkcie erytropoetínu (EPO) a zníženú odpoveď kostnej drene v dôsledku renálnej hypoperfúzie, zápalu a uremického prostredia, funkčný deficit železa sprostredkovaný hepcidínom, nutričné faktory a vplyv farmakoterapie, skrátené prežívanie erytrocytov, ako aj oxidačný stres a mitochondriálnu dysfunkciu.

Tieto vzájomne sa ovplyvňujúce mechanizmy sa odrážajú v bežne dostupných laboratórnych parametroch vrátane hemoglobínu, erytrocytových indexov, distribučnej šírky erytrocytov (RDW), feritínu a saturácie transferínu, ktoré poskytujú informácie o erytropoetickej aktivite, dostupnosti železa a obrate erytrocytov. Najmä RDW integruje poruchy erytropoézy a znížené prežívanie erytrocytov a konzistentne súvisí s nepriaznivou prognózou vo všetkých fenotypoch srdcového zlyhávania.

Anémia pri srdcovom zlyhávaní preto predstavuje dynamický prejav multisystémovej dysregulácie, a nie izolovanú hematologickú poruchu. Hodnoty hemoglobínu je preto potrebné interpretovať v kontexte objemového stavu organizmu a metabolizmu železa, nie iba so zameraním na ich izolovanú korekciu. Budúci výskum by sa mal zamerať na fenotypizáciu založenú na biomarkeroch s cieľom lepšie identifikovať dominantné patofyziologické mechanizmy anémie pri srdcovom zlyhávaní.

Keywords:
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ABSTRACT

Anemia is a common complication of heart failure (HF) and provides independent prognostic information. It affects up to half of patients and is frequently accompanied by alterations in erythrocyte indices that reflect underlying systemic dysregulation. The pathophysiology of anemia in HF is multifactorial and involves congestion-related hemodilution; impaired erythropoietin (EPO) production and marrow responsiveness due to renal hypoperfusion, inflammation, and uremic milieu; hepcidin-mediated functional iron deficiency; nutritional and medication-related influences; reduced red blood cell lifespan; and oxidative and mitochondrial dysfunction.

These interacting mechanisms are captured by routinely available laboratory parameters, including hemoglobin, mean corpuscular indices, red cell distribution width (RDW), ferritin, and transferrin saturation, which provide insight into erythropoietic activity, iron availability, and red blood cell turnover. RDW, in particular, integrates disturbed erythropoiesis and impaired erythrocyte survival and consistently associates with adverse outcomes across HF phenotypes.

Overall, anemia in HF represents a dynamic manifestation of multisystem dysregulation rather than an isolated hematologic disorder. Interpretation of hemoglobin values therefore requires integration with volume status and iron metabolism rather than isolated correction. Future research should prioritize biomarker-guided phenotyping to better delineate dominant pathophysiological drivers of anemia in heart failure.

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Introduction

Heart failure (HF) is a complex clinical syndrome affecting more than 64.3 million people worldwide.[1] Despite advances in pharmacotherapy and device therapy, heart failure remains associated with substantial morbidity and high mortality, underscoring the seriousness of the condition.[2] Among the systemic manifestations of HF, anemia and related hematological abnormalities occupy a central role. The reported prevalence of anemia in chronic heart failure varies considerably across studies, ranging from approximately 15–20% in unselected cohorts to nearly 50% in more advanced or comorbid populations, whereas iron deficiency is generally more prevalent across NYHA classes and heart failure stages, affecting approximately 30–50% of patients.[3–5] Both anemia and iron deficiency are associated with reduced functional capacity, higher rates of hospitalization, and worse clinical outcomes in patients with heart failure.[4–6]

In patients with heart failure, hemoglobin and markers of iron status such as ferritin and transferrin saturation are routinely assessed as part of guideline-recommended evaluation, reflecting their clinical relevance in diagnosis and management.[7] Their alteration in HF is not simply a bystander phenomenon but reflects systemic processes that contribute to disease progression.[8] Recent therapeutic advances have further emphasized the clinical relevance of hematological mechanisms in heart failure, including the potential benefits of intravenous iron therapy, thereby highlighting the need to better understand the pathophysiological basis of anemia in this population. Anemia in heart failure arises from a complex interplay of impaired erythropoiesis, altered iron metabolism, chronic inflammation, renal dysfunction, hemodilution, and reduced red blood cell survival.[8–11] This review focuses on the pathophysiology of anemia in heart failure, with particular emphasis on mechanisms of altered erythropoiesis, red blood cell survival, and plasma volume expansion–related hemodilution, and their implications for clinical assessment.

Pathophysiology of anemia in HF

Hemodilution and plasma expansion

Hemodilution represents an important contributor to anemia in heart failure, reflecting volume overload related to neurohumoral and renal maladaptation rather than a true reduction in red blood cell mass.[12] In HF, reduced cardiac output and arterial underfilling are sensed as a state of effective hypovolemia, despite total body fluid excess. This mismatch leads to reduced renal perfusion pressure and activation of key compensatory pathways, including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and non-osmotic release of arginine vasopressin. The downstream effects include enhanced tubular sodium reabsorption, free water retention, and progressive intravascular and interstitial volume expansion.[13] Collectively, these neurohumoral and renal responses promote sustained plasma volume expansion, thereby predisposing patients with heart failure to dilutional reductions in hemoglobin concentration despite preserved red blood cell mass.

Consequently, this pathophysiological milieu results in a characteristic hemodynamic profile of chronic heart failure, in which venous congestion and altered capillary Starling forces promote interstitial fluid accumulation. At the same time, the expanded interstitial compartment serves as a dynamic reservoir for intravascular refilling, allowing plasma volume to increase despite the absence of a parallel rise in red blood cell mass. Because these processes evolve gradually and involve ongoing redistribution of fluid between compartments, substantial hypervolemia may remain clinically occult and under-recognized in routine practice. Overall, these hemodynamic disturbances promote sustained plasma volume expansion, resulting in dilution-related reductions in circulating hemoglobin concentration.[14]

Consistent with this hemodynamic profile, studies employing quantitative blood volume analysis in patients with symptomatic advanced heart failure have demonstrated that plasma volume in hemodiluted individuals may increase to approximately 150% of predicted normal values, while red cell mass remains within normal limits, with nearly half of anemic patients exhibiting dilutional rather than true anemia.[12] Beyond this chronic phenotype, similar volume-related mechanisms operate dynamically during acute decompensation. In the setting of acute decompensated heart failure, transient hemodilution may occur early during hospitalization, likely reflecting dynamic intravascular volume refilling and fluid redistribution before effective net decongestion is achieved, with hemoglobin concentrations declining by up to approximately 1 g/dL during the first days of admission.[15,16] Taken together, these findings indicate that both chronic and acute reductions in hemoglobin in heart failure frequently reflect underlying volume dysregulation, underscoring the need to interpret hemoglobin values in close relation to volume status and its temporal evolution.[12,15,16]

