Anemia and cardiorenal syndrome in heart failure: review article

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Abstract

The presence of anemia and of cardiorenal syndrome in patients with congestive heart failure is common and multifactorial. It may lead to a worst clinical condition and higher mortality.

Lower levels of hemoglobin may be a marker of chronic renal disease and hasten renal function deterioration.

The cardiorenal syndrome is the association between chronic renal failure and chronic heart failure. This condition is associated with a worst prognosis.

Creatinine levels and creatinine clearance are useful tools to identify this pathology at an earlier stage.

If iron, ferritin and iron-binding capacity show iron deficiency, it may be useful to start therapy with erythropoietin and iron.

The optimal level of hemoglobin may be 12g/dL (36% hematocrit) and is associated with a better prognosis.

Key words: Anemia, Heart Failure, Chronic Renal Failure, CardioRenal Failure, Erithropoietin, Iron, Folic Acid.

INTRODUCTION

Anemia is very common in patients with congestive heart failure (CHF) and is proportionately associated with higher rates of mortality[1-5] and morbidity[1,5-8]. However, the underlying mechanism that causes anemia in CHF is still being studied.

Often, vascular risk factors coexist in CHF and in Chronic Renal Failure (CRF). If there is an inverse linear relationship between the Glomerular Filtration Rate (GFR) and the level of anemia,[9] then anemia may be considered a subclinical marker of chronic renal failure and an aggravating factor of CHF.[1,5]

The correction of anemia seems to be associated with a better prognosis, reduction of clinical symptoms, reduction of the number and duration of hospitalizations, and an improvement in New York Heart Association (NYHA) functional class.[3,10]

When no consensual recommendations exist, iron, ferritin and total iron-binding capacity should be determined.

Some authors allow the administration of erythropoietin (EPO) in combination with intravenous (i.v.) iron, in cases where there is iron deficiency.[10]

Abbreviations:

NSAID: Non-Steroid Anti-Inflammatory
DM: Diabetes Mellitus
EPO: Erythropoietin
LVEF: Left Ventricle Ejection Fraction
Hb: Hemoglobin
HTA: Arterial Hypertension
ACEI: Angiotension Converting Enzyme Inhibitors
CHF: Congestive Heart Failure
RCF: Renal Cardiac Failure
CRF: Chronic Renal Failure
NYHA: New York Heart Association
NO: Nitric Oxide
SNS: Sympathetic Nervous System
RAAS: Renin Angiotensin Aldosterone System
GFR: Glomerular Filtration Rate

PATHOPHYSIOLOGY OF ANEMIA IN CHF

According to the 2006 National Kidney Foundation (NKF) criteria, anemia is defined as an Hb count of less than 13.5 g/dL in males and 12.9 g/dL in females. This reference value (1) is currently decreasing, to an agreed value of 12.0 g/dL.[1,5]

Anemia seems to occur primarily in association with old age,[3,5,9,11,12] female gender [3,5,9,11,12], arterial hypertension (HT) and concomitant presence of Diabetes Mellitus (DM).[1-3,5,12] There also appears to be a positive correlation with ischemic cardiomyopathy,[12] NYHA functional class III-IV[2,3,5,9,11] and CRF.[1,3,5, 9,11]

The prevalence of anemia in CHF varies between 9.9% and 50%, according to the values used to define anemia, and the CHF functional class of the patients studied.[1]

