Anemia and heart failure: a cause of progression or only a consequence?

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ABSTRACT: Anemia is one of the most frequent co-morbidities in the patients with heart failure. Its prevalence increases from 4-7% in the subjects with asymptomatic left ventricular dysfunction to >30% in the patients with severe heart failure. Renal insufficiency, activation of inflammatory mediators, and treatment with renin-angiotensin antagonists seem to be its main determinants. The results of many studies agree in showing that anemia is a powerful independent determinant of survival in patients with heart failure. However, the mechanisms of this relation are still incompletely understood. Moreover a favourable effect on prognosis of the correction of anemia has not been shown, yet, and also controlled studies assessing its effects on exercise tolerance have yielded controversial results. (Heart International 2007; 3: 1-11)

KEY WORDS: Anemia, Heart failure, Prognosis, Erythropoietin

INTRODUCTION

The introduction of renin-angiotensin-aldosterone antagonists, beta-blockers and cardiac resynchronization therapy has improved the prognosis of heart failure (HF). The improvement in the treatment of HF has been, however, attended by an increase of the importance of comorbidities as major determinants of prognosis of this syndrome. Among them, anemia is surely one of the most important.

EPIDEMIOLOGY AND DEFINITIONS

The prevalence of anemia in patients with HF ranges from 7%-10% to 70%-80% depending on differences in HF severity, demographic variables and comorbidities of the patients studied (1-3).

Definitions

There is not an universally recognized definition of anemia. The World Health Organization (WHO) defines anemia as a decrease in hemoglobin(Hb) values below 13 gm/dl in men and 12 gm/dl in women (2). The National Kidney Foundation defines anemia as Hb values <13.5 gm/dl in adult men and <12 gm/dl in adult women (values based on the average of the lower quintile of the standard population ) (4).

In a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD), Al-Ahmad et al have shown that the prevalence of anemia could change from 22% to 4% according to differences in the hematocrit threshold value (<0.39%, corresponding to serum hemoglobin of 13 gm/dl and <0.35%, corresponding to12 gm/dl, respectively) (5).

Predisposing factors

The prevalence of anemia increases with HF severity (5). Other parameters related to HF severity, such as left ventricular (LV) ejection fraction, blood pressure, BNP or NT-proBNP plasma concentrations, are associated to the prevalence of anemia (1-3, 6, 7, 10). Left ventricular ejection fraction (LVEF) has an inverse relationship with serum Hb levels and this relation is maintained also...
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when patients with preserved left ventricular systolic function are included (7).

The prevalence of anemia also depends on the patients' demographic characteristics, since it is more frequent in the elderly, female and black patients (8, 9). Co-morbidities, namely renal failure and diabetes, are frequently and independently related to anemia (1-3, 6, 7, 10).

Recent onset anemia

New onset anemia frequently develops during the clinical course of HF. The Carvedilol or Metoprolol European Trial (COMET) enrolled 3029 patients who were followed for 58 months. In this trial the incidence of recent onset anemia was of 14% at 1 year and 27.5% at 5 years. At multivariate analysis the predictive factors of recent onset anemia were age, high furosemide dose, increase of serum creatinine, hyponatremia, hyperkalemia, and lack of aldosterone-antagonist administration (6). Another study had shown different predictive factors: low serum albumin, glomerular filtration rate, body weight, diastolic arterial pressure, an increase in furosemide dose, C-reactive protein, BNP levels and LVEF. These studies also showed that carvedilol (6) and valsartan (10) therapy, respectively, can be independent predictors of new onset anemia.

MECHANISMS

The pathogenesis of anemia in patients with HF is multifactorial (Tab. I).

Hemodilution

Anemia is correlated to HF severity. Patients with HF often show signs of congestion. Water retention and increase in plasma volume can cause a "pseudo-anemia" due to hemodilution (11). Ritz et al showed that in 97 patients with HF the reduction of glomerular filtration, erythropoietin levels and expanded plasma volume were independent predictive factors of low Hb levels. Some studies, conducted using the radiolabeled albumin technique, have demonstrated that up to 46% of patients with HF and anemia have hemodilution along with a normal red blood cells number (12). Although a lower incidence of hemodilution has been reported in other studies, this mechanism should be excluded in anemic patients with HF (13). In these patients treatment should be diuretic therapy, while erythropoietin administration could further increase total blood volume with possible adverse clinical consequences (2).

