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Cardio-Renal-Anemia Syndrome: Possible Causes and Treatment.

Ashishkumar C Zala*, Naresh D Kantharia, Shashank Deoghare, Prakash P Malam, and Chirag N Gajera.

Department of Pharmacology, Government Medical College, Surat, Gujarat, India.

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*For Correspondence

To/Post-

Grambharati, Amrapura
Ta-Mansa, Di-Gandhinagar,
Via- Unava, Balva, Gujarat
(India)

Pin Code- 382650

Tel No: +919898899441

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ABSTRACT

In many studies, a vicious link is found between heart failure (HF), kidney and Anemia. Anemia is common in HF patients, but its high prevalence in HF patients is directly related to itself or other comorbid conditions. Multiple potential mechanisms of interaction exist between anemia and the clinical syndrome of HF, including hemodilution, inflammatory activation, renal insufficiency, and malnutrition. Anemia is an independent risk factor for adverse outcomes in patients with HF as well as, it itself can precipitate HF. Anemia is an important comorbid condition and potentially novel therapeutic target in patients with heart failure (HF). Available data suggest that treatment of anemia is associated with significant symptomatic improvement in HF. Simultaneously, aggressive treatment of anemia with erythropoietin (EPO) associated with increased risk of hypertension and thrombosis. Here this review article highlights the possible mechanisms for anemia in HF and balanced treatment approach to minimize treatment associated risk.

INTRODUCTION

Cardio-renal-anemia syndrome: In simple terms, it can be viewed as a relatively low level of hemoglobin because of impact of diseased heart on kidney with the assumption that, in the presence of a healthy heart and the same kidney it will be normal or near normal. Anemia has recently been demonstrated to be a common comorbid condition in patients with HF, and multiple observational studies have demonstrated an independent association between lower hemoglobin (Hb) and adverse clinical outcomes in this syndrome. Although these findings have generated substantial interest in anemia as a potentially important therapeutic target in patients with HF, current HF guidelines provide no specific recommendations for evaluation or treatment of anemia. [1,2] The purpose of this review is to outline the current understanding of the association between anemia and HF and assess the existing and emerging data on anemia as a potential treatment target, including the potential benefits and risks of treating anemia in the setting of HF.

As early recognition of dysfunction in one organ may prove important in mitigating the spiral of co-dysfunction in both, the need for early and treatment-guiding biomarkers, along with their characteristics. [3] Heart failure is either an acute or a chronic condition. A diseased heart has numerous negative effects on kidney function but, at the same time, renal insufficiency can significantly impair cardiac function. [4] Direct and indirect effects of each organ that is dysfunctional can initiate and perpetuate the combined disorder of the two organs through a complex combination of neurohormonal feedback mechanisms.

Anemia is associated with an increased mortality in a wide variety of patients ranging from asymptomatic left ventricular dysfunction to advanced CHF. [5,6] Anemia is an independent risk factor for the development of CHF [7] and could contribute to the worsening of CHF. [7,8] Anemia could exacerbate CHF by increasing myocardial and peripheral hypoxia, promoting left ventricular hypertrophy [9], and activating neurohormonal and cytokine systems. [10] Volume overload that occurs with hemodilution could also contribute to worse outcome. Hypervolemia may be linked to increased mortality risk since beta natriuretic peptide (BNP), a cardiac-derived hormone closely correlated to left ventricular end-diastolic pressure, has been shown to be an independent predictor of survival in CHF patients. [11] Volume overload may be a key mechanism contributing to the increased mortality in CHF patients with anemia. [8] Thus it is possible that in CHF a vicious circle is set in motion wherein CHF causes anemia and the anemia then worsens the CHF. The anemia in long standing hypertension or CHF could be due to several factors.

1. Iron deficiency caused by poor intake, malabsorption or chronic blood loss from, for example, use of prophylactic aspirin. [12, 13]
2. Anemia of chronic renal failure (CRF).
CRF or end stage renal disease is a consequence of long standing hypertension or CHF. The anemia of CRF is due to a combination of many factors of which the most important is the reduced production of erythropoietin (EPO) in the kidney and hemodilution due to sympathetic overactivity. [14,15]
3. Loss of EPO and transferrin in the urine.
Proteinuria is often seen in CHF [16] and it may cause the loss of EPO in the urine. It may also cause loss of transferrin which can lead to iron deficiency anemia. [17]
4. Use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. ACE inhibitors, especially in high doses, may interfere with both EPO production in the kidney and EPO activity in the bone marrow. [18] The mechanistic basis for antihypertensive medication-related changes in hemoglobin concentration includes hemodilution, hemolytic anemia, and suppression of red blood cell production. [19-21]
5. Increased activity of cytokines such as tumor necrosis factor- α (TNF- α). TNF alpha is very elevated in chronic diseases and CHF [22] and has been shown to interfere with erythropoietin (EPO) production in the kidney, the erythropoietic response to EPO in the bone marrow, [23,24] and with the release of iron from the reticulo-endothelial system for use in the production of red cells in the bone marrow. [24] The resistance to EPO in the bone marrow may explain why anemia can be present in CHF even when the levels of EPO in the serum are elevated, as they frequently are, in CHF. [25]
6. Hemodilution.
The increase in sympathetic activity in CHF is responsible for an increase in renal afferent arteriolar constriction, leading to an increase in renin secretion and ultimately, an increase in aldosterone secretion. [26] Renin, through the effect of angiotensin and on aldosterone, is an important factor for sodium and water retention in the body. The resultant increase in blood volume leads to hemodilution and may be the cause for low haemoglobin in hypertensives. [27] The increased plasma volume in stress induced hypertension (sympatho-adrenal axis overactivity) or CHF may cause a reduced Hb. [10,27,28]
7. Chronic heart failure is associated with a profound and general bone marrow dysfunction, simultaneously affecting multiple hematopoietic lineages. [29]