Extending these mechanistic insights into the clinical domain, large cohort studies have further demonstrated that hemoglobin trajectories during hospitalization carry important prognostic information. Patients who fail to hemoconcentrate or experience a decline in hemoglobin despite therapy exhibit higher mortality and persistent congestion, consistent with unresolved volume overload rather than primary hematologic deterioration.[15] Collectively, these findings emphasize that anemia in heart failure is not a uniform entity but a heterogeneous manifestation of volume, renal, and neurohumoral dysregulation, necessitating an integrated assessment of hematologic indices alongside markers of fluid status to guide optimal management.[12,14–16]

Iron deficiency: absolute and functional

Iron deficiency (ID) is highly prevalent in patients with heart failure and contributes substantially to the overall clinical burden of the disease.[17] Beyond its role in erythropoiesis, iron is essential for multiple cellular processes, including mitochondrial oxidative phosphorylation, skeletal and cardiac muscle function, and efficient oxygen utilization.[18] Consequently, iron deficiency—even in the absence of anemia—impairs mitochondrial energy

production and skeletal muscle oxidative capacity, contributing to fatigue and reduced exercise tolerance.[17] Restoration of iron availability has been shown to improve fatigue and physical performance in iron-deficient, non-anemic individuals, underscoring the pathophysiological relevance of iron deficiency beyond hemoglobin synthesis.[9]

In heart failure, two major forms of iron deficiency are recognized: absolute and functional iron deficiency. Absolute iron deficiency reflects true depletion of total body iron stores and may arise from insufficient dietary intake, chronic gastrointestinal blood loss, or impaired intestinal iron absorption. In contrast, functional iron deficiency is characterized by preserved or increased iron stores with impaired iron availability for erythropoiesis and cellular metabolism.[17]

In patients with heart failure, absolute iron deficiency may be further exacerbated by impaired gastrointestinal perfusion and venous congestion, which contribute to mucosal dysfunction and reduced duodenal iron transport, thereby blunting the normal adaptive increase in iron absorption during iron depletion.[17] In addition, long-term use of antithrombotic therapies increases the risk of occult gastrointestinal bleeding, which may contribute to progressive iron loss and depletion of iron stores.[19]

Functional iron deficiency in heart failure predominantly arises from inflammation- and hepcidin-mediated impairment of iron mobilization, resulting in restricted iron availability for erythropoiesis and cellular metabolism despite preserved or increased iron stores.[17,20] This process is mediated by pro-inflammatory cytokines, particularly interleukin-6, which drive hepatic hepcidin synthesis and thereby reinforce iron sequestration in the setting of heart failure–associated low-grade systemic inflammation. Hepcidin acts as the central regulator of systemic iron homeostasis by binding to ferroportin, the only known cellular iron exporter, inducing its internalization and degradation. As a result, intestinal iron absorption is suppressed and iron sequestration within macrophages and hepatocytes is enhanced, leading to iron-restricted erythropoiesis despite preserved or elevated ferritin concentrations.[17,20] Accordingly, this hepcidin-mediated sequestration of iron within storage sites restricts its release into the circulation, resulting in preserved or elevated ferritin concentrations despite reduced circulating iron and highlighting the pathophysiological basis for prioritizing transferrin saturation over ferritin alone in the diagnostic assessment of iron status in heart failure.[7,17,20] Importantly, this same hepcidin-driven blockade of intestinal iron transport also explains the limited efficacy of oral iron supplementation in heart failure, as absorbed iron cannot be effectively transferred into the circulation.[20,21]

At the myocardial level, iron deficiency exerts deleterious effects on the cardiovascular system that extend beyond impaired oxygen transport. Iron is an essential cofactor for mitochondrial enzymes involved in oxidative phosphorylation, including cytochromes and iron–sulfur cluster–containing proteins, which are fundamental for cellular ATP production, particularly in energy-demanding tissues such as the myocardium. Iron deficiency impairs mitochondrial respiratory capacity, leading to reduced ATP generation and compromised cardiomyocyte contractile performance.[22,23] Experimental and translational studies have demonstrated associations between myocardial iron depletion and altered calcium handling, increased oxidative stress, and impaired excitation–contraction coupling, contributing to both systolic and diastolic dysfunction.[22–25] Together, these iron-dependent disturbances link myocardial energetic failure to impaired contractile and relaxation properties, providing a mechanistic basis for the contribution of iron deficiency to cardiac dysfunction in heart failure.

Beyond the myocardium, similar iron-dependent disturbances of mitochondrial function extend to peripheral tissues, particularly skeletal muscle, where they further amplify the functional limitations of heart failure. At the peripheral tissue level, beyond its hematological effects, iron deficiency adversely affects oxygen utilization and skeletal muscle function. Reduced iron availability impairs mitochondrial biogenesis and oxidative capacity in skeletal muscle, shifts energy metabolism toward less efficient anaerobic pathways, and increases lactate production during exertion, thereby exacerbating fatigue and exercise intolerance—hallmark features of heart failure. These peripheral metabolic disturbances increase ventilatory and circulatory requirements during exertion, necessitating higher cardiac output and heart rate to sustain oxygen delivery. The resulting mismatch between metabolic demand and limited cardiac reserve is likely to enhance sympathetic activation and neurohumoral drive, thereby reinforcing maladaptive pathways that accelerate disease progression in heart failure.[26,27]

Clinical evidence consistently demonstrates that iron deficiency in heart failure is associated with impaired functional capacity, reduced quality of life, and worse clinical outcomes, independent of the presence of overt anemia. This strong and consistent association has positioned iron deficiency as a clinically relevant and potentially modifiable therapeutic target in heart failure.[17] Randomized controlled trials have shown that correction of iron deficiency with intravenous iron therapy leads to clinically meaningful improvements in functional status and patient-reported outcomes[9–11] (**Table 1**). In the FAIR-HF trial, treatment with intravenous ferric carboxymaltose significantly improved exercise capacity, NYHA functional class, and quality of life, with comparable benefits observed in both anemic and non-anemic patients, underscoring the importance of iron-related mechanisms beyond hemoglobin synthesis.[9] These favorable effects were subsequently confirmed in pooled individual patient data analyses of randomized trials, which demonstrated sustained improvements in functional capacity and health status, as well as a reduction in heart failure-related hospitalizations.[26] Importantly, the AFFIRM-AHF trial extended these findings to patients hospitalized with acute decompensated heart failure, showing that intravenous iron repletion initiated during hospitalization was associated with a significantly reduced risk of subsequent heart failure rehospitalization.[10] Collectively, these data indicate that iron deficiency is not merely a marker of disease severity but an active contributor to the symptomatic burden and clinical course of heart failure, and that its targeted correction represents an effective disease-modifying strategy in appropriately selected patients.