There is a relevant percentage of anemic patients with HF but without hemodilution. In these patients, the cause is likely iron deficiency, chronic kidney disease, cachexia and angiotensin converting enzyme (ACE) inhibitors therapy.

Iron deficiency

The prevalence of iron deficiency in patients with HF is variable from 30% to 73% (13).

The higher percentage has been found in a study in which iron deficiency was measured also in the bone marrow. The inflammatory response in patients with HF leads to the reduction of iron absorption and anticoagulant and/or antiaggregant therapy could cause gastrointestinal bleeding. On the other hand, the iron resources in anemic patients with HF could be normal or high because of increased iron uptake and storage in macrophages (reticuloendothelial system) with a consequent reduction of its availability for hematopoiesis (14, 15). Intravenous iron therapy has been shown to increase serum Hb levels (from 11.2±0.7 to 12.6±1.2 g/dl, p=0.0007) as well as to improve exercise tolerance, quality of life and functional class (16). B12 and folate deficiency has not a significant role in pathogenesis of anemia in patients with HF (17).

| TABLE I - MAIN FACTORS RELATED TO ANEMIA IN PATIENTS WITH HEART FAILURE |
|-----------------------------------------------|
| Demographic factors (age, gender, race)      |
| Water and salt retention                     |
| Iron deficiency                              |
| Renal failure                                |
| Chronic inflammatory activation              |
| Concomitant treatment                        |
| - Angiotensin Converting Enzyme Inhibitors   |
| - Angiotensin receptor blockers              |
| - Non selective beta-blockers (carvedilol)  |
Renal failure

Moderate to severe chronic renal failure (glomerular filtration rate <60 ml/min) is one of the main determinants of anemia (1, 2, 5, 17, 18). In 30%-40% of patients with HF an inverse correlation between serum creatinine and plasmatic Hb has been reported. Chronic kidney disease causes anemia through a reduction in erythropoietin production, although patients with HF can show increased levels of erythropoietin (18-20). The main cause of anemia in HF, similarly to other chronic diseases associated to inflammatory processes, is resistance to erythropoietin effects rather than its reduced production (14).

Cytokines

Reduced body mass and cardiac cachexia have been shown to be important predictive factors for anemia in patients with HF (2, 6, 7). The activation of pro-inflammatory cytokines (TNF-α, interleukine-6, interleukine-10, interferon-γ, lipopolysaccharides) is important for both anemia and cardiac cachexia pathogenesis. Pro-inflammatory cytokines could have many effects: stimulation of erythropoietin, inhibition of gut iron absorption, inhibition of the proliferation of progenitor red cells, increased apoptosis, red cells damage, increased erythrophagocitosis, increased uptakes and storage of iron into macrophages, resistance to erythropoietin. All these effects may ultimately lead to reduced erythropoiesis (Fig. 1, Tab. II) (21). Chronic inflammation causes reduced iron availability, that is stored by macrophages of the reticuloendothelial system (22, 23).

Concomitant therapy

Neuro-hormonal antagonist and, namely, ACE-inhibitors and angiotensin II receptors blockers are important causes of anemia in patients with HF. An analysis of the SOLVD study has shown that enalapril is an independent predictive factor for low Hb levels (23). The Valsartan Heart Failure (VAlHeFT) trial has confirmed these data for angiotensin II receptors blockers (10). Angiotensin II increases erythropoietin secretion through hypoperfusion and renal hypoxia and, thus, can directly stimulate erythropoiesis (24). Antagonists of renin-angiotensin system, blocking the effects of angiotensin II, also reduce erythropoiesis. Moreover, ACE catalyzes the demolition of N-Acetil-seril-lisil-proline (Ac-SKPD), a tetra peptide inhibitor of the proliferation of haematopoietic stem cells. ACE inhibitor administration causes an increase in the plasmatic concentrations of this substance with a consequent development of anemia (25).
Differences between beta-blockers may also be important. An analysis of the Carvedilol or Metoprolol European Trial (COMET) has shown that carvedilol therapy is associated with a slight but significant Hb decrease (0.2 g/dl) compared to metoprolol therapy (6). Renal cells secreting erythropoietin or progenitor red cells have sympathetic innervation with beta-1, beta-2, and alpha adrenergic receptors (26). Beta-2 receptors have the most important role and carvedilol could cause a decrease in Hb levels through its non selective action on beta-2 adrenergic receptors.