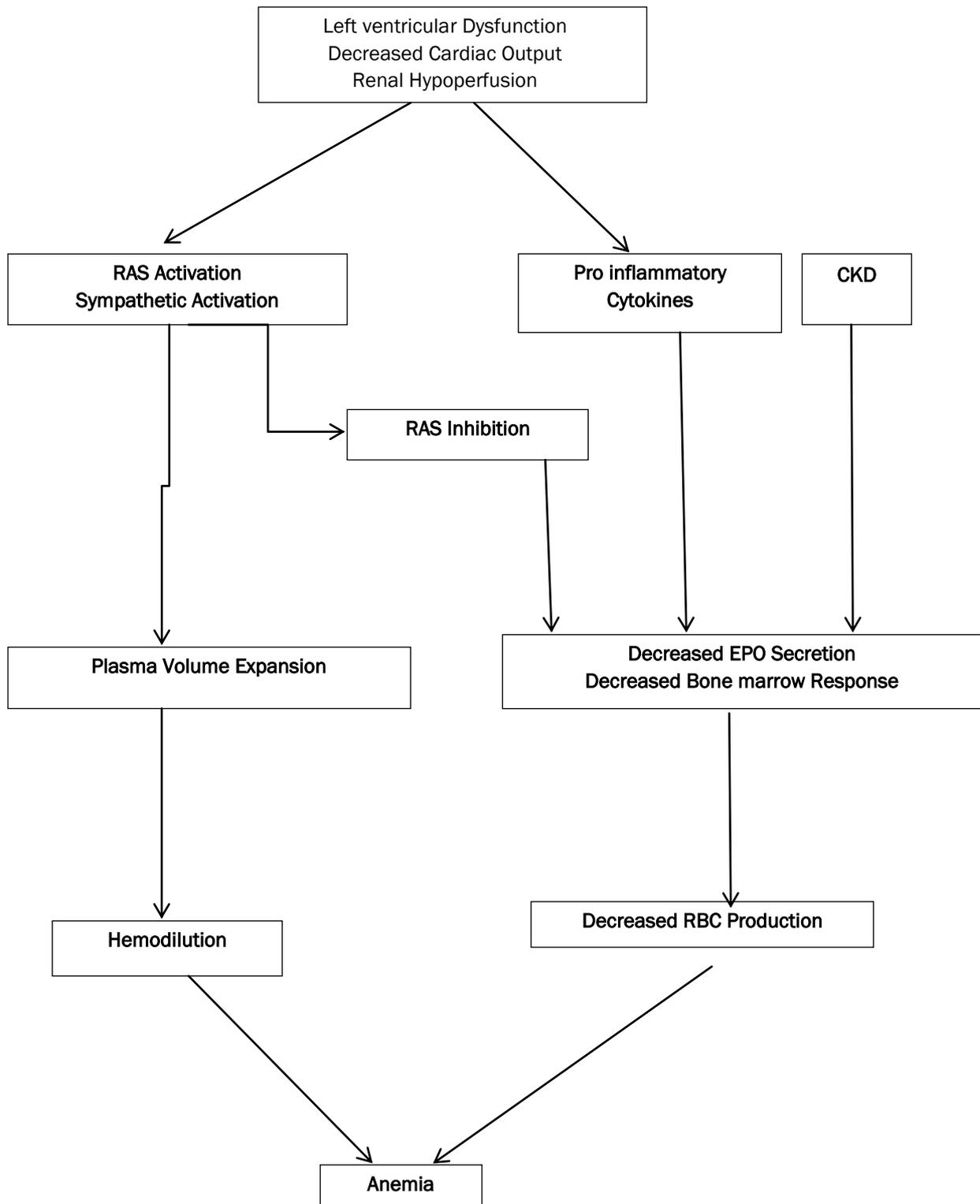
Anemia is associated with an increased mortality, morbidity and hospitalizations. Compared with nonanemic patients, the presence of anemia is associated with worse cardiac clinical status, more severe systolic and diastolic dysfunction, a higher BNP level, increased extracellular and plasma volume, a more rapid deterioration of renal function, a lower quality of life, and increased medical costs. Renal failure, cardiac failure, and anemia therefore all interact to cause or worsen each other—the so-called *cardio-renal-anemia syndrome*. [30]

Sympathetic overactivity which is seen in CHF has a major impact on the cardiovascular, autonomic and hematological parameters. Lesser hemoglobin due to sympatho-adrenal axis induced hemodilution can lead to increased cardiac output and heart failure. While addressing the complication of CHF hemoglobin level has to be mentioned.