Table 1 – Key randomized trials of intravenous ferric carboxymaltose in heart failure

Trial (year)	Population & ID criteria	Intervention	Primary outcome	Main findings (directional)	Notes / refs
FAIR-HF (2009)	Symptomatic HFrEF; ID: ferritin <100 µg/L or 100–299 µg/L with TSAT <20%	Ferric carboxymaltose (FCM) vs placebo	Patient Global Assessment & NYHA class	↑ Symptoms/QoL; ↑ 6MWT; benefits irrespective of baseline Hb	[9]
CONFIRM-HF (2015)	Ambulatory HFrEF with ID (as above)	FCM vs placebo (longer follow-up)	6-minute walk distance	Sustained ↑ 6MWT; improved symptoms/QoL; fewer HF hospitalizations (secondary)	[11]
AFFIRM-AHF (2020)	Recently hospitalized acute HF with LVEF <50% and ID	FCM vs placebo post-stabilization	HF rehospitalization & CV death (composite)	↓ HF rehospitalizations; neutral on CV death; overall composite favored FCM	[10]

CV – cardiovascular; EF – ejection fraction; FCM – ferric carboxymaltose; Hb – hemoglobin; HF – heart failure; HFrEF – HF with reduced EF; ID – iron deficiency; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; QoL – quality of life; 6MWT – 6-minute walk test.

Taken together, these observations demonstrate that iron deficiency in heart failure is not merely a comorbidity but a key pathophysiological contributor to disease progression. Its systemic effects extend beyond hematopoiesis to myocardial and skeletal muscle energetics, underscoring the importance of routine assessment and targeted correction of iron deficiency in contemporary heart failure management.

Erythropoietin dysregulation and marrow responsiveness

Erythropoietin (EPO) is the principal hormonal regulator of erythropoiesis, stimulating the survival, proliferation, and differentiation of erythroid progenitor cells. It is synthesized predominantly by renal peritubular oxygen-sensing fibroblasts and is transcriptionally regulated by hypoxia-inducible factor (HIF)-2α in an oxygen-dependent manner. Under normoxia, HIF-2α undergoes rapid hydroxylation and proteasomal degradation, whereas hypoxia promotes its stabilization and nuclear translocation, leading to transcriptional activation of the EPO gene and increased plasma EPO concentrations. This mechanism constitutes the physiological link between renal oxygen sensing and red blood cell production.[27]

In heart failure (HF), this adaptive response is profoundly disturbed.[28] Reduced cardiac output and systemic hypoperfusion impair renal oxygen delivery, while venous congestion increases interstitial pressure and compromises effective capillary perfusion.[29] Under physiological conditions, such renal hypoxia would be expected to activate HIF-2α signaling and increase EPO synthesis.[27] However, in HF, these compensatory mechanisms fail because chronic renal hypoperfusion and venous congestion activate profibrotic and inflammatory signaling pathways—particularly transforming growth factor-β—driving transdifferentiation of EPO-producing peritubular fibroblasts into non–EPO-producing myofibroblasts and accelerating tubulointerstitial fibrosis, thereby limiting the kidney's capacity to upregulate EPO synthesis.[29–31] The frequent coexistence of chronic kidney disease (CKD) in HF patients further aggravates this defect by reducing functional nephron mass and tubular integrity, thereby limiting renal EPO-producing capacity and impairing the adaptive erythropoietic response to hypoxia.[32] In addition, uremic toxins that accumulate in CKD, such as indoxyl sulfate, directly suppress EPO production and disrupt renal oxygen-sensing pathways.[33] Together, these renal and uremic factors contribute to a relatively insufficient and maladaptive EPO response in HF, despite persistent hypoxic stimuli.

Based on the renal structural and functional abnormalities described above, reduced renal EPO-producing capacity would be expected.[32] However, circulating EPO concentrations in HF are often normal or only modestly increased.[34] This apparent dissociation reflects strong compensatory stimulation of the remaining EPO-producing cells by systemic hypoxia and sustained neurohormonal activation. As a result, circulating EPO levels may be maintained or modestly increased despite reduced renal EPO-producing capacity. However, this response remains quantitatively insufficient relative to the severity of anemia and tissue hypoxia, consistent with a state of relative EPO insufficiency.[28]

More importantly, the bone marrow response to EPO is markedly blunted.[35] Proinflammatory cytokines systemically elevated in heart failure, including tumor necrosis factor-α and interleukin-1β, functionally impair JAK2/STAT5-dependent EPO signaling, thereby suppressing EPO-driven proliferation and differentiation of erythroid progenitors.[35,36] Concurrently, functional iron deficiency driven by hepcidin overexpression limits iron availability for hemoglobin synthesis by sequestering iron within macrophages and hepatocytes.[20] As a result, erythroid progenitors fail to respond adequately to EPO due to inflammatory cytokine–mediated signaling impairment and limited substrate availability, leading to ineffective erythropoiesis despite elevated EPO levels.[20,35]

Early small and largely uncontrolled studies suggested that treatment with erythropoiesis-stimulating agents (ESAs), particularly when combined with intravenous iron, could increase hemoglobin levels and be associated with improvements in functional capacity, New York Heart Association (NYHA) class, and a possible reduction in heart failure-related hospitalizations.[37]

However, these findings were not confirmed in larger, adequately powered randomized controlled trials.

In the RED-HF trial, which enrolled 2,278 patients with heart failure with reduced ejection fraction (HFrEF) and anemia, treatment with darbepoetin alfa led to only a modest increase in hemoglobin levels compared with placebo, without any reduction in all-cause mortality or heart failure hospitalizations. Moreover, ESA therapy was associated with a significantly higher incidence of thromboembolic events, raising important safety concerns and arguing against the routine use of ESAs in patients with heart failure and anemia.[38]

These findings underscore a fundamental pathophysiological distinction between heart failure-related anemia and anemia of chronic kidney disease.[39] In chronic kidney disease, anemia is predominantly driven by absolute erythropoietin deficiency, and treatment with erythropoiesis-stimulating agents—particularly when combined with adequate iron supplementation—is generally effective in correcting hemoglobin levels.[40]

In contrast, anemia in heart failure is characterized by preserved or elevated circulating EPO concentrations accompanied by reduced bone marrow responsiveness to EPO, consistent with a state of relative erythropoietin resistance.[41] As a result, pharmacological stimulation of erythropoiesis by erythropoiesis-stimulating agents has failed to translate into meaningful clinical benefit in heart failure, consistent with the concept of relative EPO resistance observed in large randomized interventional trials.[42]

Together, these observations indicate that anemia in heart failure is driven primarily by impaired erythropoietic responsiveness rather than insufficient EPO availability, highlighting the limitations of ESA-based strategies and underscoring the need for alternative therapeutic approaches.