**ANEMIA AND CLINICAL OUTCOMES**

Many retrospective analyses of clinical trials have shown that reduced Hb levels are independently associated with an increased risk of hospitalisation and mortality in patients with HF (1-3, 5-10, 12, 27-30). A recent re-analysis of SOLVD trial shows that anemia is also an independent risk factor related to new onset kidney disease (31). Some studies have demonstrated that anamia was an independent predictor for HF mortality but not for sudden cardiac death (6, 9). Anemia is associated with poor outcome not only in patients with LV systolic dysfunction, but also in patients with asymptomatic LV dysfunction (5, 32) or with preserved LVEF (7, 30).

There is a linear relationship between reduced Hb serum levels and increased mortality risk: a 1-mg/dl decrease Hb levels has been associated to an increase in mortality of 13% (relative risk [RR], 1.13; 95% confidence interval [95% IC], 1.045-1.224) (2). Low Hb levels are related to severe prognosis but it is yet unclear the effect of an increased Hb serum level. There is usually a linear relationship between high Hb levels and reduced mortality and morbidity risk. However, Sharma et al in the “Evaluation of Losartan in the Elderly II” (ELITE II) trial showed a U-shaped relation between Hb concentration and mortality risk. A minimum mortality risk was shown for physiological serum values (13 e 15 g/dl) while a major mortality rate was demonstrated for serum values >15 g/dl (28). Go et al in 59772 patients with HF (3) showed an increased mortality risk with Hb levels >17 g/dl (Fig. 2). However, other comorbidities (such as chronic obstructive pulmonary disease, COPD) could have influenced the outcome, especially in the elderly patients.

Changes in Hb levels during the clinical course of HF could influence the prognosis. Results from COMET trial have shown that patients with a 2-3 g/dl decrease in serum Hb have an increased mortality risk of 47% (RR, 1.466; IC95%, 1.092-1.969; p=0.0109), while a Hb reduction >3 g/dl was associated to a three fold greater mortality rate (RR, 3.37; IC95%, 2.464-4.611; p<0.0001) (6).
Mechanisms (Tab. III)

Myocardial Hypertrophy. Anemia is strictly related to cardiac hypertrophy (33, 34). These evidences have been confirmed in an analysis of “The Randomized Etanecort North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) Trial” (31). In 66 patients the Hb values were related to the LV myocardial mass assessed by magnetic resonance imaging (MRI) after six-months follow-up. LV myocardial index (LVMI) increased by +1.6±7.9 g/m² in patients with stable or decreased Hb values while it decreased by -7.5±12.1 g/m² in patients with increased serum Hb level (p=0.0008). An inverse correlation was observed between changes in Hb levels and LVMI changes (r=0.32, P=0.0086) (31). However, other clinical trials did not find any relationship between changes in serum Hb values and LV myocardial mass and no favourable effect of increased Hb levels on cardiac structure and function have been shown, to date (35-39).

Oxygen uptake in peripheral tissues. The decreased availability of oxygen substrates to the peripheral tissues represents another untoward effect of anemia. In patients with anemia and HF the reduced cardiac output can not compensate the reduced Hb levels and this could explain the more severe symptoms of anaemic patients, with a more severe impairment in exercise capacity and a greater risk of rehospitalisation (8). A positive correlation has been shown between peak VO₂ and serum Hb values (40, 41). The administration of erythropoiesis stimulating agents (ESA) has been related to an improvement in exercise capacity either in patients with renal failure (42) or in patients with HF (16, 43, 44).

The reduced peripheral oxygen demand can lead to an increased cardiac work with a consequent myocardial ischaemia and LV remodelling increasing mortality and cardiovascular hospitalisation (2, 3).

Other Mechanisms. Anemia causes neurohormonal activation, oxidative stress and reduced nitric oxide production (30). It may also cause salt and water retention and peripheral edema with consequent poor prognosis in patients with HF (2).

