

# Effect of Erythropoietin in a Patient with Severe Congestive Heart Failure – A Case Report

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## ABSTRACT

*Erythropoietin (EPO), traditionally known as a hematopoietic hormone, has recently been shown to have effects beyond hematopoiesis such as prevention of neuronal and cardiac apoptosis secondary to ischemia and induction of neoangiogenesis<sup>4,5,12,13</sup>. Patients with congestive heart failure (CHF) suffer considerable morbidity and mortality despite advances in therapy. Anemia, CHF, and chronic kidney insufficiency often coexist and interact to cause or worsen each other in the so-called cardio-renal anemia syndrome<sup>3</sup>. Treatment with EPO has shown promise in such patients. The paper reviews a case of a successful recovery of cardiac function in a patient with a severe CHF during the treatment with EPO.*

**Key words:** cardio-renal anemia, heart failure, erythropoietin, apoptosis

## Introduction

Considerable morbidity and mortality are still associated with congestive heart failure (CHF) syndromes, despite improvement in therapy. Anemia, found in about one-third of all cases of CHF and chronic kidney insufficiency (CKI), present in about half of all CHF cases have been showed to be associated with heightened risk for cardiovascular death and hospitalization in CHF<sup>1,2</sup>. The CKI is likely to be due to the renal vasoconstriction that often accompanies CHF and can cause long-standing renal ischemia. This reduces the amount of erythropoietin (EPO) produced in the kidney and leads to anemia. Increased cardiac work during a long-standing anaemia can cause left ventricular hypertrophy (LVH), cardiac cell death through apoptosis, ultimately leading to dilatation of the ventricle. Therefore, a vicious circle, termed as the cardio renal anaemia syndrome is set up, wherein CHF causes anaemia, the anaemia causes more CHF, and both damage the kidneys, worsening the anaemia and the CHF further<sup>3</sup>. Adequate treatment of anemia could slow down the progression of both the CHF and CKI.

Erythropoietin (EPO) is haematopoietic growth factor produced in the fetal liver and the adult kidney. The premise that EPO is required only for erythropoiesis has initially been altered by studies using animal and in vitro

models which demonstrated the existence of EPO and its receptor in other organs and tissues such as the brain and heart. Some studies are suggesting possible direct protective effect of EPO on myocardial cells by increase in cardiac cell proliferation and reduction of myocardiocyte apoptosis during ischemia or reperfusion injury, thus leading to improved left ventricular function<sup>4,5</sup>.

Even though there are several published trials which evaluated the effects of administering EPO and/or iron to patients with CHF, the results still remain controversial. Here we present a case of an exceptionally good recovery of cardiac function in a patient with New York Heart Association (NYHA) stage III/IV CHF, CKI and anaemia, which we believe could be at least in part due to direct effect of EPO on the myocardium.

## Case Report

A 49-year old woman first presents with severe weakness and fatigue, dyspnea and intolerance to even the slightest activity. Shortness of breath appears after just a few meters of slow walk. She is pale, obviously dyspnoic, gasping for air, she can hardly speak, leaning with her

palms on her knees. Her medical history reveals Paget's disease, dilated cardiomyopathy, arterial hypertension and CKI. Her regular therapy taken orally consists of furosemide 250 mg, ramipril 5 mg, carvedilol 3.125 mg and amlodipine 10 mg. Skin and visible mucosal surfaces are pale, heart action on auscultation is regular with silent heart sounds and holosystolic murmur over the apex and aortic valve. Moist rales are heard widely over both lungs on inspiration. The lower border of the liver is palpable 2 cm below the costal margin, oedema is present bilaterally in pretibial regions and around the ankles. Blood pressure is 140/90 mmHg. Electrocardiograph (ECG) shows sinus rhythm 78/min. and signs of left ventricular strain. Roentgenogram of the chest showed an enlarged heart silhouette occupying more than two thirds of the chest, with enlarged pulmonary vessels and no signs of infiltration on pulmonary fields, nor signs of fluid collections. Echocardiographic examination showed heart dimensions of LVIDd 7.22 cm, LVIDs 6.1 cm, ejection fraction of the left ventricle of 30%, left ventricular (LV) diastolic dysfunction type III and signs of pericardial effusion.

Initial laboratory findings were: erythrocyte count (E) of  $3.69 \times 10^{12}/L$ , hemoglobin (Hb) level of 101 g/L, hematocrit (Htc) 0.320, urea 15 mmol/L, creatinine 197  $\mu\text{mol}/L$ , Fe 10,6  $\mu\text{mol}/L$ , TIBC 52,5  $\mu\text{mol}/L$ , UIBC 47,4  $\mu\text{mol}/L$ .

Based on her symptoms, this patient would be classified as class III/IV according to NYHA functional classification of CHF.

During the two weeks of hospitalization she was given furosemide intravenously, starting with 160 mg/day, with gradual decrease in dosage until it was substituted with oral dose of 80 mg/day. Doses of ramipril, carvedilol and amlodipine were unchanged throughout the hospitalization and the follow-up period. Considering the fact that she suffered from CKI and anaemia, she was given EPO in the dose of 4,000 I.U. a week subcutaneously, starting with the first week of hospitalization, in order to correct the renal anaemia.

Subsequent laboratory controls of E, Hb, Htc, urea and creatinine were done on a monthly basis (Table 1).

