Anemia in heart failure

Kalp yetersizliğinde anemi

Alev Kılıçgedik, Cihan Dündar[1], Mustafa Kürşat Tigen[1]

Clinic of Cardiology, Kocaeli State Hospital, Kocaeli
[1]Clinic of Cardiology, Kartal Koşuyolu Training and Research Hospital, İstanbul-*Turkey*

ABSTRACT

Chronic heart failure is a common problem and a major cause of death, hospital admission, poor physical function and impaired quality of life. In addition to the direct effect of heart failure on prognosis, several modifiable and non-modifiable factors contribute to the worse prognosis in heart failure. Anemia, which is common in patients with heart failure, may represent a modifiable risk factor for adverse outcome. It is also a marker for co-morbidity burden and greater disease severity. If anemia is a marker, treatment may not obviate the increased risk associated with anemia, but if it is a mediator, treatment may be helpful to reduce morbidity and mortality in heart failure. As anemia has been identified as an independent prognostic factor of both morbidity and mortality for patients with congestive heart failure, there is an increased interest in the hypothesis that the correction of anemia with erythropoietin or iron supplementation might lead to an improvement on patients' symptoms and functional status. Large randomized trials are necessary to show the effect of anemia and the specific treatments on the outcome in these patients. This article reviews the mechanisms, impact on outcomes and therapy of anemia in patients with heart failure.
(Anadolu Kardiyol Derg 2012; 12: 65-70)
Key words: Heart failure, anemia, outcome, treatment

ÖZET

Kronik kalp yetersizliği genel bir sorun ve ölüm, hastaneye başvuru, kötü fonksiyonel kapasite ve bozulmuş yaşam kalitesinin en önemli nedenlerinden biridir. Kalp yetersizliğinin prognoz üzerine direk etkisi yanında çeşitli iyileştirilebilir ve iyileştirilemez faktörler kalp yetersizliğinin prognozunu kötüleştirir. Kalp yetersizliğinde sıkça görülen anemi kötü sonlanım için iyileştirilebilir bir risk faktörüdür. Aynı zamanda anemi komorbidite yükü ve hastalık ciddiyeti için de bir göstergedir. Aneminin hastalık ciddiyetini gösteren bir belirteç olması durumunda tedavi ile anemiyle ilişkili artmış risk önlenemeyebilir, fakat aneminin bir mediyatör olması durumunda anemi sebebini bilmek ve tedavi etmek kalp yetersizliğinde mortalite ve morbiditenin azalmasına katkı sağlayabilir. Anemi konjestif kalp yetersizliğinde hem mortalite hem de morbidite için bağımsız bir risk faktörü olarak tanımlandığından beri, aneminin eritropoetin veya demir desteği ile düzeltilmesinin hastanın semptomlarında ve fonksiyonel durumunda iyileşme sağlayabileceği hipotezine ilgi artmıştır. Fakat hala aneminin ve spesifik tedavilerin bu hastalarda sonlanım üzerine etkisini gösterebilmek için geniş randomize çalışmalara ihtiyaç vardır. Bu derlemede kalp yetersizlikli hastalarda aneminin mekanizması, olumsuz sonlanım üzerine etkisi ve tedavisi anlatılmıştır. *(Anadolu Kardiyol Derg 2012; 12: 65-70)*
Anahtar kelimeler: Kalp yetersizliği, anemi, sonlanım olayları, tedavi

Introduction

Chronic heart failure (HF), which affects 1-2% of population, is an important cause of mortality and disability (1, 2). Despite current medical therapies, the annual mortality rate is 20% (1). The rate of HF is 20% in developed countries. 30-40% of patients with HF die within the first year and 60-70% of these patients die within five years following the diagnosis (2). In the management of these patients, it is quite helpful to be aware of the factors that are associated with mortality and morbidity. Over the past decade, it has been found that anemia plays an increased significant role in the pathophysiology, therapy and prognosis of HF (3). Anemia is frequently noted in congestive HF, and it contributes to worsening of clinical status (4). The presence of anemia, regard-

Address for Correspondence/Yazışma Adresi: Dr. Alev Kılıçgedik, Kocaeli Devlet Hastanesi, Kardiyoloji Kliniği, Kocaeli-*Türkiye*
Phone: +90 505 445 06 58 Fax: +90 216 459 63 21 E-mail: akilicgedik@yahoo.com
Accepted Date/Kabul Tarihi: 29.04.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 04.01.2012

doi:10.5152/akd.2012.011

less of other risk factors including chronic kidney disease (CKD) and diabetes mellitus (DM), is associated with increased mortality, hospitalization and morbidity (4). However, it remains an enigma whether the anemia is a marker of inflammation such as C-reactive protein, phospolipase A2 and high white blood cell count or a mediator of poor prognosis (5).