Inflammation as an upstream driver of anemia in heart failure

Heart failure is increasingly recognized as a chronic low-grade inflammatory condition, in which sustained activation of innate immune pathways—particularly monocyte/macrophage activation, inflammasome signaling, and pattern-recognition receptor–mediated responses—contributes to adverse cardiac remodeling and disease progression. This inflammatory state arises from a convergence of hemodynamic stress, repetitive ischemia–reperfusion injury, neurohormonal activation, endothelial dysfunction, and tissue hypoxia, which collectively promote immune cell activation and cytokine release.[43]

Pro-inflammatory cytokines characteristically elevated in heart failure—particularly tumor necrosis factor-α, interleukin-6, and interleukin-1β—converge to suppress effective erythropoiesis through complementary and reinforcing mechanisms. TNF-α and IL-1β directly impair erythroid progenitor survival and proliferation by promoting apoptosis and cell-cycle arrest, while also attenuating erythropoietin-mediated signaling at the bone marrow level. In parallel, IL-6-driven inflammatory signaling restricts iron availability predominantly through STAT3-mediated induction of hepcidin and contributes to erythropoietin resistance by impairing erythroid progenitor differentiation, as discussed above.[44] The combined effects of reduced erythroid progenitor viability, impaired differentiation, limited substrate availability, and blunted responsiveness to hypoxic stimuli result in ineffective erythropoiesis and the development of anemia in heart failure.[35,44]

Clinically, inflammatory activation in heart failure is reflected by modest elevations in C-reactive protein (CRP), typically quantified using high-sensitivity assays (hsCRP) which carry independent prognostic information and are consistently associated with increased all-cause and cardiovascular mortality. Accordingly, current heart failure guidelines do not recommend routine CRP measurement for diagnostic or therapeutic decision-making, as hsCRP provides prognostic information without directly guiding management strategies. Similarly, targeted anti-inflammatory therapies have not demonstrated consistent clinical benefit in heart failure and are therefore not recommended in routine clinical practice.[45] Clinical trials of cytokine-directed interventions, most notably tumor necrosis factor-α inhibitors such as etanercept and infliximab, failed to improve clinical outcomes and, at higher doses, were associated with worsening heart failure and increased mortality.[46] Other anti-inflammatory strategies, including nonsteroidal anti-inflammatory drugs and systemic glucocorticoids, have been associated with fluid retention and an increased risk of heart failure decompensation, further limiting their use in this population.[47] Consequently, inflammation remains a mechanistic driver and prognostic marker rather than a direct therapeutic target in contemporary heart failure management.[45]

Oxidative stress

Oxidative stress represents a central pathophysiological mechanism in heart failure (HF) and reflects a chronic imbalance between excessive generation of reactive oxygen species (ROS) and insufficient endogenous antioxidant defenses. Under physiological conditions, ROS are produced at low, tightly regulated levels and function as essential second messengers in intracellular signaling pathways.[48] At these concentrations, ROS modulate processes such as cellular proliferation, differentiation, adaptive stress responses, and hypoxia signaling through reversible redox modification of key proteins involved in signal transduction and transcriptional regulation.[49] These potentially harmful species are tightly controlled by antioxidant systems, including superoxide dismutase, catalase, and glutathione peroxidase, which coordinate the detoxification of superoxide anions and hydrogen peroxide to preserve cellular redox homeostasis. Maintenance of redox homeostasis is essential for normal cellular function, as it ensures appropriate redox-dependent signaling, preserves mitochondrial integrity, protects macromolecules from oxidative damage, and prevents inappropriate activation of inflammatory and apoptotic pathways.[48]

When ROS production exceeds the buffering capacity of antioxidant defenses, however, their role shifts from physiological signaling to pathological injury. Excessive ROS induce oxidative damage to lipids, proteins, and nucleic acids, disrupt mitochondrial function, and activate pro-inflammatory and pro-apoptotic signaling pathways.[49] In the context of HF, sustained oxidative stress thereby contributes to progressive cellular dysfunction,

adverse tissue remodeling, and impaired regenerative capacity.[48]

Excessive ROS generation in HF arises from multiple converging sources within the failing cardiovascular system. Mitochondrial dysfunction in HF, characterized by impaired electron transport chain efficiency and increased electron leakage—particularly at complexes I and III—represents a major source of superoxide generation in failing cardiomyocytes. In parallel, activation of NADPH oxidases in cardiomyocytes, endothelial cells, and vascular smooth muscle cells plays a pivotal role in HF-associated oxidative stress, as these enzymes directly generate superoxide anions through electron transfer from NADPH to molecular oxygen, thereby constituting a major non-mitochondrial source of pathological ROS production. This pathological ROS generation is further amplified by chronic neurohormonal activation and mechanical stress, ultimately establishing a self-sustaining state of oxidative imbalance that perpetuates myocardial injury and drives disease progression in HF.[48]

Oxidative stress in HF is closely intertwined with chronic low-grade inflammation, with both processes acting in concert to perpetuate cellular injury and disease progression. Pro-inflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), stimulate ROS production through activation of NADPH oxidases and mitochondrial pathways, while oxidative stress in turn amplifies inflammatory signaling by activating redox-sensitive transcription factors such as nuclear factor-κB (NF-κB). Through ROS-induced oxidative modifications, this bidirectional interaction enhances cytokine expression, promotes endothelial activation, and facilitates immune cell recruitment, thereby establishing a self-perpetuating inflammatory–oxidative cycle that sustains cellular injury even in the absence of acute ischemic insults.[50] In the context of HF, this persistent inflammatory–oxidative interplay contributes not only to progressive myocardial dysfunction but also to systemic consequences, including bone marrow impairment and ineffective erythropoiesis, as discussed below.[44,50]

Beyond its deleterious effects on myocardial structure and function, oxidative stress exerts systemic consequences that are directly relevant to the development of anemia in HF.[48,51] Circulating erythrocytes are particularly vulnerable to oxidative injury due to their continuous exposure to high oxygen tension and limited intrinsic antioxidant capacity. Reactive oxygen species induce lipid peroxidation of erythrocyte membranes and oxidative cross-linking of cytoskeletal proteins, resulting in reduced cellular deformability. As normal erythrocyte deformability is essential for passage through the narrow splenic sinusoids, loss of this mechanical flexibility promotes mechanical retention and recognition of damaged erythrocytes by splenic macrophages, thereby accelerating splenic clearance. In parallel, oxidative modification of hemoglobin promotes methemoglobin formation and enhances erythrophagocytosis, thereby further shortening erythrocyte lifespan.[52]