Can anemia cause CHF?

Anemia of any cause may produce CHF. Vasodilatation caused by the accompanying tissue hypoxia lowers the blood pressure, thus activating the sympathetic nervous system (SNS). This causes peripheral vasoconstriction and tachycardia which are needed to maintain the blood pressure. The associated renal vasoconstriction activates the renin angiotensin aldosterone system (RAAS). The high angiotensin II levels further increase renal and peripheral vasoconstriction and increase aldosterone production. The resultant reduction in renal blood flow (RBF) and glomerular filtration rate (GFR) can cause renal ischemia and fluid retention. The renal insufficiency thus produced may also cause anemia through reduced

Figure 1: Vicious cycle of cardio renal anemia.



EPO production and bone marrow activity. The increased aldosterone further increases the fluid retention. Thus there is a marked increase in plasma and extracellular volume which can manifest itself as ventricular dilation and central and peripheral edema. The long-term effects of all these factors on the heart can be disastrous. The heart is faced on the one hand with an increased workload with increased heart rate and stroke volume, and on the other hand, the oxygen carrying capacity of the blood is reduced by the anemia itself. The heart undergoes 'remodeling' with ventricular dilation and left ventricular hypertrophy (LVH). Both the SNS and RAA contribute to this remodeling. Eventually the LV dilation and hypertrophy lead to myocardial cell death (apoptosis and necrosis), cardiac fibrosis, myocardialopathy and further CHF. [31,32]

Increased susceptibility of the damaged heart to anemia

In patients with coronary artery disease the effects of anemia on the heart may be even more severe than in normal people. In the damaged heart, ischemia can occur at a higher Hb level than in those with a normal heart. While patients with normal hearts undergoing surgery can tolerate low hemoglobin levels without increasing cardiovascular (CV) risk, those with coronary heart disease are more likely to have CV complications at low Hb levels. [33-36]

Treatment of anemia in HF

There is poor attention paid to anemia, its causes and treatment. Current treatment strategies appear to be insufficient at improving patient outcome in terms of rehospitalization rate reduction, generating high costs, which could be avoided through an optimized treatment strategy. Therefore, more efficacious, efficient and cost-effective treatment strategies are required for HF patients with anemia to meet this unmet medical need.³⁷ Iron supplementation or replacement is a treatment option for patients with HF and anemia, but questions about the safety of intravenous iron and absorption problems with oral formulations have prevented its widespread use to date. Number of studies with intravenous iron has shown promising results. Therefore, this treatment approach is likely to become an attractive option for patients with HF and iron deficiency, both with and without anemia. [38]

Erythropoietin (EPO) & Erythropoiesis-Stimulating Agents (ESA)

Meta-analysis of small RCTs suggest that treatment with ESA can improve exercise tolerance, reduce and have benefits on clinical outcomes in anemic patients with heart failure. [39] Despite initial studies indicating a possible beneficial effect of erythropoiesis-stimulating agents in the treatment of anemic heart failure patients, information on the long-term safety is still lacking. Ongoing large-scale trials will have the potential to provide such information in the future. [40,41] EPO is associated with serious adverse effects beginning from hypertension, headaches to an increased number of thrombotic events and death. Moreover, EPO withdrawal may be complicated by neocytolysis – hemolysis of young red blood cells in the presence of increased hematocrit. [42] The most common side effect of recombinant human erythropoietin (rHuEPO) therapy is hypertension which may occur even in healthy subjects [43,44] and rHuEPO enhances pro-coagulant pathways. [45] So better correction of anemia with higher Hb target is associated with increased risk for stroke, hypertension, vascular thrombosis compared with a lower Hb target. [46] By keeping in mind these serious side effect that can adversely affect the outcome of HF patient, a balanced and short term use of EPO treatment in HF patient with anemia seems more judicious.

EPO and Iron

Iron deficiency will cause a resistance to EPO therapy and increase the need for higher and higher doses to maintain the Hb level. [47,48] Treatment of the anemia with EPO and IV iron may be a useful addition to the physicians' armamentarium in CHF. [49]

CONCLUDING REMARK

Many patients with mild CHF and most patients with moderate to severe CHF are anemic. The degree of anemia parallels the degree of deterioration of cardiac and renal function and may contribute to this deterioration. The correction of the anemia is associated with an impressive improvement in cardiac function that is reflected in a marked improvement in the NYHA functional class, an improvement in renal function and a striking reduction in hospitalizations and use of oral and IV furosemide. [49]

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