http://www.inosr.net/inosr-experimental-sciences/
Obeagu *et al*
INOSR Experimental Sciences 11(2):1-16, 2023.

International Network Organization for Scientific Research ISSN: 2705-1692

An Update of Aneamia in Adults with Heart Failure

Emmanuel Ifeanyi Obeagu[1], Maria Mudei Ali[1], Esther U. Alum[2,3], Getrude Uzoma Obeagu[4], P.C. Okechukwu Ugwu[3] and Umi Omar Bunu[5]

[1]Department of Medical Laboratory Science, Kampala International University, Uganda.
[2]Department of Biochemistry, Ebonyi State University, Abakaliki, Nigeria.
[3]Department of Publication and Extension, Kampala International University, Uganda.
[4]Department of Nursing Science, Kampala International University, Uganda.
[5]Department of Public Health, Kampala International University, Uganda.
Email:emmanuelobeagu@yahoo.com

ABSTRACT

Anaemia in adults with heart failure occurs when there is a deficiency of erythrocytes or haemoglobin in the blood, which further lowers the already limited oxygen supply to the body's tissues in heart failure. Anaemia is typically caused by poor nutrition, chronic kidney disease, inflammation, and certain medications used to treat heart failure. Symptoms of anaemia in adults with heart failure can include fatigue, weakness, and shortness of breath, increased heart rate, and chest pain. Treatment involves addressing underlying causes, improving nutrition, and in some cases, iron supplementation to increase red blood cell production. Close monitoring and coordination with healthcare providers is important to manage both heart failure and anaemia in adults, erythropoietin-stimulating agents has been considered alone or in combination with iron. Available and emerging new agents in the treatment of anaemia of heart failure will need to be tested in randomized, controlled studies.

Keywords: anaemia, adults, heart failure, haemoglobin, erythrocytes, iron

INTRODUCTION

Anaemia is condition in which the blood doesn't have enough healthy red blood cells [1-7]. Anaemia results from a lack of red blood cells or dysfunctional red blood cells in the body. This leads to reduced oxygen flow to the body's organs. Symptoms may include fatigue, skin pallor, shortness of breath, light-headedness, dizziness or a fast heartbeat. Anaemia affects one-third of heart failure patients and is associated with increased morbidity and mortality [8-12]. Aneamia is also defined as low haemoglobin levels (<12 g/dL in women and <13 g/dL in men). Anaemia is common in patients with heart failure, and is a multifactorial and multidimensional problem [13]. Anaemia is a commonly occurring comorbidity in patients with heart failure (HF). Although there are a few reports of a higher prevalence of mortality and hospitalization-related outcomes due to accompanying anaemia, other studies suggest that anaemia does not have an adverse impact on the prognostic outcomes of HF. Two meta-analyses in the past decade had reported the adverse impact of anaemia on both mortality and hospitalization- related outcomes. However, only one of these studies had evaluated the outcome while using multivariable adjusted hazard ratios. Moreover, several studies since then reported the prognostic influence of anaemia in HF. In this present study, we evaluate the prognostic impact of anaemia on mortality and hospitalization outcomes in patients with HF. There has been increasing appreciation of the significance of anaemia in the pathophysiology, treatment, and prognosis of heart failure. Once considered a downstream complication of heart failure, anaemia is now emerging as a crucial and potentially modifiable