Tanner et al[13] found a 15% prevalence of anemia

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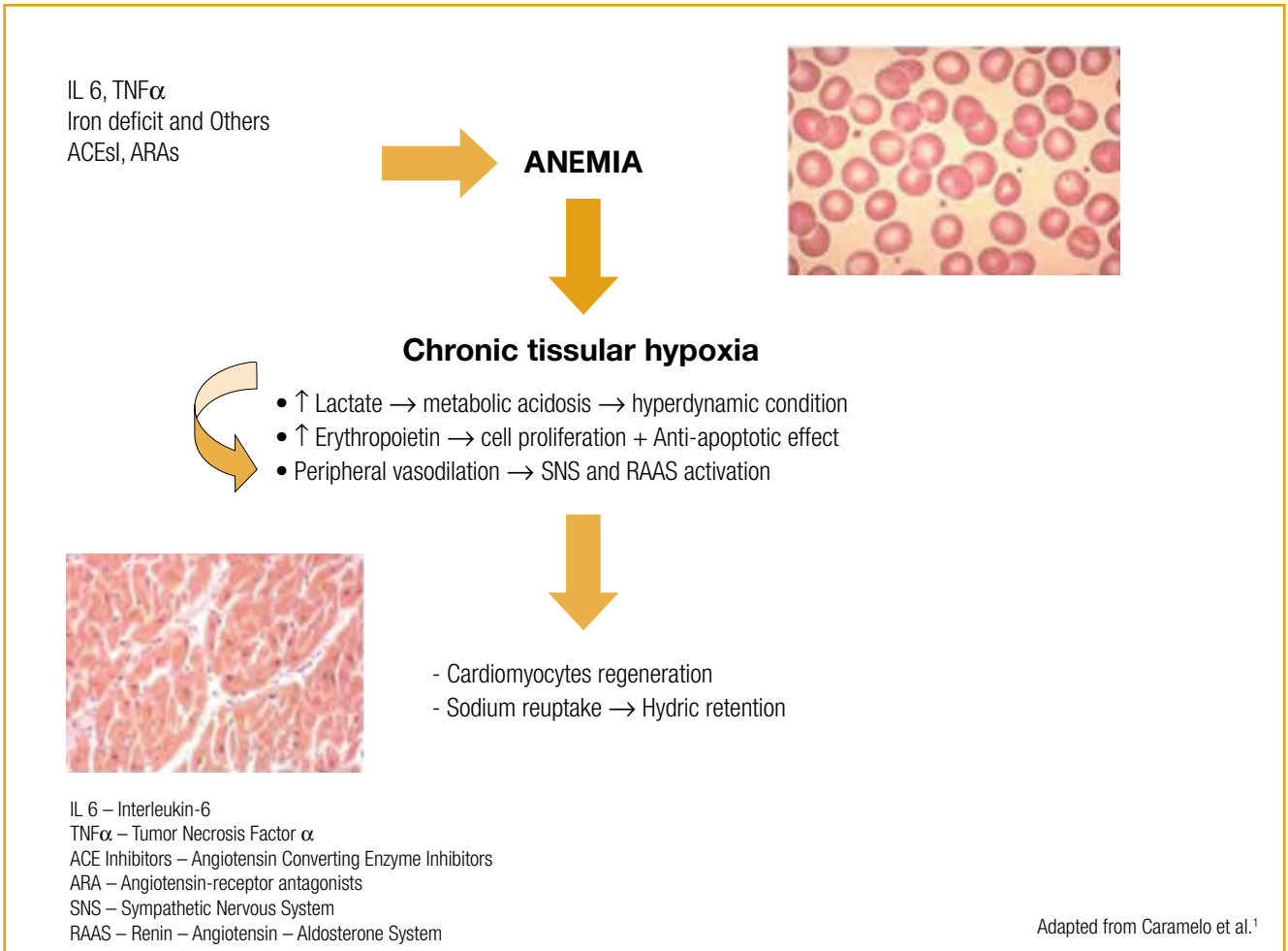


Possible adverse effects of anemia in CHF.

FIG. 1

in patients with CHF, and a correlation between this and NYHA class ($p<0.05$).

THE FOLLOWING CAN BE CITED AS POSSIBLE MECHANISMS PRODUCING ANEMIA IN CHF (SEE FIG. 1):

• The release of interleukin-6 (IL); IL-1, IL-10, interferon, C-reactive protein and TNFα (tumor necrosis factor α) decreases the synthesis of erythropoietin and its action on the erythrocyte precursors[1,2,14-16] causing bone marrow depression.[10] Okonko et al[11] reported that an increase in the amounts of these cytokines raises EPO levels, while increasing the resistance to its effects;

• The possible release of hepcidin, which is produced in the liver and is responsible for the homeostatic regulation of the iron content in the body, prevents the efflux of this ion from the enterocytes, hepatocytes and macrophages, reducing its bioavailability for the production of erythrocytes in the bone marrow. Further studies are awaited, that should demonstrate the relationship between hepcidin levels and CHF;[1,2,6]

- The concomitant existence of nutritional deficiency, particularly iron deficiency;[3,11,14-16]

- Uremic gastritis;[11,16]

-The use of ACEs (angiotensin converting enzyme) inhibitors and ARAs (angiotensin receptor antagonists).[10-12,15,17]

Although the use of these drugs is associated with an overall decrease in mortality, some studies have also observed a decrease in hematocrit count, which can cause anemia due to a decrease in EPO levels[1,11]

by inhibiting the growth of erythroid progenitors due to lower levels of circulating angiotensin II,[4] a decrease in the IGF levels, or inhibition of N-acetyl-seryl-aspartyl-proline catabolism.

This effect is increased during the first 3 months of therapy, remains stable thereafter and reverts 3-4 months after administration is discontinued.[1,10] J. Szachniewicz et al[2] did not find this association. In the Studies of Left Ventricular Dysfunction (SOLVD), long-term therapy with enalapril did not decrease the hematocrit count when compared with the placebo effect;[11]

• The use of non-steroidal anti-inflammatory drugs (NSAIDs) may decrease the erythropoiesis stimulating factor by the prostaglandins ;[1,3]

• Medular hypoperfusion, with decreased capacity of erythropoiesis;[3]

• Hemodilution,[3,11,16] which provides a poorer diagnosis than the isolated presence of "actual anemia";[11,14,15]

• Renal failure impairing EPO production.[2,6,11,14,16] Beck da Silva et al[6] reported that an increase in EPO levels in CHF is normally observed, acting as a compensatory mechanism;

• Proteinuria with possible loss of EPO and transferrin;[14]

• Hemorrhage favored by antiplatelet and/or anticoagulation therapy.[1,3,14-16]

Sharma et al[18] did not find any significant differences between patients receiving thiazide diuretic therapy and placebo (14.1 vs. 14.0 g/dL, p = 0.10). They also found no differences between the Hb levels among patients receiving aspirin, heparin or warfarin.