In this review, we will discuss the role of anemia in HF together with its etiology, pathophysiology, clinical outcome and therapy options.

The definition of anemia

There is no consensus concerning the cut-off value of anemia in HF. According to WHO, hemoglobin cut-off value <13 g/dl for men and <12 g/dl for women; according to National Kidney Foundation, cut-off value <12 g/dl independent of gender, <13.5 g/dl for men and <12 g/dl for women is defined as anemia. Many other researchers define anemia for hemoglobin values <12 g/dl for men and <11 g/dl for women. Although hemoglobin and hematocrit levels correlate well in direct comparisons, criteria defined by hematocrit may identify far more patients with a diagnosis of anemia. A range of cut-off hematocrit value is 35%- 39% (3).

Prevalence of anemia

Though the exact prevalence depends on clinical situations, anemia is common in HF patients. Groenveld et al. (6) found the prevalence of anemia to be 37.2% in a recent meta-analysis of 34 studies between 2001 and 2007 on 150.180 patients with HF. In the light of numerous studies, the prevalence of anemia in HF patients vary from 4% to 61% according to the definition of anemia and the study population (7). One year- incidence of new onset anemia is 9.6% in SOLVD trial, 16.9% in VaL-HeFT, and 14.2% in COMET trial. Due to fluctuating volume in real life, the ratios can be as high as 20% (3).

Etiology of anemia

Causes of anemia in HF patients include nutritional deficiencies (malabsorption, impaired metabolism), acute blood loss (gastrointestinal bleeding), decrease in erythropoietin production and response to erythropoietin due to the intrinsic renal disease, hemodilution because of volume expansion, relative iron deficiency, chronic disease anemia, etc. Advanced age, the presence of DM and renal failure are associated with anemia.

Nutritional deficiencies, iron deficiency

Levels of serum B12 and folic acid are decreased in minority of HF patients. Gastrointestinal functions are abnormal in HF patients, which can cause malabsorbtion. Malnutrition, uremic gastritis, edematous intestinal wall, chronic ASA and anticoagulant usage and abnormal iron mobilization due to the cytokine activation may cause iron deficiency. Despite the lack of standard criteria, the prevalence of iron deficiency varies 5%-21%. Most of the patients have normocytic anemia (8, 9). Microcytic anemia is seen in 6% of these patients (8). Nanas et al. (10) found iron deficiency of iron stores in bone marrow in 73% of HF patients despite the presence of normal serum iron, ferritin and erythropoietin.

Renal failure

Impaired renal function [glomerular filtration rate (GFR)<60 ml/min/1.73 m^2] is associated with a 3-fold higher likelihood of developing anemia. The degree of anemia is directly proportional to the degree of renal dysfunction (3). Although the kidneys take 25% of cardiac output, they use 10% of received oxygen and are prone to hypoxia. In HF, renal blood flow decreases and 50% of HF patients experience renal dysfunction. Decreased production of renal erythropoietin leads to anemia in HF (8, 11, 12). Erythropoietin is a glycoprotein hormone that regulates erythroid cell proliferation in bone marrow response to tissue hypoxia. The synthesis of erythropoietin is triggered by decrease of oxygen tension at the level of peritubular fibroblasts. Lower PO2 activates the hypoxia-inducible factor-1 (HIF-1) that induces transcription of erythropoietin gene (8, 12). Decreased response to erythropoietin is thought in HF patients whose erythropoietin levels are normal or increased. The reasons for diminished response include inflammation, iron deficiency, blood loss, infections, malignancies, secondary hyperparathyroidism, vitamin B12 or folate deficiency, intrinsic bone marrow dysfunction, red cell enzyme defects, hemolysis, some drug interactions (13). Erythropoietin has various pleiotropic effects on several nonerythropoietic cells. Erythropoietin is produced not only in kidneys but also it is produced in several other extrarenal tissues in response to metabolic and oxidative stress or in cases of injuries. Myocardium is one of these tissues that produce specific erythropoietin receptors and response to this hormone. Hypoxic myocardium produces HIF-1 that increases the transcription of erythropoietin (13).