factor in the overall treatment strategy for patients with chronic heart failure [14]. The World Health Organization classifies anaemia as haemoglobin (Hb) levels <12 g/dL in women and <13 g/dL in men, however, the classification may differ when age, pregnancy status, altitude, and smoking status are considered. The diagnostic criteria for anaemia in heart failure patients are serum ferritin levels of less than 30 mcg/L in patients without kidney disease and less than 100 mcg/L in patients with chronic kidney disease or serum ferritin levels of 100-299 mcg/L with passing saturation of less than 20% in patients with chronic kidney disease [15]. The prevalence of anaemia in heart failure patients ranges from 9% to 69.6% with an increased risk of hospital admissions and mortality in nearly 46.8% of patients in comparison to 29.5% in nonanemic patients [16]. The presence of other co-morbid medical conditions like chronic kidney disease (CKD) and advanced age as well as the severity of heart failure has also been associated with an increased prevalence of anaemia [17]. Though low haemoglobin levels are associated with poor outcomes, the correction of anaemia has not been consistently associated with improved outcomes. Parenteral iron improves the functional capacity in iron deficient heart failure patients, the effects are independent of haemoglobin levels, and also the evidence on hard clinical outcomes is yet to be ascertained. The specific cause of anaemia in heart failure patients is still unclear and has been thought to be multifactorial, with iron deficiency (IDA) and inflammation having the strongest evidence-based data [18]. The current treatment modalities in treating anaemia in patients with heart failure include the use of erythropoietic agents - epoetin-α, epoetin-β, and darbepoetin-α and intravenous or oral iron supplementation. The role of blood transfusion in patients with heart failure is controversial with different ''transfusion thresholds'' in patients with cardiovascular diseases, debatable benefits in reducing mortality, and the presence of adverse side effects [19]. Blood transfusion can be viewed as an acute treatment for extreme anaemia on an individual basis, but it does not appear to be a feasible therapeutic strategy for the long-term management of chronic anaemia in CHF, based on the risk-benefit profile [20].

Pathophysiology of anaemia

Iron Deficiency Anaemia (IDA)

Iron is one of the most important elements found in the human body. It is involved in erythropoiesis, transport, delivery, and utilization of oxygen, and is found in many enzymes responsible for crucial body functions. Iron deficiency anaemia in heart failure patients can be described as absolute or functional. Ferritin levels of < 100 μg/L or < 300 μg/L and low transferrin saturation (TSAT) of <20% have been used to diagnose heart failure patients with both absolute and functional ID [21].Absolute iron deficiency is defined when total body iron levels are reduced and was identified in 15% of individuals with heart failure. This can be attributed to anorexia, cardiac cachexia, decreased iron absorption due to intestinal edema, hepcidin-induced downregulation of iron transporters such as ferroprotein, gastrointestinal blood loss caused by aspirin, antiplatelet agents, or anticoagulants, as well as serious coexisting conditions like gastrointestinal or genitourinary malignancies [22].Functional iron deficiency is described when iron levels are sufficient but not adequate to supply the target tissues due to maldistribution, Functional iron deficiency was found in 18% of heart failure patients [23]. Iron deficiency anaemia in heart failure patients is a common occurrence and is linked with severity, poorer prognosis, and outcomes as evidenced in an international, multicentre cohort study conducted with 1,506 participants with chronic heart failure. Out of these 1,506, 753 participants were found to be iron deficient and 426 anaemics. These patients were found to have a higher New York Heart Association (NYHA) class, higher prevalence of comorbidities, and increased levels of biomarkers as compared to patients with normal iron and haemoglobin levels [24]. Myocardial dysfunction has been linked to chronic

ID due to changes in structure and function of the myocardium due to impaired oxygen metabolism, cellular activities, and immune mechanisms. Impaired levels of reactive oxygen species (ROS) protective enzymes like catalase, glutathione peroxidase, and superoxide dismutase along with decreased mitochondrial oxygen consumption and reduced levels of aconitase and citrate synthase have been associated with reduced myocardial iron stores and impaired mitochondrial function in patients with heart failure. Iron deficiency has also been linked to reduced exercise endurance, poor quality of life, and increased morbidity and mortality even without the presence of anaemia [25].

Chronic Inflammation

Anaemia of inflammation is the presence of normochromic normocytic anaemia in the setting of an infection, inflammatory disease, or a malignant condition. A study conducted by Opasich et al. in 2005 established a relationship between anaemia and congestive heart failure. In this particular study, out of the 148 patients with stable heart failure (New York Heart Association class II and III) and haemoglobin concentrations of <13 g/dL (if males) or <12 g/dL (if females), 57% showed evidence of anaemia of chronic disease, defined here as reduced concentrations of serum iron, transferrin, and total iron binding capacity; normal or raised ferritin; normal or slightly increased soluble transferrin receptor [26].