Komajda et al,[5] Beck da Silva et al,[6] and Sharma et al[18] did not find a specific cause for anemia, classifying it as anemia of chronic disease.

Nanas et al[16] conducted a trial to determine the etiology of anemia (<12 g/dL in males and <11.5 g/dL in females) in patients with CHF; patients with a creatinine count above 3 mg/dL were excluded. The trial concluded that 73% of patients had iron deficiency anemia, 5.4% hemodilution, 2.7% drug-induced anemia (enalapril), 18.9% anemia of chronic disease. Low levels of EPO (68.6 ± 54.7 µU/ml) and normal levels of ferritin (113.2± 94.4 ng/mL) were also found. Ferritin does not seem to be a reliable marker for iron deficiency, due to the possibility of its count increasing in the context of inflammation caused by the CHF itself.

These authors also suggest that a therapeutic test with iron in all patients with CHF should be performed, but there is no consensus as to this approach.

The increase in mortality sometimes associated with the presence of anemia[3] does not seem to occur in the initial stages of CHF.[3]

The appearance of other morbidities when worsening of cardiac dysfunction is registered may explain this increase in mortality rates.[3]

Kosoborod et al[19] conclude, in their analysis, that anemia is associated with increased mortality in patients with CHF due to the severity of the comorbidities. Thus, anemia may act as a marker, not as a mediator.

Nevertheless, there is no consensus in the literature. For example, it was found that in young patients referred for heart transplant, the presence of anemia was not a determining factor of overall mortality.[3]

J. Szachniewicz et al[2] found a lower survival rate in patients with CHF and anemia (67%) compared with patients with CHF only (87%) (p=0.016), based on a reference value of Hb < 12g/dL.

It was also observed that the presence of anemia in CHF doubles the risk associated with other factors, such as diabetes mellitus (DM), age, tobacco, and low left ventricular ejection fraction (LVEF).[1]

CONSEQUENCES OF ANEMIA IN CHF (TABLE I A AND I B)

Anemia can be both a cause and a consequence of CHF.[15]

J. Szachniewicz et al[2] observed, in their trial, that patients with more symptomatic CHF tended to have lower Hb levels (p<0.05). Okonko et al[11] reported that EPO levels appear to increase in proportion to the intensity of the clinical symptoms.

Chronic tissue hypoxia resulting from anemia[4,14,15,18,20] may cause alterations which, if persistent, can exacerbate sodium reabsorption, causing water retention which, in turn, may lead to remodeling of the cardiomyocytes.[1,9,14] Left ventricular hypertrophy or dilation may occur.[15]

The alterations (see Fig. 1) caused by hypoxia may include:

• Increased levels of lactate and consequent lactic acidosis, leading to a hyperdynamic state;[1]

• Increased EPO levels, causing antiapoptotic effects and proliferation of myocytes;[1,20]

TABLE I A

Framingham Criteria for Defining Cardiac Failure: 2 major or 1 major + 2 minor

Major	Minor
Paroxysmal Nocturnal Dyspnea	Effort dyspnea
Orthopnoea	Peripheral edema
Crackles	Hepatomegaly
Jugular Vein Engorgement	Pleural Effusion
S3	
Signs of Lung Congestion Chest X-Ray	
Cardiomegaly	

TABLE I B

Possible Consequences of Anemia in CHF

Left ventricular hypertrophy
Earlier Onset of Heart Failure
Earlier Onset of Chronic Renal Failure
Exacerbation of Myocardial Ischemia
Reduction of aerobic capacity
Decreased exercise tolerance
Compromised higher mental functions
Deterioration of quality of life

Adapted from Caramelo et al.[1]

• Peripheral vasodilatation (decreased inhibitory effect of Nitric Oxide (NO) by hemoglobin).[1,18] This vasodilatation may be absent due to the prevalence of the vasoconstrictor response caused by low perfusion and consequent low energy expenditure.[1]

• Activation of the SNS (sympathetic nervous system);[1,9,14]

• Activation of the RAAS (Renin Angiotensin Aldosterone System),[1,9,11] with increased risk of hyperkalemia;[9,14]

• Release of vasopressin.[1,9]

Anemia, when not cured, may eventually contribute to left ventricular hypertrophy, earlier onset of CHF and CRF, exacerbation of ischemic cardiopathies, reduced aerobic capacity, decreased tolerance to exercise, and impaired higher mental functions, resulting in deterioration of quality of life.[1]

With regard to the consequences of anemia in CHF, considering its impact on mortality in the trial carried out McClellan et al, cited by Gil et al,[9] the mortality rates of patients with CHF and anemia was 44.9%, compared with 31.9% in patients with CHF without anemia.