Oxidative stress also compromises erythropoiesis at the level of the bone marrow microenvironment. Elevated ROS induce oxidative DNA damage in hematopoietic stem and progenitor cells, impairing their self-renewal capacity and limiting effective erythroid differentiation. These detrimental effects are further exacerbated by inflammation-associated oxidative signaling, providing a mechanistic link between systemic inflammatory activation and intrinsic dysfunction of the hematopoietic compartment.[53]

Collectively, the combined effects of reduced erythrocyte survival and impaired erythropoietic output establish oxidative stress as a key mechanistic contributor to anemia in chronic HF. By bridging inflammation, bone marrow dysfunction, and ineffective erythropoiesis, oxidative stress represents a critical intermediary pathway in the complex pathophysiology of HF-associated anemia.[50,51]

Bone marrow microenvironment in heart failure

The bone marrow constitutes a highly specialized regulatory niche in which erythropoiesis is orchestrated through tightly coordinated interactions between long-term self-renewing hematopoietic stem cells, which maintain the regenerative capacity of the hematopoietic system, and lineage-committed hematopoietic progenitor cells responsible for immediate erythroid output, together with mesenchymal stromal cells, endothelial cells, and extracellular matrix components.[54] This niche integrates erythropoietin-dependent signaling with local oxygen availability and hypoxia-responsive niche signaling, reflecting spatial oxygen microgradients within the bone marrow, as well as iron availability and paracrine regulatory cues that collectively modulate erythroid progenitor fate.[54–58] In chronic heart failure, disruption of these interdependent regulatory circuits renders the marrow microenvironment maladaptive, thereby constraining erythroid lineage commitment and limiting the capacity of progenitor cells to mount an effective erythropoietic response despite preserved systemic stimuli.[59]

In chronic heart failure, erythropoietin-dependent signaling is functionally impaired despite preserved or elevated circulating erythropoietin levels, reflecting a state of erythropoietin resistance at the level of erythroid progenitors.[34] As discussed in detail above, chronic inflammation, oxidative stress, and concomitant renal dysfunction—hallmarks of chronic heart failure—attenuate downstream erythropoietin receptor signaling, ultimately limiting effective erythroid differentiation.[60]

Chronic heart failure is associated with systemic microvascular dysfunction and reduced cardiac output, which are expected to impair bone marrow perfusion and endothelial function, given the critical dependence of the hematopoietic niche on intact vascular regulation.[55,61] These changes disrupt physiologic oxygen microgradients that normally segregate proliferative and differentiative erythroid compartments according to their distinct metabolic requirements, hypoxia-responsive signaling profiles, and tolerance to oxidative stress. Rather than being exposed to spatially organized oxygen niches, erythroid progenitors experience fluctuating or diffuse hypoxic conditions that disrupt coordinated hypoxia-adaptive signaling.[55,56,62] This abnormal oxygen milieu leads to inappropriate activation or suppression of hypoxia-inducible transcriptional programs and altered metabolic switching between oxidative phosphorylation and glycolysis, thereby increasing oxidative stress.[56,62,63] As a result, early

erythroid progenitors fail to sustain proliferative capacity, while later-stage erythroblasts undergo premature apoptosis or incomplete maturation, ultimately shifting erythropoiesis toward an inefficient, stress-dominated phenotype.[56,59,63]

Heart failure is commonly associated with functional iron deficiency driven by inflammation-mediated hepcidin upregulation, as discussed above.[17] At the level of the bone marrow niche, restricted systemic iron mobilization is further compounded by impaired macrophage-mediated iron recycling within erythropoietic islands, reducing local iron availability for hemoglobin synthesis and thereby limiting effective erythroid maturation and further inhibiting erythropoiesis.[20,58,64]

Paracrine regulation within the bone marrow niche is profoundly altered in chronic heart failure.[65] Elevated levels of inhibitory cytokines such as IL-6, TNF-α, and IFN-γ suppress erythroid differentiation and reduce progenitor responsiveness to erythropoietin.[20,44] Structural and functional remodeling of mesenchymal stromal and endothelial cells diminishes the availability of supportive growth factors and chemokines, including stem cell factor and CXCL12, while extracellular matrix alterations disrupt cell–cell and cell–matrix interactions essential for erythropoietic organization.[54,55,66] Together, these paracrine disturbances destabilize the erythropoietic niche and further impair coordinated erythroid lineage commitment and maturation in chronic heart failure.[54,59,65]

Collectively, dysfunction of the bone marrow microenvironment represents a central pathophysiological link between systemic heart failure–associated stressors and impaired red blood cell production. This integrative framework explains the frequent persistence of anemia in heart failure despite normal or elevated circulating erythropoietin concentrations and provides a conceptual bridge between impaired erythropoiesis and downstream abnormalities in erythrocyte survival and phenotype.[54,59,65]

Reduced RBC lifespan and deformability

Under physiological conditions, red blood cells circulate for approximately 120 days before being cleared by the reticuloendothelial system.[67] In chronic heart failure, erythrocyte survival is modestly but clinically relevantly shortened, reflecting accelerated erythrocyte turnover, and contributes to anemia in conjunction with impaired erythropoiesis.[68]

As discussed in the preceding section, chronic heart failure is characterized by sustained oxidative stress, which induces structural damage to erythrocyte membranes and cytoskeletal proteins, resulting in reduced cellular deformability—a key determinant of erythrocyte survival.[48,69] Impaired membrane flexibility promotes mechanical retention within the microcirculation and splenic sinusoids, enhancing macrophage-mediated clearance and ultimately shortening erythrocyte lifespan.[69]

Inflammatory activation provides an additional mechanism linking HF to reduced RBC survival.[68] Pro-inflammatory cytokines—including interleukin-6 and interleukin-1β—promote eryptosis by inducing phosphatidylserine exposure on the outer leaflet of the erythrocyte membrane, a process experimentally demonstrated in vitro.[70] Phosphatidylserine serves as a key "eat-me" signal, facilitating recognition and clearance by the mononuclear phagocyte system.[71] In chronic HF, sustained low-grade inflammation provides a permissive milieu for cytokine-driven eryptosis, thereby directly linking inflammatory activation to accelerated erythrocyte clearance and the development of anemia.[68,70]

Beyond oxidative and inflammatory injury, endothelial dysfunction and reduced nitric oxide bioavailability—hallmarks of chronic heart failure—represent additional contributors to altered erythrocyte biomechanics, as nitric oxide plays a critical role in maintaining red blood cell deformability.[48,72] In a murine model of chronic HF, progressive impairment of NO production was accompanied by reduced RBC deformability and increased erythrocyte rigidity, changes that may hinder microvascular transit and favor premature erythrocyte clearance.[48,73]