The pathophysiology behind this process is still largely unknown but is thought to be related to the increased levels of pro-inflammatory cytokines and hepcidin. Endotoxin-induced immune activation due to bowel edema, myocardial production due to hemodynamic overload, and peripheral extra myocardial production due to tissue hypoperfusion and hypoxia have all been suggested as sources of cytokine production in heart failure. Elevated levels of tumour necrosis factor alpha (TNF-alpha), interleukin (IL)-6, and IL-1 have been found in heart failure patients and are linked with a poorer prognosis and outcomes. The surface of cardiomyocytes and fibroblasts are known to generate TNF-alpha and IL-6, whereas endothelial cells and interstitial macrophages are believed to be involved in the immunoreactivity of IL-1 [27].TNF-alpha and IL-6 have been shown to not only inhibit the production of erythropoietin in the kidneys via the activation of GATA 2 binding protein and nuclear factor-kB but are also involved in the suppression of erythroid progenitor cell proliferation in the bone marrow. Additionally, IL-6 activates the synthesis of an acute phase protein, hepcidin in the liver which is involved in the downregulation of ferroprotein. Hepcidin also decreases the duodenal iron absorption and the release of iron from its stores in the reticuloendothelial system giving rise to functional and absolute iron deficiency anaemia [19].

Erythropoietin Levels

Human Erythropoietin (Epo) is a 169 amino acid long glycoprotein hormone with a molecular mass of 30.4 kDa synthesized primarily in the peritubular fibroblasts found in the renal cortex and the liver in a fetus. Detectable levels have also been found in other organs such as the liver, spleen, bone marrow, lung, and brain. The production of Epo is controlled by hypoxia-inducible transcription factors (HIF) and is mainly triggered in the presence of renal hypoxia and low concentrations of haemoglobin. In heart failure patients, elevated levels of Epo inconsistent with the haemoglobin levels are found and are associated with an increased risk of morbidity and mortality [28].The cause for the elevated levels is multifactorial. One of the proposed causes was the chronic inflammatory state associated with heart failure. The release of pro-inflammatory cytokines has been linked with the impaired expression of Epo leading to an Epo resistance in the bone marrow ultimately resulting in elevated levels of endogenous Epo. The production of Epo in response to angiotensin, despite the presence of angiotensin enzyme inhibitors, is another proposed cause. The myocardium is one of the few non-renal tissues that can synthesize Epo in response to oxidative or metabolic stress

or the presence of renal tissue impairment due to the presence of Epo receptors (EpoR) via the synthesis of HIF [29].

Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is a hormonal system that is activated in response to renal hypoxia leading to the cleavage of angiotensinogen to form angiotensin I in the liver, and then angiotensin II by the angiotensin-converting enzyme (ACE) predominantly in the lungs. Angiotensin II then further activates aldosterone which causes increased sodium uptake from the renal tubules and increases the extracellular volume and blood pressure [30].

The renin-angiotensin-aldosterone system (RAAS) is an important mediator in the pathophysiology of heart failure. The increased activity of RAAS in heart failure, although initially improves cardiac output, however, over time is associated with various adverse effects such as cardiac remodelling and sympathetic nervous system activation and progressively worsens the condition. The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is a major tool in the management of heart failure, but it may hamper the haemoglobin levels due to the effect of angiotensin II on erythropoietin synthesis and the erythroid progenitor cell production in the bone marrow. Moreover, ACEIs are associated with a modest decrease in haemoglobin levels due to the inhibition of the breakdown of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a haematopoiesis inhibitor [31].

Other Causes of anemia in heart failure

Anaemia in heart failure patients may be due to haemodilution brought upon as a consequence of sodium and water retention due to the activation of the RAAS pathway. The use of medications such as beta-blockers (particularly carvedilol) and digoxin have shown to be associated with reduced haemoglobin levels [32].