A more recent trial showed that for every 1 g/dL decrease in hemoglobin, there is an increase of 13% in mortality rate.[9]

Lupón et al[14] evaluated the prognostic value of hemoglobin levels related to death by CHF, and the number of hospitalizations due to CHF over a one-year period. Anemia was defined as an Hb count of less than 12 g/dL. 30% of the patients in the selected sample were anemic.

It was concluded that there was an association between Hb levels and mortality (average value 13.0±1.7 g/dl *versus* 11.6±1.7 g/dl in the patients who died, p<0.001).

The Hb levels were also associated with a need for hospitalization: 13.1±1.7 g/dL in patients who were not hospitalized versus 12.2±1.7 g/dL in the patients who were hospitalized at least once, p<0.001.

31% of all anemic patients were hospitalized at least once, compared with only 15% of patients who were not anemic, p=0.001.

Lupón et al (14) also described the relation between anemia and age (p<0.001), gender (p<0.001), NYHA class (p<0.001), diabetes (p<0.001), hypercholesterolemia (p<0.001), creatinine and urea (p<0.001).

Lupón et al (14) reported a 40% decline in risk of mortality, with a 1% increase in hematocrit count and a 21% decrease in the need for hospitalization.

Sharma et al[18] measured the Hb levels in 3044 patients with CHF. It was demonstrated that the patient's age, NYHA class, creatinine levels and LVEF are linear factors of survival; however, Hb proved not to be a prognostic marker (p=0.26) if used as a continuous variable.

When analyzing hemoglobin as a discontinuous variable, the classification of patients by increases in 1.0 g/dL in Hb showed a nonlinear relationship of survival. The optimal interval has a symmetric distribution of around 14.5 g/dL, regardless of the presence of other factors (p<0.001). Patients with the worst prognosis were those at the extreme ends of the scale, i.e. the most anemic and the most polycythemic.

The same trial concluded that Hb concentration has independent prognostic value for mortality in

patients with CHF, with anemic and polycythemic patients having the lowest survival rates.

As a possible explanation for the poorer prognosis in polycythemic patients, the authors suggest an increase in thromboembolic events, increased cardiac work, vasoconstriction due to the lower amount of NO, and reduced supply of oxygen peripherally.

Van der Meer et al[21] concluded that high levels of EPO are associated with a poor prognosis ($p<0.05$), and are poorly correlated with Hb count in patients with CHF. They also found a statistical association between EPO and BNP levels ($p<0.001$) and NYHA class ($p=0.01$). In the same trial, there was no correlation between the EPO and LVEF levels or LV diastolic dimension.

CHF, ANEMIA AND CRF

Anemia seems to favor the progression of CRF in patients with CHF. It can also be a risk factor that is predictive of the development of CHF in patients with chronic renal failure.[1,2,22]

The estimated prevalence of CHF in Europe is 0.4%-2% [9]. The incidence increases with age, reaching 3% in people aged over 75 years. Among the patients with CHF, the prevalence of CRF (defined as creatinine clearance < 60ml/min) was 39% and mortality after one year seemed to increase by 0.2% for every 1 µmol/L increase in creatine.[9]

The reciprocal, negative influence represented by the concomitant existence of CHF and CRF is referred to as cardiorenal anemia syndrome, anemia being an aggravating factor.[1,11] Van der Meer et al[15] also reported that renal anemia is a cardiovascular risk factor.

Given that there is an inverse linear relationship between GFR and anemia levels, anemia can be considered as a subclinical marker of chronic renal failure in patients with CHF.[1,9,22] The coexistence of CHF and CRF is referred to as cardiorenal disease (CRD). CRD assume concomitant existence of serious, but largely reversible functional lesion of the heart and kidney[9], and can include acute or chronic failure.[22]

The literature is not unanimous. For example, J. Szachniewicz et al[2] did not find any relation between Hb levels, LVEF and creatinine ($p>0.2$).

Gil et al[9] suggested that the CRD may be a critical factor that contributes to a mortality rate of 50% observed 3 years after the diagnosis of CHF in European patients aged over 75 years.

Shamagian et al[23] observed that CRF is common in hospitalized patients with CHF and is a strong predictor of mortality in those patients, regardless of whether the systolic function is poorer or preserved. This relationship is independent of the existence of other cardiovascular risk factors.

In the prospective PRAISE Trial, also cited by Gil et al,[9] a 1% decrease in hematocrit count is related to a 3% increase in mortality.[9]

Gil et al[9] found that patients with CRF have a greater chance of dying from cardiovascular events than from progression of renal failure.