Direct assessment of erythrocyte lifespan using chromium-51 or biotin labeling techniques remains the gold standard; however, such approaches are rarely applied in clinical HF populations due to methodological and logistical constraints.[67,74] Consequently, indirect hematologic markers have gained importance.[74] Red cell distribution width (RDW), reflecting heterogeneity in erythrocyte size, is consistently elevated in patients with heart failure and independently predicts adverse outcomes, including increased all-cause and cardiovascular mortality, higher rates of heart failure–related hospitalization, and worse overall prognosis in large clinical cohorts.[75–77] Increased RDW is thought to reflect disturbed erythrocyte homeostasis, integrating both impaired erythropoiesis and enhanced clearance of circulating red blood cells. Compensatory release of larger, immature reticulocytes together with shortened survival of damaged mature erythrocytes contributes to anisocytosis and widening of the red blood cell volume distribution.[78] Thus, RDW serves not merely as a prognostic biomarker but as an integrative surrogate of disrupted erythropoiesis and reduced erythrocyte survival in heart failure.[75,78]

Collectively, these mechanisms indicate that reduced erythrocyte lifespan represents a clinically relevant and pathophysiologically integrated contributor to anemia in chronic heart failure. Accelerated erythrocyte clearance, driven by oxidative injury, inflammatory signaling, and endothelial dysfunction, acts synergistically with impaired erythropoietic output to limit effective red blood cell mass. Together, these upstream and downstream abnormalities establish a state of heightened erythrocyte turnover that is inadequately compensated by bone marrow erythropoiesis, thereby perpetuating anemia and contributing to disease progression in heart failure.[48,68,74]

Nutritional and metabolic influences

Nutritional deficiencies are highly prevalent in heart failure and represent an important, yet often underrecognized, contributor to the development or progression of anemia. Multiple mechanisms converge, including reduced oral intake due to anorexia or early satiety, intestinal edema and congestion impairing nutrient absorption, increased metabolic demands, and enhanced catabolism driven by systemic inflammation and neurohormonal activation. These disturbances are particularly pronounced in elderly patients and in those with cardiac cachexia.[79]

Patients with heart failure frequently experience anorexia and early satiety, largely as a consequence of gastrointestinal congestion, hepatomegaly, and altered gut perfusion. Elevated central venous pressure and splanchnic congestion impair gastric emptying and intestinal motility, while hepatic congestion may further exacerbate nausea and appetite suppression. In parallel, venous congestion and intestinal wall edema disrupt normal gastrointestinal function and significantly impair nutrient absorption by compromising mucosal integrity and digestive capacity. Edematous thickening of the intestinal mucosa reduces the efficiency of iron and micronutrient uptake, while congestion-associated alterations in gut permeability further exacerbate malabsorption. Impaired intestinal absorption may lead to true iron deficiency due to reduced transcellular iron transport across the duodenal epithelium, resulting in insufficient iron delivery to the circulation and subsequent iron-restricted erythropoiesis.[79]

Reduced dietary intake and decreased absorptive capacity result in an insufficient supply of essential substrates required for effective erythropoiesis, including iron as well as other key hematopoietic micronutrients such as vitamin B12 and folate, and high-quality protein.[79] While iron deficiency primarily affects heme synthesis, deficiencies of vitamin B12 and folate impair DNA synthesis, leading to ineffective erythroid maturation and intramedullary apoptosis of erythroid precursors. In more advanced or prolonged deficiency states, impaired nuclear maturation may manifest as megaloblastic anemia and, in severe cases, may be accompanied by leukopenia and thrombocytopenia, resulting in pancytopenia.[80] Moreover, inadequate protein intake further restricts the availability of amino acids necessary for globin chain synthesis and erythroid cell proliferation.[81]

Over time, these combined deficiencies contribute to a hypoproliferative pattern of anemia characterized by reduced reticulocyte production and impaired red blood cell output, a phenotype frequently observed in advanced heart failure.[59] Importantly, these nutritional deficits may coexist with preserved or even elevated iron stores in the context of inflammation, masking true functional substrate deficiency and complicating the clinical recognition of nutrition-related anemia.[82]

Heart failure is characterized by a chronic hypermetabolic state driven by heightened myocardial energy expenditure, sustained activation of compensatory neurohormonal mechanisms, and additional systemic energy demands related to respiratory effort.[83] Elevated metabolic demands and altered metabolic regulation in heart failure increase the requirement for nutrients and micronutrients essential for erythropoiesis, predisposing patients to iron and vitamin depletion.[84] When nutritional intake and absorption fail to meet these heightened requirements, a negative balance ensues, contributing to impaired red blood cell production and reduced hemoglobin levels.[85]

Beyond the previously discussed disturbances in iron homeostasis and erythropoietic regulation, persistent systemic inflammation and sustained neurohormonal activation represent central features of heart failure pathophysiology that exert additional suppressive effects on red blood cell production.[44,79,86] Proinflammatory cytokines promote skeletal muscle protein breakdown and induce a state of negative nitrogen balance, thereby reducing the systemic availability of amino acids and metabolic substrates required for effective erythropoiesis.[44,86,87] Neurohormonal mediators further exacerbate erythropoietic dysfunction by altering cellular energy utilization and redox homeostasis, impairing the capacity of erythroid precursors to sustain proliferation and hemoglobin synthesis despite preserved substrate availability.[88–90]

Through the convergence of these mechanisms, nutritional and metabolic derangements create a state of relative nutrient deficiency, iron-restricted erythropoiesis, and impaired red blood cell production, thereby substantially contributing to the burden of anemia in heart failure.

Medication-related effects on erythropoiesis

Several pharmacologic agents routinely used in the management of HF may influence erythropoiesis and iron homeostasis through diverse and often overlapping mechanisms.[85] These include renin–angiotensin system (RAS) inhibitors such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and angiotensin receptor–neprilysin inhibitors (ARNIs); diuretic therapy; sodium–glucose cotransporter 2 (SGLT-2) inhibitors; antiplatelet and anticoagulant therapies.[85,91] The net effect of these therapies on hemoglobin concentration reflects a balance between direct effects on erythroid progenitor cells, modulation of erythropoietin production, changes in plasma volume, renal function, and treatment-associated blood or iron losses.[85]

Inhibition of the renin–angiotensin system represents a cornerstone of HF therapy but is associated with modest effects on erythropoiesis. Angiotensin II directly stimulates erythroid progenitor cell proliferation and enhances erythropoietin (EPO) production; therefore, pharmacologic blockade with ACEIs or ARBs attenuates these pathways, leading to small but measurable reductions in hemoglobin concentration. In addition, suppression of angiotensin II-mediated renal hemodynamic regulation may impair renal oxygen sensing and EPO synthesis, particularly in patients with concomitant chronic kidney disease or reduced renal reserve.[92] Angiotensin receptor–neprilysin inhibitors appear to exert similar or slightly attenuated effects compared with ACEIs/ARBs, although data remain limited.[93] Clinically, the hemoglobin-lowering effect of RAS inhibition is usually mild and outweighed by its survival benefit but may become relevant in patients with multiple anemia-promoting comorbidities.[85]