Anemia can also be considered a consequence of HF severity. Its exact role in HF must, however, be shown by controlled trials showing an improvement in survival with anemia correction.

| TABLE III - NEGATIVE EFFECTS OF ANEMIA ON OUTCOME IN PATIENTS WITH HEART FAILURE |
|---------------------------------------------------------------|
| Myocardial hypertrophy |
| Reduced oxygen uptake in peripheral tissues |
| - Increased cardiac output |
| Neuro-hormonal activation |
| Worsening renal failure |
| Edema and fluid retention induction |

TREATMENT APPROACHES

Hemotransfusion. According to the American Guidelines, blood transfusion is recommended for Hb levels in the range from 6 to 8 g/dl. The clinical utility of hemotransfusion for higher Hb levels is still unsettled. Generally, hemotransfusion is not considered for Hb values >10 g/dl (45).

In 78, 974 elderly patients hospitalised with acute myocardial infarction, blood transfusion was associated with a lower mortality rate at 30 days in patients with an hematocrit <30% on admission (46). Conversely, in 838 patients (26% with cardiovascular disease), stable Hb levels between 10-12 g/dl did not provide additional
benefits on mortality compared with Hb concentration of 7-9 g/dl (47).

Moreover, the blood transfusion may be associated with some adverse effects such as immunosuppression, increased infection risk, iron overload and the sensitization to HLA antigens (48). Transfusion may be considered only an acute phase treatment for severe anemia and it is not available as a long-term therapeutic strategy.

Iron therapy. It is commonly accepted that patients with chronic HF have relative iron deficiency (2, 22). Total body iron content may be normal. However, HF, like other chronic inflammatory diseases, is associated to increased uptake and storage of iron within the reticulo-endothelial system (11, 14). Thus, less iron is available for erythropoiesis despite possibly increased total body iron stores (so called “reticulo-endothelial block”).

Several small studies have demonstrated that iron therapy may cause a slight but significant increase in serum Hb levels and improve symptoms and exercise tolerance (16, 49). The IRON-HF study is an ongoing trial designed to assess the clinical impact of iron supplementation (intravenous or oral administration), compared to placebo, in patients with HF and low serum iron and transferrin concentrations (50).

Iron therapy is also used in association with ESA. Current guidelines from the National Kidney Foundation recommend the use of intravenous iron (because of the reduced enteric absorption) to maintain serum ferritin levels of 100 to 800 ng/ml and a transferrin saturation of 20% to 50% in order to optimize the response to ESA (4).

It must be, however, pointed out that high doses iron therapy has severe side effects such as an increased oxydative stress with endothelial dysfunction and atherosclerosis progression (51).

**Erythropoiesis stimulating agents (ESA)**

An increased level of serum erythropoietin can occur in patients with HF and is correlated to a more severe outcome (18, 19). However, erythropoietin levels of HF patients with anemia are lower, compared to patients with similar Hb levels without HF. In addition, HF, like other chronic inflammatory diseases, is associated to peripheral resistance to erythropoietin actions (11, 22, 53). This is mainly caused by the neurohormonal and inflammatory activation. ACE inhibitor therapy may also play a role (23, 24). These observations suggest an important role for therapy with ESA, associated with iron supplementation, in patients with anemia and HF.

**Available agents.** There are three currently available ESA for the treatment of anemia: epoetin-α, epoetin-β (both of which are recombinant human erythropoietins, rHuEpo) and darbepoetin-α (analog of human erythropoietin). These agents can be administered either intravenously or subcutaneously. Plasma half-life of epoetin-α and epoetin-β after intravenous dosing is 6 to 8 hours. After subcutaneous administration, the plasma half-life is increased to more of 24 hours. Thus, epoetin-α and epoetin-β should be administered subcutaneously once to three times a week. Darbepoetin-α has a stronger affinity for erythropoietin receptors with a longer plasma half-life (approximately 48 hours), and, hence, longer dosing intervals (1 to 2 weeks) may be used during maintenance therapy (2, 4).