Hemodilution

Androne et al. (14) found that **i**n patients with advanced HF 46% of anemia was due to hemodilution and 54% of anemia was owing to true anemia.

Anemia due to chronic disease and inflammation

In a study, chronic kidney disease, deficiencies of iron, B12 or folate were found in 43% of cases and 57% had anemia of chronic disease (8). Anemia of chronic disease was determined to be the most frequent cause of anemia in HF patients (8). The feature of anemia of chronic disease is that iron is stored in macrophages, thus, limiting its bioavailability (15). Cytokines, including interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α alpha rise in HF patients, thereby they diminish erythropoietin production (8, 12, 16). Furthermore, these factors directly inhibit the differentiation and proliferation of erythroid progenitor cells (8, 12, 17). IL-6 interferes with the intestinal absorption of iron by inhibiting the production of an acute phase protein, hepcidin. IL-6 impedes iron oscillation from body stores by down- regulat-

ing the expression of ferroportin as well. In VEST (Vesnarinone Heart Failure Trial) study, the effects of cytokines explain the anemia in 2% of all anemic patients (18). Patients with NYHA class IV symptoms, cardiac cachexia and decompensated edematous patients have the highest TNF-α levels.

The role of renin-angiotensin-aldosterone system and drug interactions

High levels of angiotensin lower oxygen supply by reducing renal blood flow in HF. Also, a drop seen in GFR induced by angiotensin II raises proximal tubular sodium reabsorption, which increases the need for oxygen. By diminishing the oxygen supply at the level of the cells that produce erythropoietin, these factors increase the production of erythropoietin (8). The drugs including angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and carvedilol used in the treatment of HF also lead to anemia. Inhibiting renin- angiotensin- aldosterone system by using ACEI and ARB is associated with decreased erythropoietin production and diminished hemoglobin levels. The effect of ACE inhibition on hematocrit levels is complex. While diminishing the production of red blood cells, inhibition of ACE also decreases plasma volume. A small but statistically significant decrease in hemoglobin value is monitored. Van der Meer et al. (19) found that a tetrapeptid; N-asetyl-seril-aspartyl-lysyl-proline that inhibits hematopoesis and is a substrate for ACE was higher in anemic HF patients. Serum activity is 73% lower in anemic patients compared with nonanemic HF patients. COMET, COPERNICUS and CHRISTMAS trials showed that carvedilol caused a small but significant drop in hemoglobin levels compared to metoprolol. This is because the cells that produce erythropoietin have extensive sympathetic innervations and erythroid progenitor cells have beta 1, beta 2 and alpha-adrenergic surface receptors. Blocking just beta 2 receptors abolishes both the production of erythropoietin and proliferation of erythroid progenitor cells. While carvedilol blocks beta1, beta 2 and alpha- adrenergic receptors, metoprolol blocks only beta 1 adrenergic receptors and does not cause anemia (20).

Pathophysiology of anemia

In HF, because of being defective, erythropoiesis renders a hemodynamic response. In chronic severe anemia, low hemoglobin levels decrease systemic vascular resistance (SVR) by diminishing blood viscosity and increasing nitric oxide (NO)-dependent vasodilatation (8, 21). Decreased SVR leads to baroreceptor mediated neurohormonal activation and fall in blood pressure. Increased activity of sympathetic and renin angiotensin systems diminish renal blood flow and GFR, resulting in water and salt retention. Thus, both the expansion of extracellular volume and that of plasma volume occur. The symptoms of HF become obvious (8). Anemia raises workload leading to increase in heart rate and stroke volume. In response to increased work load, the heart undergoes 'remodeling' by developing left ventricular hypertrophy (LVH) and dilation (6). The presence of anemia is associated with severe signs and symptoms of HF (3). Whether the same effects are seen in less severe anemia remains unclear. In the presence of anemia, the increase of E/E', thus the increase of left ventricular (LV) filling pressures is observed. E/E' is negatively correlated with hemoglobin levels (22). Even if left ventricular hypertrophy (LVH) and renal failure is absent, anemia is strongly associated with diastolic dysfunction. In RENAISSANCE trial, low hemoglobin levels are found to be associated with more severe disease, increased left ventricular mass index, rehospitalization and mortality (23). Tigen et al. (24) found that anemia and left atrial enlargement in patients with nonischemic dilated cardiomyopathy with normal kidney function is an independent predictor of moderate and severe mitral regurgitation.