The low concentrations of hemoglobin relate to increased levels of urea and creatinine, reduced albumin, lower cholesterol levels, lower functional class and lower oxygen consumption. Myocardial ischemia and hypertrophy have proven to be more sensitive to anemia.[1]

The relation between CHF and CRF is probably due to a renal vasoconstriction and ischemia mechanism,[1] with an eventual insufficient renal erythropoietic response.[11] It should be noted that aging is related to a slow process of progressive renal sclerosis, associated with loss of nephrons (about 30% in people aged over 50) and reduced vasodilatation capacity.

30% to 50% of patients with CHF have levels of glomerular filtration rate (GFR) < 60 mL/min and creatinine < 2 mg/dL, which can justify the diagnosis, sometimes delayed, of CRF.[1]

Caramelo and Gil[22] report an incidence of 56.5% of CRF in similar trials.

Renal function, in conjunction with NYHA class and left ventricular ejection fraction, appear to be an indirect marker of cardiac function.[1,22] In the HOPE and HOT Trials,[22] it was demonstrated that CRF increases the risk of incidence and death from cardiovascular disease.

Gil et al[9] suggested that calculation of creatinine clearance is adopted as a rule in patients with CHF (in addition to monitoring serum creatinine values), in order to identify patients with CRD.

Drugs such as ACE inhibitors, δblockers and spironolactone have proven benefits when used as therapy in CHF. Some trials[9] suggest that its effect in CRD is at least as effective as it is in CHF, however, more trials are needed to provide supporting evidence.[9]

It is not established which safe therapy or doses of the current drugs, such as aspirin and statins, should be used in patients with CRD[9], neither the drugs that

are contraindicated in this pathology.

Shamaigan et al[23] also suggest that laboratory assessment of renal function should be performed routinely in patients with CHF.[23]

Gil et al[9] lists the factors that may precipitate acute renal failure (ARF) in the context of a CRF: persistently low urinary sodium; increased urea/creatinine ratio; increased uric acid; hyponatremia; average blood pressure lower than 90mmHg; changed effective circulating volume (changes in salt intake, diarrhea, vomiting, loss of blood or others); dehydration (e.g., fever, tachypnoea); use of intravenous contrast; old age; diabetes mellitus; surgery *(Table II)*

The same authors also report that patients with CRD, particularly those with high urea/creatinine ratio and hyponatremia, are very sensitive to the renal effects of NSAIDs, therefore their use can be harmful.

This group of investigators proposes early screening of complications in patients with CRD, through objective examination, measurement of weight, blood pressure, urea and electrolytes in the blood and urine.

Shamaigan et al[23] carried out a two-year follow up of 522 patients hospitalized with CHF and different degrees of renal dysfunction (GFR>60, GFR 30-60, and GFR<30 mL/min per 1.73 m2). They conclude that patients with more severe CRF had also a worse cardiovascular risk profile – advanced age, anemia, increased blood inflammatory markers, and lower doses of ACE inhibitors. The survival rate in this group was lower than in the other groups (RR=2.4). The use of ACE inhibitors seemed to attenuate the negative impact of CRF in the prognosis.

TABLE II

Factors that may precipitate Acute Renal Failure in Cardiorenal Failure

Persistently low urinary sodium
Increased Urea/Creatinine ratio
Increased uric acid
Hyponatremia
Average Blood Pressure less than 80 mmHg
Alterations in effective circulating volume (change in salt intake, diarrhea, vomiting, loss of red blood cells, or others)
Loss of fluids (e.g., fever, tachypnoea)
Use of intravenous contrast
Advanced age
Diabetes mellitus
Surgery

Adapted from Gil et al.[9]

TREATMENT OF ANEMIA IN CHF

The treatment of anemia in CHF has been associated with increased LVEF;[1,2,10,15] prevention of left ventricle dilation;[10] increased cardiac output[10] and improved NYHA functional class.[1,3,14,16]

A decrease in left ventricular mass,[1,2,10,18] improvement in myocardial ischemia,[1,2] and improvement in the ability to use oxygen during exercises have also been observed.[1,2,9,10,20]

There still seems to be an association with stabilization of creatinine levels;[1,2] reductions in levels of diuretics[1-3,10] and iron;[1,2] reduction in the number[1,2,10,14] and duration of hospitalizations;[1,2,9,15] increased quality of life[1,2,3,16] and symptomatic improvement.[7,15]

Van der Meer et al[15] also suggest that EPO has pro-angiogenic effects on the endothelial cells.

Some authors[1] claim that a correction of Hb by 1g results in a 40% decrease in mortality rates over one year.[1,14]

Silverberg et al[10] conducted a trial lasting 7.2±5.5 months, comprising 142 patients with CHF, aimed at assessing the prevalence and severity of anemia and its association with cardiac and renal functions, and hospitalization.

It was found that the prevalence of anemia increases with the severity of CHF.