**Clinical efficacy.** The effect of rHuEpo treatment in anaemic patients with HF was first reported by Silveberg et al in 2000 (52). Twenty-six anemic patients with advanced HF and serum Hb <12 g/dl were treated with subcutaneous rHuEpo and intravenous iron sucrose. After 6-7 months of treatment with rHuEpo, mean Hb levels increased from 10.2 g/dl to 12.1 g/dl, with an improvement in New York Heart Association (NYHA) functional class, LVEF (from 28±5% to 35±8%, p<0.001), decreased needs for intravenous furosemide and a decreased hospitalisation rate (54). The same investigators reported a significant reduction in hospitalisations and days of hospitalisation in another randomised open label trial in 32 patients (53).

Mancini et al conducted a single-blind, randomised, placebo-controlled trial of rHuEpo therapy in 26 patients with advanced HF and anemia (hematocrit <35%) (43). Patients received 5000 Units of subcutaneous rHuEpo three times per week and supplemental oral iron and folate, adjusted to raise hematocrit to >45%. Compared with the placebo group, rHuEpo therapy was associated with significant increase in Hb values from 11.0±0.5 to 14.3±1.0 g/dl, with a concomitant increase in treadmill exercise duration and peak oxygen uptake (11.0±1.8 to 12.7±2.8 ml/min per kilogram, p<0.05). Increases in serum Hb levels were linearly related to peak oxygen uptake changes.

Another more recent study conducted in Italy confirmed the clinical benefits of rHuEpo therapy. Forty patients with severe HF were randomised to receive, in a
double blind fashion, either subcutaneous rHuEpo for three months twice a week, or placebo (saline solution). The treated group showed a significant increase in Hb values (from 10.4±0.6 to 12.4±0.8 g/dl, p<0.01), an improvement in NYHA functional class (from 3.5±0.6 to 2.8±0.5, p<0.05), and an increase in peak oxygen consumption (from 12.8±2.8 to 15.1±2.8 ml/Kg per minute, p<0.05). There was also a fall in plasma BNP levels, a reduction in serum creatinine and an increase in estimated creatinine clearance (54).

Studies with Darbepoetin-α. In a randomized, placebo-controlled trial in 41 patients with HF and anemia, darbepoetin-α administration, once every 2 weeks for 26 weeks, was associated with an increase in serum Hb values from 11.8±0.2 to 13.9±0.4 g/dl (versus 11.6±0.2 to 12.3±0.4 g/dl in the placebo group). Darbepoetin-α administration was also associated to an improvement in quality of life, evaluated by the patients’ Global Assessment score. However, the Kansas City Cardiomyopathy and the Minnesota Living with Heart Failure scores, exercise duration and peak VO2 did not show any significant change compared to placebo. Peak VO2 increased by 0.5 ml/Kg/min in the darbepoetin-α group, versus +0.1 ml/Kg/min in the placebo group (p=0.40). No significant correlation between Hb concentrations and exercise tolerance was shown (44).

Although the results of this trial may have been caused by chance, they may also suggest that a more rigorous approach, with double-blind placebo control, allowed a more accurate assessment of the real effects of therapy with ESA on quality of life and exercise tolerance, compared to previous studies (43). It might also be that the number of patients studied was insufficient to reach statistical significance. In the MIRACLE trial (Multicenter InSync Randomized Clinical Evaluation) enrollment of 369 patients was necessary to show a significant improvement in exercise tolerance with CRT versus control (55).

A recent combined analysis of two randomised double-blind, placebo-controlled trials comparing darbepoetin-α versus placebo in 475 patients did not show any improvement in NYHA class and Quality of Life with darbepoetin-α. This study also showed a trend to a decrease in the risk of composite outcome (death or HF hospitalization) and mortality in the darbepoetin-α group versus placebo group (39/266, 15% vs 46/209, 22%; HR 0.67, 95% CI 0.44-1.03, p=0.06) with also a tendency to a lower mortality in the darbepoetin-α group (6% vs 9%; HR, 0.76) (49, 56).

A large-scale, mortality trial on 3400 patients with anemia and HF (Reduction of Events with Darbepoeitin-α in Heart Failure, RED-HF) is ongoing and will likely definitively show the effects of darbepoetin-α on outcome in these patients (56).