The diagnosis of anemia

Anemia is evaluated with standard laboratory tests, including iron saturation, ferritin, folate, vitamin B12, reticulocyte count, fecal occult blood, the levels of erythropoietin and soluble transferrin receptors. When inflammation occurs, ferritin may be found falsely high as it is an acute phase protein. With a simple test, oral iron absorption test we can differentiate iron deficiency anemia from the anemia of chronic disease. The concentration of serum ferritin <100 ng/ml and transferrin saturation <20% may identify iron deficiency anemia (25). Weiss and Goudnough reported that transferrin saturation <16% and ferritin levels <30 ng/ml in the presence of inflammation and anemia may diagnose iron deficiency anemia. Moreover, ferritin >100 ng/ml may diagnose the anemia of chronic disease (15). Assessment of iron contents in bone marrow is gold standard for evaluating iron stores but it is an invasive method and not practical in routine practice.

Anemia and outcomes

The presence of anemia in HF regardless of other risk factors, including renal failure and DM, is associated with increased mortality, hospitalization and morbidity (4, 26). In many comprehensive randomized clinical studies, anemia is reported to be an independent predictor of mortality (20, 27-29) anemia is also an independent predictor of survival in patients who have diastolic HF (30). OPTIME-CHF trial showed that every 1 g/dl fall in hemoglobin level is an independent risk factor for death and re-hospitalization (31). Anemia is associated with worsening structural heart disease, diastolic dysfunction, LVH, increased left ventricular mass index and higher pulmonary pressures (13). The relationship between anemia and mortality and morbidity is not the effect of anemia per se. Moreover, anemia is associated with intensive co-morbidity burden as a marker of severe disease. In STAMINA-HF trial, impaired renal function, advanced age, female gender, African Americans, the presence of DM, edema and decreased diastolic blood pressure were shown to be independent predictors of low hemoglobin concentrations (32).

Tang et al. (33) found that anemic HF patients were older, and suffered from DM, received more intensive therapy for HF, had higher mortality, more severe diastolic HF, increased brain natriuretic peptide (BNP) levels and blood urea nitrogen values. Permanent anemia is frequent in patients who had LV ejection fraction (LVEF) > 30%, BNP > 325 pg/ml, eGFR< 60 ml/min/1.73 m^2 and who had DM. In a Spanish study of 99 patients with HF and anemia who needed hospitalization, only anemia was shown as a marker of poor prognosis. The higher incidence of anemia was found in patients needing hospitalization than the outpatients, and anemia was thought to be a marker of more severe disease (25). Kosiborod et al. (34) in National Heart Project trial investigated the association between anemia and outcome in 50.405 patients with HF. They found an increase in unadjusted mortality risk in two groups whose hematocrit values were the lowest. The risk plunged to non-significant levels after non-cardiac morbidities controlled for. In the next highest hematocrit values they also found a significantly increased unadjusted mortality risk. After non-cardiac morbidities (other cardiovascular conditions, the severity of HF, basal laboratory values, vital signs and drugs) were controlled by these values the risk seemed to decrease but was still significant. According to Kosiborod, the relationship between anemia and mortality can be explained by the presence of co-morbid conditions, including renal failure, cerebrovascular disease, pulmonary dysfunction, DM and other co morbid conditions. On the other hand, low hematocrit value is associated with significant increase in one year- hospitalization risk. Thus, the effect of anemia on mortality is thought that anemia is a marker however; the effect of anemia on re-hospitalization, on quality of life, and on functional capacity is thought to be anemia's direct effect (31, 34). The lower the hemoglobin values the higher the mortality (25). The longitudinal measurements of anemia are more important prognostic factors than basal measurements (35, 36). The risk is higher in permanently low and decreasing hemoglobin levels (35). The patients with anemia at the time of diagnosis have poor prognosis than those without anemia and the patients with permanent anemia have poorest prognosis (33).