(from Hb 13.73±0.83 g/dL in NYHA class I to 10.90±1.70 g/dL in NYHA class IV (p<0.01), reaching 9.1% in class I and 79.1% in patients with CHF, NYHA class IV. The creatinine levels also increase in proportion to the CHF functional class, from 1.18±0.38 mg/dL in NYHA class I to 2.0±1.89 mg/dL in NYHA class IV, p<0.001). The percentage of patients with creatinine > 1.5 mg/dL increased from 18.2% in class I to 58.2% in class IV.

LVEF decreased from 37.67±15.74% in NYHA class I to 27.72±9.68% (p<0.005) in class IV.

Therapy with EPO + iron iv was begun, to keep the values above 12g/dL. After that, hematocrit increased from 30.14±3.12% to 35.9±4.22% (p <0.001); the average concentration of Hb increased from 10.16±0.95 g% to 12.10±1.21 g% (p<0.001).

An increase from 27.7±4.8 to 35.4±7.6% (p<0.001) in LVEF was observed (an increase of 27.8%). The number of hospitalizations decreased by 91.9% (from 2.72±1.21 to 0.22±0.65 per patient (p<0.05). Functional class decreased from 3.66±0.47 to 2.66±0.70 (p<0.05), as well as the required dose of diuretics. The reduction in GFR decreased with the treatment. The variations in creatinine levels were not significant. No significant changes were found in mean systolic and diastolic pressures.

The erythropoietin acts by induction of transferring genes, mobilizing the iron for use in erythropoiesis; of the vascular endothelial growth factor (VEGF), stimulating angiogenesis; of tyrosine hydroxylase, which will increase oxygenation through the respiratory rate; and of NO synthesis, promoting vasodilatation.[1] *(Fig. 2)*.

Mancini et al[20] administered therapy with EPO for three months to a group of patients with CHF, and placebo to another group.

In the first group, a symptomatic improvement was observed (from 11.0±0.5 to 14.3±1.0 g/dL, *p*<0.05), with increased oxygen consumption (from 11.0±1.8 to 12.7±2.8 mL min^{-1} kg^{-1}, p<0.05), and longer duration of exercises (from 590±107 to 657±119 s, p<0.004)

No significant changes for the same parameters were observed in the patients that received placebo.

Mancini et al[20] did not observe any improvement in renal function, increase in blood pressure or peripheral vascular resistance after the therapy with EPO.

The authors suggest, as a possible cause of the clinical improvement observed in patients receiving EPO, a reduction of oxidative stress through the reduction of O2 free radicals, with improved endothelial function and increased oxygen supply.

The ideal hematocrit and hemoglobin count have not been established.

The target levels of 35-36% hematocrit and 12g/dL hemoglobin seem to be cautious,[1,9] and higher counts should be avoided.[9]

The risk/benefit ratio of using EPO should also be considered, since it may predict an increased risk of high blood pressure[24] and thromboembolic events.[24]

Silverberg et al[10] found that the prevalence of anemia increased with the severity of the heart failure. The treatment with EPO and iron, iv, increased the hemoglobin levels to 12.1±1.21g/dL (Htc 35.9±4.22%), associated with a decrease in the CHF functional class (from 3.66±0.47 to 2.66±0.70, p<0.05), improved cardiac function (LVEF from 27.7±4.8 to 35.4±7.6, p<0.05) and renal function, and a decrease in the dose of diuretics and in the number of hospitalizations.

It was not defined that correction to values of 14g/dL would be needed to improve the patients' medical condition.

Some authors recommend the therapy with EPO and iron iv concomitantly, since the therapy with EPO alone could lead to deficiency of this ion[10] and demand higher doses of EPO, which could lead to an increase in blood pressure.[10]

The drugs used are erythropoiesis-stimulating agents: recombinant EPO-δ, recombinant EPO-δ darbepoetin; EPO receptor activator and prolyl hydrolase inhibitors (stabilization of HF1) in the future.

Iron iv should be used concomitantly with an erythropoiesis stimulating agent.[1,8,22]

There may be a nutritional iron deficit caused by the use of EPO,[1] cardiac cachexia,[3,10] malabsorption,[3,13,11,16] use of aspirin[3,10,11,16] or proteinuria.[11]

In the trials cited by Okonko et al,[11] the anemia was corrected by EPO + iron + folic acid; all patients showed clinical improvement.