Optimal target level of Hb. In November 2006, two large-scale, controlled studies with ESA in patients with chronic kidney disease (CKD) were published (Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR] and Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin beta [CREATE]) (57, 58). Both these studies were prematurely stopped because of a tendency to a worse outcome in the ESA treated patients (59, 60). In CHOIR, 1432 patients with anemia and renal insufficiency (23% patients with a history of HF), were treated with two different erythropoietin regimes to reach Hb target levels of 13.5 g/dl or 11.3 g/dl. During a median follow-up of 16 months, the higher Hb target group had an increase in the composite endpoint of death, myocardial infarction, HF hospitalisation and stroke (HR, 1.34; p=0.03). There was also a tendency to an increased risk of the composite endpoint of death or nonfatal myocardial infarction in the group assigned to a higher hematocrit (HR, 1.3; 95% CI 0.9-1.9) (61).

Differently, in CREATE study (57) (603 patients with anemia and renal failure, 33% with HF), there was not an increase in cardiovascular events in the patients assigned to reach the target Hb levels after epoietin-β treatment (13.0-15.0 gm/dl). However, the number of patients requiring haemodialysis and with high blood pressure values was greater in the group assigned to higher target Hb values (13 vs 23). Similar results were obtained in another study in diabetic patients (38, 58). A tendency to an increase in the risk of death was shown by preliminary results of two studies in patients with cancer and anemia.

On the basis of these results, on 9 march 2007, the Food and Drug Administration (FDA) recommended to avoid the achievement of Hb levels >12 g/dl and to stop erythropoietin therapy when these are > 12 g/dl. The administration of low doses of ESA are still recommended with Hb values < 10 g/dl (60). The National Kidney Foundation recommends to achieve a serum Hb value of 11-12 g/dl (4, 60).
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Adverse effects of ESA administration. The increased cardiovascular events rates in patients with high level of Hb after ESA therapy may be due to increased blood viscosity and high blood pressure (59).

The increased blood viscosity associated with high hematocrit in patients with diffuse atherosclerosis and kidney disease, increases thrombotic events. Direct effect of erythropoietin on platelets and endothelium increases the thrombotic risk (62). These evidences are not confirmed in patients with HF because the frequent concomitant therapy with antiplatelet and anticoagulant medications may reduce prothrombotic effects of erythropoietic agents. To confirm these data, large trials with long-term follow up are necessary (49, 59).

ESA therapy causes an increased blood pressure by increased blood viscosity, activation of the neurohormonal system, and direct effects on microvascular structure and function. However, blood pressure was significantly increased only in a single study (58) and in patients with HF no changes in blood pressure or in peripheral resistances have been observed after erythropoietin therapy (60).

Recommendations and future directions

RECOMMENDATIONS AND FUTURE DIRECTIONS

The role of anemia as an independent prognostic factor is now well known. Anemia is frequent in patients with advanced HF and its etiology is generally multifactorial. It is not only related with impaired renal perfusion and kidney failure, but also it could be triggered by an inflammatory and neurohormonal activation and/or by renin angiotensin system therapy. The prognostic value of anemia is not clear and there are no evidences about the correction of low Hb values and improving survival rate in patients with HF.

The administration of erythropoietic stimulating agents remains the more effective therapy to improve Hb serum level. According to the 2005 Guidelines about the diagnosis and treatment of chronic HF of the European Society of Cardiology (ESC), anemia is a risk factor for worsening Hf but the treatment is not defined (63). According to the 2005 Guidelines of American Heart Association (AHA)/American College of Cardiology (ACC), benefits of ESA therapy in anaemic patients with HF has not been shown, yet, (class IIB recommendation, level of evidence C) (64). The treatment with ESA is commonly considered effective only in patients with kidney diseases (4).

In HF patients with moderate-to-severe anemia (Hb < 11 g/dl), current guidelines of FDA and of National Kidney Foundation recommend treatment with ESA to reach Hb target value of 10-12 g/dl and improve the quality of life. However, there are no clinical data supporting the use of ESA to improve the outcome in HF patients. Large trials with long term follow up are needed to determine the effects on morbidity and mortality (59).

ESA may have antiapoptotic and antischaeic effects with a pro-angiogenic activity on endothelial cells (3, 65-68). Cytoprotective and antiapoptotic effects have been shown (69, 70) as well as a beneficial action on central nervous system injury and in experimental models of myocardial hypoxia. These evidences showed the possibility that derivatives of rHuEpo may be useful to protect cardiomyocytes by ischaemic injury and to improve the myocardial function in patients with HF, rather than reducing other co-morbidities.

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