Clinical characteristics with anaemia in heart failure

Age

Although the incidence varies widely depending on the definition used, it is estimated that almost 11% of men and 10% of women over the age of 65 years in the US are anaemic. Moreover, this proportion doubles in the elderly population over the age of 85 years. Anaemia in the elderly is associated with numerous poor outcomes, including a progressive decline in functional capacity, increased vulnerability to falling, and impaired cognition. Elderly patients with anaemia often have significant comorbidities, including heart failure and chronic kidney disease. Studies have also demonstrated that, overall, patients with heart failure and anaemia tend to be older than their nonanemic counterparts. In contrast with anaemia in younger people, anaemia in elderly persons is more common in men than in women. Anaemia is also approximately three times more prevalent in elderly African-Americans than among non-Hispanic Caucasians. Nutritional deficiencies account for approximately 34% of cases of anaemia in the elderly, while anaemia of chronic disease, with or without renal insufficiency, accounts for an additional 33%. Studies have shown that, compared with nonanemic patients, the 5-year mortality of anaemic men and women is 2.4 and 1.6 times greater, respectively. It should be noted that the increased mortality associated with anaemia remains unchanged even after adjusting for pre-existing comorbid conditions. Thus, the presence of anaemia has important prognostic implications in older patients, irrespective of heart failure [33].

Female gender

The data supporting the higher risk for anaemia in women compared with men with heart failure are scarce, in part because of the overwhelming male predominance in most CHF studies. For example, a recent study of anaemia in ambulatory patients with CHF reported a 64% male predominance. However, anaemia studies in HF patients have noted that the percentage of women steadily increases as the severity of anaemia increases [34].

Physiopathological consequences of anaemia

In the presence of chronic anaemia, low tissue oxygenation results, which leads to the development of compensatory mechanisms: hemodynamic and non-hemodynamic. The two main non-hemodynamic mechanisms are erythropoiesis stimulation, which leads to an increased capacity of oxygen transport, and a lowering of haemoglobin affinity for oxygen, leading to a rise in oxygen levels being transported to the tissues. These are rapid and reversible mechanisms, allowing for immediate changes in binding and releasing oxygen to peripheral tissue. The hemodynamic compensatory mechanisms are significantly more complex and slower and associate numerous unfavourable effects. Initially, there is a reduction in the peripheral vascular resistance as a consequence of both low haematocrit values and the vasodilation mediated by high levels of nitric oxide. These events lead to low blood pressure, which causes a reflex rise in cardiac debit, to maintain balanced blood pressure and tissue perfusion. A rise in sympathetic and RAAS activity determines vasoconstriction and low renal perfusion. Water and salt retention results, with plasmatic and extracellular expansion. Over the long term, these mechanisms are responsible for the development of HF in patients with severe anaemia (<7 g/dL). In patients who associate HF, a lower grade anaemia may lead to heart function deterioration by activation of neurohormonal mechanisms [35].

CONCLUSION

Anaemia is a common condition in adults with heart failure and can worsen the already limited oxygen supply to the body's tissues. Anaemia is typically caused by poor nutrition, chronic kidney disease, and inflammation, and can be further exacerbated by medications used to treat heart failure. Symptoms of anaemia in adults with heart failure include fatigue, weakness, shortness of breath, and additional symptoms such as increased heart rate and chest pain. Treatment for anaemia in adults with heart failure involves identifying and addressing the underlying causes, improving nutrition, managing inflammation, and in some cases, iron supplementation. Close coordination with healthcare providers and regular monitoring is necessary to effectively manage both heart failure and anaemia in adults.

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Emmanuel Ifeanyi Obeagu, Maria Mudei Ali, Esther U. Alum, Getrude Uzoma Obeagu, P.C. Okechukwu Ugwu and Umi Omar Bunu (2023). *INOSR Experimental Sciences* 11(2):1-16.