Therapy options

In the past, anemia was cured only when hemoglobin values were <9 g/dl. However, it has recently been known that every degree of anemia worsens the prognosis of HF. Anemia can be a reason for HF but it is also a consequence of HF (25). There are three ways of therapy: emergent therapy, iron replacement therapy and erythrocytosis stimulant agent (ESA). Blood transfusion is an acute therapy choice for severe anemia. American College of Physicians and American Society of Anesthesiology suggest blood transfusion when hemoglobin values are 6-8 g/dl (36). There are still no target hemoglobin values that require reaching. Silverberg et al.(4) reported that hemoglobin value 12 g/dl is a safe target value to reach.

Iron replacement therapy

Exact and relative iron deficiency is common in HF. This may require iron replacement therapy for the first choice therapy method in patients with HF (37). All major proteins in skeleton muscle that are responsible for oxygen transfer and transport contain iron (15). This can explain the improvement in exercise capacity by iron replacement therapy. Iron is an important element for the enzymatic system of cardiac myocytes and it is stored in these cells. Iron is necessary for collagen production. The collagen content is decreased in myocardium of animals with iron deficiency (13). Experimental studies showed that iron deficiency was associated with diastolic HF, LVH, and dilation, fibrosis and cellular dysfunction. Silverberg et al.(37) reported that thrombocytosis that is increased by iron deficiency might lead to thrombosis, atherosclerosis and increased mortality. Iron deficiency can be an important condition in HF patients even if there is no anemia. Bolger et al. (38) showed that IV iron replacement therapy is safe and effective, increases hemoglobin values and improve exercise capacity. Thirty-five patients were included in FERRIC HF study in iron-treated group, significant improvement was noted in NYHA functional class in patient global assessment, and in fatigue scores (39). FAIR HF study demonstrated that IV ferric carboxymaltose improved patient's global assessment, NYHA functional class, and 6-minute walking distance (40). IRON HF is an ongoing and randomized clinical trial investigating the effect of IV iron replacement on 3-month maximal exercise capacity (41). Concerns about iron replacement therapy include anaphylactic reactions, oxidative stress and free radicals (42).

Using ESA

There are three ESA agent used: epoetin alpha, epoetin beta and darbopoetin. After the studies by Silverberg et al. (43-46) showed efficacy of using ESA in patients with HF many studies have been designed with ESA. In a recent meta-analysis, it was observed that the hospitalization risk was lower in patients using ESA but there was no mortality differences (42). Attention was drawn by TREAT study that darbopoetin usage was associated with increased risk of stroke in patients who had chronic kidney disease, DM and anemia (47). ESA resistance is a common problem and because of the potential adverse effects arising from higher dosages of ESA, the reasons for the resistance such as iron deficiency should be sought. In the presence of iron deficiency, the use of ESA may lead to thrombosis by causing trombocytosis (42). Iron replacement therapy in conjunction with ESA usage may reduce the ESA dose and the potential risk for side effects, and may provide a more rapid recovery from anemia. Silverberg et al. (48) showed that using iron replacement therapy in conjunction with ESA, there were a marked increase in hemoglobin values, a prominent improvement in NYHA class, LVEF and a striking decrease in the rate of hospitalization. It was also found that in hemodialysis patients with correction of anemia by using ESA, there was both a decrease in LV end-diastolic diameter and a reduction in the development of LVH.

In many studies, the use of ESA, irrespective of Hg values, was shown to decrease experimental infarct size, reduce hypoxic injury, prevent myocyte apoptosis, and mobilize endothelial progenitor cells (21, 49). In animal models, the use of epoetin, independent of hematocrit levels, was shown to decreases myocardial infarction size caused by ischemia and the same effects were also observed in patients with stroke (50). Recent findings showed that in oncology patients, the use of ESA decreased survival and increased growth of tumor and thromboembolic events (51). Some effects of erythropoietin are driven by endothelial NO synthase transcription and increasing NO bioavailability (13). The multicenter, double-blind placebo-controlled RED HF trial comprising 2600 patients is an ongoing study to investigate the relationship between darbopoetin alpha and the mortality and morbidity of patients with HF and anemia (52).