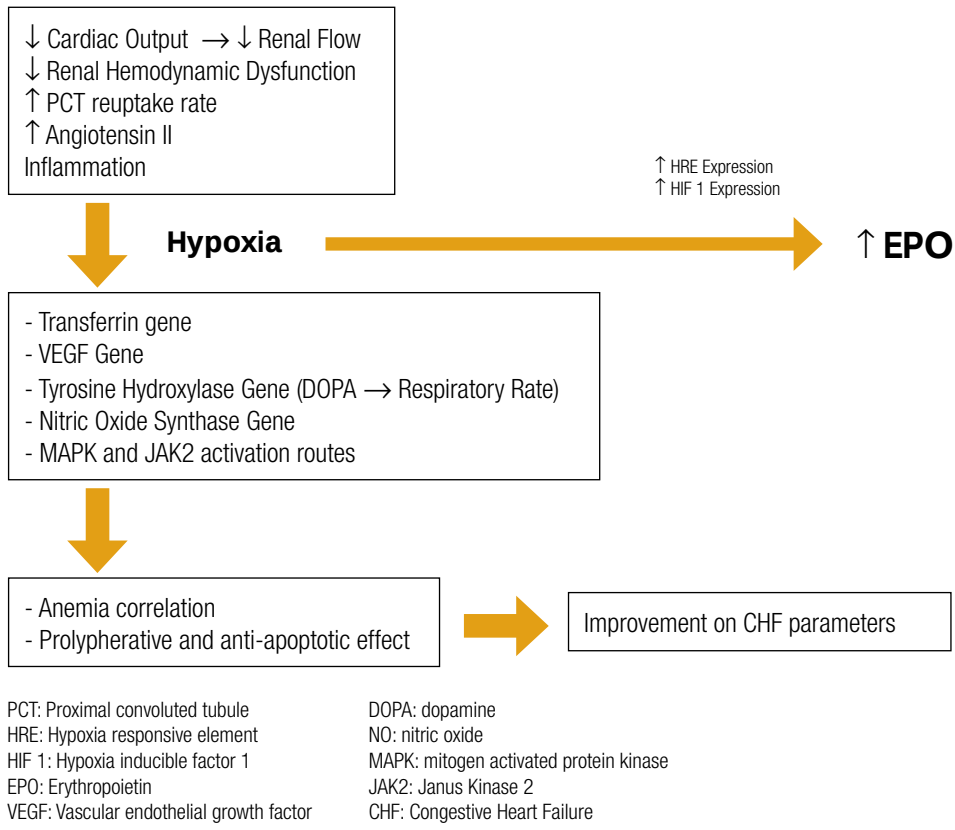
Therapy with EPO in CHF, particularly ischemic CHF, is also beneficial through angiogenic and antiapoptotic mechanisms and the action of mitogen-activated protein kinase (MAPK) and janus kinase 2 (JAK2).[1]

When therapy with EPO is ineffective, the following common resistance mechanisms should be studied: loss of red blood cells; iron deficiency; CRD; chronic and/or acute inflammation; use of ACE NSAID inhibitors; nutritional deficits; bone marrow depression.[1]

The therapy with EPO currently available can be administered subcutaneously (15-200U/Kg, divided in one to three doses/week) and intravenously (400U/Kg, divided in one to three doses/week) and its effect lasts seven days; the effect of darbepoetin lasts 15-30 days.[1]

Since there are insufficient data, the same doses is used in the trials on the therapy with EPO in CRF and CHF.[1]

Some authors suggest that concomitant therapy with EPO + iron iv must be used. One suggested form is the administration of iron gluconate (62.5mg) or iron sucrose (100mg) once a week in cycles of 6-9 weeks, according to ferritin levels.[1]



Erythropoietin in Heart Failure.

FIG. 2

A trial currently in progress (Beck da Silva et al),[6] aimed at investigating the effects of the administration of iron in patients with CHF and iron deficiency anemia suggests that intravenous administration is more effective due to the eviction of blockage by the reticuloendothelial system that is observed with the oral administration.

Bolger et al[7] observed increased hemoglobin levels (from 11.2±0.7 to 12.6±1.2g/dL) (p=0.0007), improved symptoms and increased ability to exercise after therapy with iron iv (without EPO) in patients with CHF and anemia (44% iron deficiency anemia). Patients with lower levels of Hb were those who benefited most from the treatment (p=0.006).

The average increase in hemoglobin concentrations was 1.4±1.3g/dL, compared with previous results of 2.6g/dL (12) and 3.3g/dL (19) in trials conducted with iron iv associated with EPO.

These authors found no changes in serum creatinine or creatinine clearance. The decrease of cystatin C (from 1.71±0.52 to 1.50±0.53 mg/L, p= 0.08), a GFR marker, may suggest an improvement in the glomerular filtration rate.

In relation to the treatment of CRD, Grigorian-Shamagian[22] reported that the prescription of ACE inhibitors in patients with CRF attenuates the effects of the disease on cardiovascular prognosis; therefore, it is fundamental to determine the effective level of circulating volume before initiating the therapy, starting with low doses and using drugs with a short half-life and preferably with no renal metabolism. In patients with CRF who depend on high levels of angiotensin II to maintain the GFR, the condition will be aggravated by the administration of ACE inhibitors.[22]

Ishani et al[4] used the database of the SOLVD Trial, which studied patients with CHF without anemia on admission. The researchers calculated the probability of these patients developing anemia after one year

under therapy with enalapril or placebo; whether the occurrence of anemia, of whatever cause, was associated with an increase in mortality; whether the therapy with enalapril in patients with CHF would still be beneficial if the patients developed anemia.