Diuretics influence hemoglobin concentration predominantly through changes in plasma volume rather than direct effects on red blood cell production. Acute initiation or intensification of diuretic therapy—particularly with loop diuretics—often results in hemoconcentration, leading to transient increases in hemoglobin and hematocrit that reflect plasma volume contraction rather than true augmentation of red cell mass.[94] In contrast, chronic loop diuretic use, particularly at high doses, reduces effective circulating volume and renal perfusion, triggering sustained activation of the renin–angiotensin–aldosterone system and sympathetic nervous system.[95]

This neurohormonal activation promotes renal vasoconstriction, inflammatory signaling, and medullary hypoxia, ultimately impairing renal oxygen sensing and erythropoietin production and thereby indirectly suppressing erythropoiesis.[92]

Thiazide diuretics, typically administered at lower doses or as adjunctive therapy, exert relatively mild and stable effects on intravascular volume. Consequently, any associated changes in hemoglobin concentration are generally small and most likely reflect volume-related effects rather than direct modulation of erythropoiesis.[95]

Mineralocorticoid receptor antagonists, while not potent diuretics, may further modulate hemoglobin levels indirectly through their effects on renal hemodynamics and electrolyte balance, as well as through attenuation of aldosterone-mediated inflammatory and profibrotic signaling. Although aldosterone blockade may theoretically attenuate inflammation-associated suppression of erythropoiesis, any favorable effects on hemoglobin appear modest and are frequently offset by reductions in erythropoietin production related to impaired renal function or hyperkalemia, resulting in a largely neutral net effect on hemoglobin concentration.[85,92,96]

Consequently, interpretation of hemoglobin levels in heart failure patients receiving diuretic therapy requires careful assessment of volume status and renal function, as apparent anemia or normalization of hemoglobin may reflect dilutional or concentration effects rather than true changes in erythropoiesis.[75,95]

Sodium–glucose cotransporter 2 (SGLT-2) inhibitors have consistently been shown to increase hemoglobin and hematocrit levels in patients with heart failure, irrespective of diabetes status.[97] Although this effect was initially attributed to hemoconcentration resulting from osmotic diuresis, accumulating evidence indicates that SGLT-2 inhibitors directly stimulate erythropoiesis. Proposed mechanisms include improved renal cortical oxygenation, reduced tubular workload, attenuation of inflammatory signaling, and enhanced erythropoietin production. Notably, increases in hemoglobin associated with SGLT-2 inhibitor therapy appear sustained over time and may represent one of several mechanisms contributing to the observed prognostic benefits of this drug class, distinguishing SGLT-2 inhibitors from most other heart failure therapies, which are generally neutral or mildly suppressive with respect to erythropoiesis.[98]

Antiplatelet agents and oral anticoagulants are commonly prescribed in patients with heart failure, particularly in the presence of ischemic heart disease or atrial fibrillation, but are associated with an increased risk of gastrointestinal bleeding.[99] Beyond overt hemorrhagic events, chronic occult gastrointestinal microbleeding may occur and lead to progressive iron loss and depletion of iron stores. Over time, this results in absolute iron deficiency and iron-deficiency anemia, typically characterized by microcytosis, hypochromia, and increased red cell distribution width.[58] Elderly patients and those with concomitant gastrointestinal pathology or exposure to nonsteroidal anti-inflammatory drugs appear particularly vulnerable, rendering long-term antithrombotic therapy a clinically relevant contributor to anemia in heart failure.[85]

Taken together, these treatment-related mechanisms illustrate the complexity of anemia in HF. While the survival benefits of ACEIs, ARBs, and anticoagulants clearly outweigh their hematologic side effects, awareness of these interactions is crucial. Regular monitoring of complete blood counts, ferritin, and transferrin saturation is recommended in patients on chronic HF therapy, especially in those who are elderly, have chronic kidney disease, or receive long-term anticoagulation. Early recognition of treatment-associated anemia allows timely correction of iron deficiency and prevents additive negative effects on exercise tolerance and prognosis.

Integration of mechanisms

Anemia in heart failure (HF) does not arise from a single dominant defect but rather reflects the convergence of multiple interdependent mechanisms that jointly impair effective red blood cell (RBC) mass and function. These mechanisms—volume dysregulation, iron deficiency, impaired erythropoiesis, reduced RBC survival, and bone marrow dysfunction—are tightly interconnected and amplified by shared upstream drivers such as neurohormonal activation, renal dysfunction, inflammation, and oxidative stress. Consequently, reduced hemoglobin concentration in HF may reflect true anemia, dilutional "pseudoanemia," or, most commonly, a combination of both.[7,85]

A fundamental component of this integrated phenotype is plasma volume expansion and hemodilution. Neurohormonal and renal maladaptation promote sodium and water retention, increasing plasma volume and lowering measured hemoglobin concentration without a proportional reduction in RBC mass. This dilutional component may be clinically occult in chronic congestion and is particularly dynamic during episodes of acute decompensation, when intravascular refilling and fluid redistribution can transiently reduce hemoglobin concentration. Thus, hemoglobin trajectories in HF frequently reflect changes in volume status rather than isolated hematologic processes.[85]

Superimposed on volume-related effects, iron deficiency represents a central pathophysiological link between impaired erythropoiesis and reduced tissue energetics. Absolute iron deficiency may arise from impaired intestinal absorption due to venous congestion or chronic gastrointestinal blood loss, whereas functional iron deficiency is driven by inflammation-mediated hepcidin overexpression, which restricts iron mobilization despite preserved or increased iron stores. In both settings, limited iron availability constrains hemoglobin synthesis and disrupts mitochondrial function in cardiac and skeletal muscle, thereby exacerbating fatigue, exercise intolerance, and disease progression independently of anemia severity, underscoring the clinical relevance of iron deficiency beyond hemoglobin concentration alone.[85]

At the level of erythropoietic regulation, heart failure is characterized by relative erythropoietin (EPO) insufficiency and resistance rather than absolute EPO deficiency.[34] Renal hypoperfusion, venous congestion, and progressive structural kidney damage reduce effective EPO-producing capacity, while persistent hypoxic and neurohormonal stimuli maintain circulating EPO concen-

trations that remain inadequate relative to the severity of anemia.[3] In parallel, inflammatory cytokines and the uremic milieu impair EPO receptor signaling in the bone marrow, resulting in blunted erythroid progenitor responsiveness and inappropriately low reticulocyte production despite preserved or modestly increased EPO levels.[33–35] Functional iron deficiency further restricts erythroid responsiveness, reinforcing ineffective erythropoiesis and limiting compensatory red blood cell production.[44] Together, these mechanisms define a state of relative erythropoietin insufficiency and resistance in heart failure, in which erythropoietic drive is preserved but functionally ineffective, explaining the limited efficacy of erythropoiesis-stimulating strategies in this population.[34,38]