Conclusion

Anemia is the clinical condition, which is rather frequently seen in patients with HF that disrupts the quality of life and functional capacity increasing re-hospitalization and is associated with increased mortality and morbidity. However, the question as to whether anemia itself is responsible for all these adverse effects or is a marker for more severe disease and co morbidity remains to be answered. If anemia is a marker, treatment may not obviate the increased risk associated with anemia, but if it is a mediator, knowing the factors that cause anemia and treatment may be helpful to reduce morbidity and mortality in HF. The measurement and follow-up of Hg levels in patients with HF and evaluation of treatment options and risk stratification of patients are necessary for the detection of curable conditions such as iron deficiency. Further randomized clinical studies are required to specify the necessity for correcting anemia and for determining the therapy option to be selected for correction of anemia in these patients.

Conflict of interest: None declared.

References

1. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006; 27: 65-75. [CrosRef]
2. Velavan P, Khan NK, Goode K, Rigby AS, Loh PH, Komajda M, et al. Predictors of short term mortality in heart failure - insights from the Euro Heart Failure survey. Int J Cardiol 2010; 138: 63-9. [CrosRef]
3. Tang WH, Yeo PS. Epidemiology of anemia in heart failure. Heart Fail Clin 2010; 6: 271-8. [CrosRef]
4. Silverberg DS, Wexler D, Iaina A, Schwartz D. The role of correction of anaemia in patients with congestive heart failure: a short review. Eur J Heart Fail 2008; 10: 819-23. [CrosRef]
5. Levy WC. Anemia in heart failure: marker or mediator of adverse prognosis? J Am Coll Cardiol 2008; 51: 577-8. [CrosRef]
6. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 2008; 52: 818-27. [CrosRef]
7. Sandhu A, Soman S, Hudson M, Besarab A. Managing anemia in patients with chronic heart failure: what do we know? Vasc Health Risk Manag 2010; 6: 237-52.
8. Anand IS. Pathophysiology of anemia in heart failure. Heart Fail Clin 2010; 6: 279-88. [CrosRef]
9. de Silva R, Rigby AS, Witte KK, Nikitin NP, Tin L, Goode K, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol 2006; 98: 391-8. [CrosRef]
10. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006; 48: 2485-9. [CrosRef]
11. Ng Kam Chuen MJ, MacFadyen RJ. Variable aetiologies contributing to the anaemia of systolic heart failure are important to individual patient management. Eur Heart J 2007; 28: 143-5. [CrosRef]
12. Le Jemtel TH, Arain S. Mediators of anemia in chronic heart failure. Heart Fail Clin 2010; 6: 289-93. [CrosRef]
13. Jankowska EA, Ponikowski P. Molecular changes in myocardium in the course of anemia or iron deficiency. Heart Fail Clin 2010; 6: 295-304. [CrosRef]
14. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003; 107: 226-9. [CrosRef]
15. Jelani QU, Attanasio P, Katz SD, Anker SD. Treatment with iron of patients with heart failure with and without anemia. Heart Fail Clin 2010; 6: 305-12. [CrosRef]
16. Drakos SG, Anastasiou-Nana MI, Malliaras KG, Nanas JN. Anemia in chronic heart failure. Congest Heart Fail 2009; 15: 87-92. [CrosRef]
17. Reis FJ, Fernandes AM, Bitencourt AG, Neves FB, Kuwano AY, França VH, et al. Prevalence of anemia and renal insufficiency in non-hospitalized patients with heart failure. Arq Bras Cardiol 2009; 93: 268-74. [CrosRef]
18. Anand IS, Rector T, Deswal A, Iversan E, Anderson S, Mann D, et al. Relationship between proinfammatory cytokines and anemia in heart failure. Eur Heart J 2006;27 (suppl 1): 485.
19. Van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, et al. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation 2005;112:1743-7. [CrosRef]
20. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J 2006; 27: 1440-6. [CrosRef]
21. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol 2008; 52: 501-11. [CrosRef]
22. Kim YR, Pyun WB, Shin GJ. Relation of anemia to echocardiographically estimated left ventricular filling pressure in hypertensive patients over 50 year-old. J Cardiovasc Ultrasound 2010; 18: 86-90. [CrosRef]
23. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004; 110: 149-54. [CrosRef]
24. Tigen K, Karaahmet T, Kırma C, Kılıçgedik A, Dündar C, Pala S, et al. The association of functional mitral regurgitation and anemia in patients with non-ischemic dilated cardiomyopathy. Cardiol J 2010; 17: 274-80.
25. Cardoso J, Brito MI, Ochiai ME, Novaes M, Berganin F, Thicon T, et al. Anemia in patients with advanced heart failure. Arq Bras Cardiol 2010; 95: 524-8. [CrosRef]