During the follow – up visits she is obviously feeling better, she is no longer dyspnoic. She can tolerate moderate physical activity without difficulties. Oedemas have disappeared, physical findings on the lungs become normal. The dose of furosemide is lowered further to 40 mg/day, with other therapy unchanged. ECGs were unchanged. Roentgenogram done 3 months after the initial visit showed the reduction of the heart silhouette by about 1/5 from its original size. Echocardiography showed heart dimensions of LVIDd 6.88 cm, LVIDs 5.84 cm, ejection fraction of the left ventricle of 40%, LV diastolic dysfunction type II and no signs of pericardial effusion. After 9 months of treatment she fits into NYHA classification of CHF class I/II.

## Discussion

Although the cardiorenal anemia syndrome in congestive heart failure (CHF) is an independent risk factor for vascular morbidity and mortality, little is known about the effect of its correction with erythropoietin (EPO) on cardiac structure and function. So far, several different approaches to the correction of anemia in patients with CHF have been tested, and published results are still somewhat controversial. Studies of anaemia correction with erythropoietin, though on small groups, showed promising results<sup>6-8</sup>. On the other hand, two double-blind placebo-controlled darbepoetin (long-acting EPO analog) studies have been published in full and neither showed an improvement in functional capacity or consistent effect on patient reported symptoms and quality of life<sup>9,10</sup>. Small trials showed that intravenous iron alone increases Hb, reduces symptoms, and improves exercise capacity in anemic patients with CHF<sup>11</sup>. More studies are needed and certain issues, particularly the optimal hemoglobin level, should still be resolved before recommendations for anemia treatment in CHF are established.

Our patient initially presented with signs of NYHA class III/IV CHF. After she was hemodynamically stabilized with increased dose of furosemide, she was started on EPO 4,000 I.U. a week. No other modifications of the therapeutic regimen were done.

TABLE 1  
LABORATORY CONTROLS DURING 9 MONTHS

| Date        | E    | Hgb | Htc   | Urea | Creatinine |
|-------------|------|-----|-------|------|------------|
| 01.06.2005. | 3.69 | 101 | 0.320 | 15.0 | 197        |
| 14.07.2005. | 3.54 | 115 | 0.371 | 16.1 | 248        |
| 16.08.2005. | 3.68 | 104 | 0.322 | 15.8 | 326        |
| 28.09.2005. | 3.72 | 108 | 0.328 | 16.5 | 315        |
| 19.10.2005. | 3.93 | 113 | 0.344 | 18.4 | 275        |
| 14.11.2005. | 3.99 | 112 | 0.347 | 16.9 | 269        |
| 14.12.2005. | 3.97 | 112 | 0.354 | 17.3 | 270        |
| 12.01.2006. | 3.76 | 110 | 0.336 | 19.7 | 271        |
| 16.02.2006. | 3.99 | 112 | 0.347 | 29.8 | 362        |

After nine months of treatment her functional capacity improved to NYHA class I/II, echocardiography showed improvement in both systolic and diastolic function of LV and the need for diuretic was lowered. The fact that no significant increase in hemoglobin level was noted during the follow-up led us to believe that some mechanisms of direct effect of EPO on myocardial tissue have been involved in improvement of this patient heart's functional ability. Despite the improvement in functional capacity of the heart, renal function slightly deteriorated during the course of follow-up, which could be expected because CKI is generally thought to be a progressive disorder regardless of etiology.

Several in vitro studies and animal models showed cardioprotective effects of EPO following ischemia/reperfusion injury without an increase in hematocrit (eliminating oxygen delivery as an etiologic factor in myocyte survival and function) and demonstrating that EPO can directly protect the ischemic and infarcted heart<sup>12</sup>. EPO protects vascular endothelial cells from apoptosis, mobilizes endothelial progenitor cells and acts as an angiogenic factor<sup>13</sup>. Although it is impossible to draw conclusions based on treatment of a single patient, we find this case

to be consistent with numerous currently ongoing trials investigating direct cardioprotective and neuroprotective effects of EPO<sup>14</sup>.

## Conclusion

New approaches to the treatment of cardiovascular diseases suggest protective effects of EPO in the ischemic heart. EPO is now considered to have applicability in a variety of disorders that include cerebral ischemia, myocardial infarction and CHF. Anemia is increasingly recognized as a common, important and treatable condition in patients with CHF. Despite increasing knowledge of anemia, as well as its co-association with chronic renal disease, advanced NYHA class and worse prognosis, there are very few evidence-based recommendations for treatment. Larger, double-blind, placebo-controlled studies are needed and certain issues, particularly the optimal hemoglobin level, in the treatment of CHF with EPO should still be resolved.

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## UČINAK ERITROPOETINA U BOLESNIKA S TEŠKIM KONGESTIVNIM ZATAJENJEM SRCA – PRIKAZ SLUČAJA

### SAŽETAK

Za eritropoetin (EPO), hormon dugo poznat samo kao hematopoetski faktor rasta, se pokazalo da ima ulogu i izvan hematopoetskog sustava, poput prevencije apoptoze neurona i miokardiocita za vrijeme ishemijske i poticanja neoangiogeneze<sup>4,5,12,13</sup>. Unatoč napretku u liječenju, pacijenti s kongestivnim zatajenjem srca (KZS) još uvijek trpe značajan morbiditet i mortalitet. Anemija, kongestivno zatajenje srca i kronično zatajenje bubrega često koegzistiraju i međusobno djeluju uzrokujući ili pogoršavajući jedno drugo u takozvanom sindromu srčanobubrežne anemije<sup>3</sup>. Liječenje EPO-om se pokazalo obećavajućim kod ovakvih bolesnika. U radu je prikazan slučaj uspješnog oporavka srčane funkcije bolesnice s teškim kongestivnim zatajenjem srca tijekom liječenja EPO-om.