Inflammation and oxidative stress act as central amplifiers that integrate disturbances in iron metabolism, erythropoietic regulation, and red blood cell survival in heart failure.[6] Pro-inflammatory cytokines promote hepcidin synthesis, suppress erythroid progenitor survival and differentiation, and impair erythropoietin signaling, thereby directly linking immune activation to functional iron restriction and bone marrow dysfunction.[6,44] Oxidative stress, arising from mitochondrial dysfunction and excessive generation of reactive oxygen species, interacts bidirectionally with inflammation and amplifies cellular injury across multiple compartments.[48] Oxidative damage to mature red blood cell membranes and cytoskeletal proteins reduces erythrocyte deformability and promotes premature clearance from the circulation, while parallel injury to hematopoietic progenitors limits effective red blood cell production in the bone marrow.[48,53,69] Clinically, this combined disturbance of erythropoiesis and red blood cell survival manifests as increased red cell distribution width, a robust integrative marker that consistently associates with adverse outcomes in heart failure.[75,78] Collectively, these processes highlight anemia in heart failure as an integrated consequence of inflammatory, oxidative, and erythropoietic dysregulation.[85]

These processes are further shaped by disruption of the bone marrow niche and by systemic modifiers characteristic of heart failure.[65] Reduced marrow perfusion and persistent inflammatory signaling in heart failure destabilize the erythropoietic microenvironment by impairing iron availability and erythroid progenitor maturation, thereby favoring ineffective erythropoiesis.[6,48,85] In parallel, nutritional deficiencies, malabsorption related to intestinal congestion, and catabolic metabolic signaling reduce the availability of substrates essential for effective erythropoiesis.[79,85,86] Medication-related factors—including renin–angiotensin system inhibition, diuretic-induced volume shifts, and chronic antithrombotic therapy—add further complexity by modulating plasma volume, erythropoietic signaling, and iron balance, thereby reinforcing anemia through multiple converging pathways.[6,18,85,92,94,95] Collectively, these factors reinforce anemia in heart failure as a multifactorial and dynamically regulated condition requiring integrated pathophysiological interpretation.

This integrated pathophysiological framework helps explain why therapeutic strategies targeting single mechanisms have largely failed to improve clinical outcomes in heart failure–associated anemia.[85] Erythropoiesis-stimulating agents increase hemoglobin only modestly and do not overcome the combined barriers of iron restriction, inflammation, oxidative stress, and bone marrow resistance, while oral iron supplementation is frequently ineffective due to hepcidin-mediated blockade of intestinal absorption.[20,38,85] In contrast, interventions that act on multiple pathways simultaneously—such as intravenous iron therapy or sodium–glucose cotransporter 2 inhibitors—have demonstrated more consistent clinical benefit, likely by restoring functional iron availability, improving erythropoietic signaling, and modulating renal and volume homeostasis.[9,85,97] Taken together, this integrated framework highlights anemia in heart failure as a pathophysiological marker of systemic disease severity rather than an isolated therapeutic target.

In summary, heart failure-associated anemia represents a multifactorial manifestation of systemic disease severity rather than an isolated hematologic disorder.[3,6,85] Overlapping disturbances in volume regulation, iron metabolism, erythropoietin signaling, bone marrow function, and red blood cell survival—amplified by inflammation and oxidative stress—necessitate an integrated clinical interpretation. Consequently, hemoglobin concentration should be evaluated and managed in the context of iron status, volume dynamics, and underlying disease processes rather than targeted in isolation.[85]

Discussion

Anemia in heart failure represents the integrated outcome of multiple interdependent physiological disturbances rather than a single dominant abnormality. The mechanisms discussed in this review—encompassing volume regulation, iron handling, erythropoietic signaling, red blood cell production and survival, inflammation, and metabolic stress—interact dynamically and vary in relative importance across disease stages and clinical contexts.

A key implication of this integrated framework is that hemoglobin concentration functions as a composite marker rather than a direct surrogate of red blood cell mass or oxygen-carrying capacity. Changes in hemoglobin may therefore reflect true anemia, dilutional effects, or both, complicating clinical interpretation when hemoglobin is considered in isolation. This complexity provides a plausible explanation for the limited and inconsistent success of therapeutic strategies targeting individual pathways.

Iron deficiency constitutes an important and clinically relevant component of this spectrum, but it does not operate in isolation. Its interaction with inflammatory signaling, erythropoietic responsiveness, and volume status underscores the need to interpret iron-related abnormalities within a broader systemic context. Similarly, disturbances in erythropoietin signaling, bone marrow function, and red blood cell survival contribute independently and synergistically to anemia severity and persistence.

Several conceptual and methodological gaps remain. It is not fully established whether anemia in heart failure acts primarily as a mediator of disease progression or as a marker of systemic illness severity. In addition, heterogeneity in study design, reliance on hemoglobin as a soli-

tary endpoint, and limited integration of volume- and erythropoiesis-related parameters constrain interpretation of existing evidence.

Future research should prioritize integrative phenotyping approaches that capture the multidimensional nature of anemia in heart failure. Such strategies may improve risk stratification, refine therapeutic targeting, and support more personalized management frameworks. Collectively, these considerations support viewing anemia in heart failure as a dynamic manifestation of multisystem dysregulation rather than an isolated hematologic disorder.

Conclusion

Anemia is a frequent and clinically relevant feature of heart failure that reflects the convergence of multiple interrelated pathophysiological disturbances, including volume dysregulation, impaired erythropoietic signaling, inflammation, altered iron handling, and oxidative stress. Rather than representing a secondary or isolated abnormality, anemia constitutes an integrated component of the systemic dysregulation characteristic of heart failure, with important functional and prognostic associations.

Current evidence indicates that hemoglobin concentration alone provides an incomplete representation of this complex phenotype. Meaningful clinical interpretation requires consideration of iron status, volume dynamics, and underlying regulatory mechanisms that jointly shape anemia expression across different stages of heart failure.

From a clinical perspective, these insights support the need for a more integrated approach to anemia assessment and management in heart failure. Future research should focus on multidimensional phenotyping strategies that move beyond single biomarkers, clarify the mechanistic hierarchy underlying anemia, and inform more personalized therapeutic frameworks. Collectively, such approaches may improve risk stratification and contribute to more effective, mechanism-informed management of patients with heart failure.

Conflict of interest

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