26. Setoguchi S, Stevenson LW. Hospitalizations in patients with heart failure: who and why. J Am Coll Cardiol 2009; 54: 1703-5.
27. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 2005; 112: 1121-7.
28. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol 2003; 41: 1933-9.
29. Dunlay SM, Weston SA, Redfield MM, Killian JM, Roger VL. Anemia and heart failure: a community study. Am J Med 2008; 121: 726-32.
30. Tehrani F, Phan A, Morrissey R, Chien C, Rafique A, Schwarz ER. The prognostic value of anemia in patients with diastolic heart failure. Tex Heart Inst J 2009; 36: 220-5.
31. Salisbury AC, Kosiborod M. Outcomes associated with anemia in patients with heart failure. Heart Fail Clin 2010; 6: 359-72.
32. Adams KF Jr, Patterson JH, Oren RM, Mehra MR, O'Connor CM, Piña IL, et al. Prospective assessment of the occurrence of anemia in patients with heart failure: results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. Am Heart J 2009; 157: 926-32.
33. Tang WH, Tong W, Jain A, Francis GS, Harris CM, Young JB. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. J Am Coll Cardiol 2008; 51: 569-76.
34. Kosiborod M, Curtis JP, Wang Y, Smith GL, Masoudi FA, Foody JM, et al. Anemia and outcomes in patients with heart failure: a study from the National Heart Care Project. Arch Intern Med 2005; 165: 2237-44.
35. Peterson PN, Magid DJ, Lyons EE, Clarke CL, Zeng C, Fitzgerald A, et al. Association of longitudinal measures of hemoglobin and outcomes after hospitalization for heart failure. Am Heart J 2010; 159: 81-9.
36. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation 2006; 113: 2454-61.
37. Kaldara-Papatheodorou EE, Terrovitis JV, Nanas JN. Anemia in heart failure: should we supplement iron in patients with chronic heart failure? Pol Arch Med Wewn 2010; 120: 354-60.
38. Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol 2006; 48: 1225-7.
39. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008; 51: 103-12.
40. Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Rationale and design of Ferinject assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail 2009; 11: 1084-91.
41. Beck-da-Silva L, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, et al. Rationale and design of the IRON-HF study: a randomized trial to assess the effects of iron supplementation in heart failure patients with anemia. J Card Fail 2007; 13: 14-7.
42. Agarwal AK, Katz SD. Future directions in management of anemia in heart failure. Heart Fail Clin 2010; 6: 385-95.
43. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000; 35: 1737-44.
44. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001; 37: 1775-80.
45. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355: 2085-98.
46. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355: 2071-84.
47. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019-32.
48. Silverberg DS, Wexler D, Blum M, Iaina A, Sheps D, Keren G, et al. Effects of treatment with epoetin beta on outcomes in patients with anaemia and chronic heart failure. Kidney Blood Press Res 2005; 28: 41-7.
49. Francis GS, Kanderian A. Anemia and heart failure a new pathway? J Am Coll Cardiol 2007; 50: 1666-7.
50. Akram K, Pearlman BL. Congestive heart failure-related anemia and a role for erythropoietin. Int J Cardiol 2007; 117: 296-305.
51. Murphy NF, McDonald K. Treatment of anaemia in chronic heart failure-optimal approach still unclear. Eur Heart J 2007; 28: 2185-7.
52. McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, et al. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail 2009; 11: 795-801.