The prevalence of anemia in patients with CHF at the start of the trial was 18.4%, and after one year, this figure was 9.6%.

The therapy with enalapril increased the likelihood of anemia occurring by 56% ($p<0.0001$) (defined as a hematocrit count of 39% in males and 36% in females after six weeks of treatment).

In patients with anemia on admission, a 44% increase in the mortality rate was recorded (confidence interval 1.27 to 1.64).

In the patients who developed anemia during the trial, the increase in the mortality rate was 108% (confidence interval 1.82 to 2.38).

A single episode of anemia was associated with a 38% increase in mortality (confidence interval 1.16 to 1.63) in patients receiving enalapril and a 56% increase (confidence interval 1.32 to 1.84) in patients receiving placebo.

Each 1% increase in the hematocrit count was associated with a 3% reduction in the mortality rates (confidence interval 0.96 to 0.98).

After adjusting the incidence and prevalence of anemia, the use of enalapril was associated with an increase in survival (confidence interval of 0.80 to 0.98). It was not possible to find a ready dose of enalapril that would confer this benefit to patients, since the doses used were personalized according to the clinical situation of each patient.

Caramelo and Gil[22] report that the use of loop diuretics should be used (and is more beneficial if prescribed intravenously) if necessary in association with other diuretics acting in other sites of the nephron. Renal creatinine clearance < 40 mL/min contraindicates the use of thiazide diuretics without loop diuretics.[22]

Gil et al[9] report that antagonists of vasopressin V2 receptor, such as tolvaptan, reduced mortality rates by 40% in patients with LVEF resistant to the standard therapy for CHF. They also reported that, in the trial by Ventura HO cited by Gil P. et al,[9] the LVEF of patients with CRD who underwent kidney transplant increased from 31.6±6.7 to 52.2±12 one year after transplant and that in 70% of patients, LVEF returned to normal values.

TABLE III

Expected effects of the use of vasopressin receptor antagonists

Increased cardiac output;
Reduced peripheral resistance;
Reduced average blood pressure;
Reduced congestion;
Reduced preload;
Increased concentration of plasma sodium.

Adapted from Gil et al.[9]

Caramelo and Gil[22] also mention the vasopressin antagonists 'vaptans'. They may be V2 antagonists (e.g.: tolvaptan), the only function of which is to increase the elimination of water by the kidneys; and antagonists V2 + V1a (e.g.: conivaptan) which also fights the vasoconstrictor effect of vasopressin.

These drugs are particularly useful in patients with hyponatremia, allowing an increase in the concentration of plasma sodium *(Table III)*, or in patients who are resistant to loop diuretics.[22]

The action of these drugs is expected to result in a reduction in average blood pressure, increased cardiac output, decreased preload and reduced peripheral vascular resistance. As a consequence, a reduction in pulmonary congestion can be observed.

The same authors[22] described the trial carried out by Costello-Boerrigter et al, which makes a comparison between the use of tolvaptan and furosemide in patients with mild/moderate CHF. The diuretic effect found was the same, but in the patients that received furosemide, a decrease in renal perfusion and changes in plasma sodium and potassium concentrations were observed.

Caramelo and Gil[22] report that the use of recombinant atrial natriuretic peptides (ANP) (e.g. carperitide) and ventricular natriuretic peptides (BNP) (e.g. nesiritide) may be associated with a worsening or the absence of effect on renal function in patients with CRF. They also report that the recovery of myocardial function was marked in some patients with CHF when dialysis or ultrafiltration was begun.

Roig[3] reported that the use of new endothelin-receptor inhibitors and TNFα was disappointing for the treatment of anemia.

The therapy used should be personalized according to the cardiac and renal reserve of each patient[9] and, in the presence of CRD, both CHF and CRF should not be treated as isolated pathologies.[22]

CONCLUSION

Trials conducted to date indicate that the correction of anemia in CHF results in improved cardiac function (increase in LVEF, increased cardiac output, decreased left ventricular mass, prevention of left ventricular dilatation, improved NYHA functional class and myocardial ischemia) and renal function (stabilization of creatinine levels).

Increased hemoglobin concentration enables a reduction in the levels of diuretics and iron.[1,2,9,10,16] An improvement in the symptoms has also been observed,[3,7] as well as a decrease in the number and duration of hospitalizations and improved quality of life.

New trials are expected to determine whether the correction of anemia is associated with an increase in survival rates.[25]

Nevertheless, there are doubts about the mechanisms that cause anemia in CHF; the reciprocal relationship CHF-CRF; the optimal concentration of hemoglobin to be achieved with the therapy (too high a concentration can be harmful)[10] and the adverse effects of long term therapy with EPO (thrombosis, high blood pressure).[3]

New trials are expected from which further consensual recommendations may be established. ■

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