

# Correction of Anemia with Erythropoietin in Chronic Kidney Disease (stage 3 or 4): Effects on Cardiac Performance

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## Abstract

**Background** It is not clear whether the correction of anemia with erythropoietin (rhuEpo) in patients with chronic kidney disease (CKD) has any benefit on cardiac function and geometry. Most studies are based on indices of systolic function and left ventricular mass (LVM) and the results are conflicting.

**Patients and methods** We sought to investigate the effect of rhuEpo on LV systolic and diastolic performance using conventional and novel echocardiographic indices. Thirty one patients with CKD (stage 3 or 4) were included. Fifteen patients (group I) treated with rhuEpo targeting at Hb  $\geq$  13.0 g/dL, while the remaining (group II) were not treated. Clinical and laboratory parameters were recorded at baseline and 1 year later. Ejection fraction (EF) and LVM were carefully determined. Diastolic function was assessed by mitral inflow indices (E and A wave velocities, Edt deceleration time and E/A) and novel indices of mitral annulus motion using Tissue

Doppler Imaging (Em, Am, and E/Em). An index of global cardiac function (Tei) was also calculated.

**Results** At baseline, the 2 groups had comparable clinical and laboratory characteristics. After 1 year, a significant improvement in Hb levels ( $13.6 \pm 1.2$  vs  $10.3 \pm 1.2$  g/dL,  $p < 0.05$ ) as well as in systolic and diastolic function indexes was observed in group I compared to group II patients: EF ( $70.5 \pm 7.6$  vs  $63.4 \pm 9.3\%$ ,  $p < 0.05$ ), LVM ( $116.5 \pm 34.9$  vs  $155.6 \pm 51.6$  g/m<sup>2</sup>,  $p < 0.05$ ), Edt ( $233.9 \pm 98.6$  vs  $166.9 \pm 45.1$  ms,  $p < 0.05$ ), Tei index ( $0.35 \pm 0.12$  vs  $0.51 \pm 0.17$ ,  $p < 0.01$ ) and E/Em ( $9.7 \pm 2.4$  vs  $14.8 \pm 5.2$ ,  $p < 0.05$ ), respectively. Blood pressure and heart rate did not show significant changes.

**Conclusions** Correction of anemia with rhuEpo in patients with CKD seems to improve cardiac performance and geometry.

**Key words** chronic kidney disease · cardiac performance · systolic function · diastolic function · erythropoietin · echocardiography · tissue doppler imaging

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## Introduction

Cardiovascular disease is the main cause of morbidity and mortality in patients with chronic kidney disease (CKD) not yet requiring dialysis as well as in those on chronic renal replacement therapy [1–3]. Prominent features of cardiovascular involvement in CKD patients (stages 2–5) are left ventricular hypertrophy (LVH) and dysfunction [4–6]. LVH is recognized as a powerful independent predictor of death and morbidity in CKD patients, along with anemia, hypertension, malnutrition, hyperparathyroidism and an elevated calcium x phosphorus product [7–10].

Chronic anemia, usually observed when creatinine clearance decreases below 40 ml/min (CKD stage 3 or 4), may adversely affect cardiovascular function inducing a long-term hyperdynamic circulatory state with increased cardiac output leading to LVH [6, 11, 12]. Therefore, therapies that can reverse the development of LVH among patients with CKD (stage 2–4) may help to reduce the increased cardiovascular risk.

It has been suggested that the correction of renal anemia using recombinant human erythropoietin (rhuEpo) could be associated with an improvement of cardiac function and a reduction of LV mass. However, the effect of long-term administration of rhuEpo on cardiac structure and performance in predialysis patients has not been well studied while some inconsistent results have been published in the literature [13–19]. Moreover, no study to date has investigated the effect of such a treatment on LV diastolic function.

We therefore sought to investigate the effects of long-term rhuEpo treatment on cardiac function (systolic and diastolic) and structure in CKD patients (stage 3 or 4) in a nested sub-study performed in the framework of our recently published prospective randomized clinical study [20].

## Patients and methods

Thirty one predialysis patients recruited from our center (17 males) aged  $64.3 \pm 19.5$  (range 35–81) years, out of 88 CKD patients who were enrolled in our published multicenter prospective randomized clinical study [20] were included in this study. Inclusion criteria were: CKD stage 3 or 4 [creatinine clearance 30–59, 15–29, respectively] (creatinine clearance was estimated using the Cockcroft–Gault formula [21]), age >18 years, Hb <12 g/dL, no apparent heart disease and patients who had not previously received rhuEpo treatments. Patients with arrhythmias, angina, myocardial infarction, cerebrovascular disease, uncontrolled hypertension, hepatic insufficiency, active hepatitis, uncontrolled hypothyroidism, chronic alcoholism, congestive heart failure (New York Heart Association class III or IV), severe obesity (body mass index >40 kg/m<sup>2</sup>), diabetes mellitus, systemic diseases, infections or inflammatory conditions that might inhibit the effect of rhuEpo had been excluded from the study.

The causes of primary kidney disease of the patients were: glomerulonephritis 5, urolithiasis 1, polycystic kidney disease 4 and unknown 21.

Monitoring of arterial blood pressure and treatment of hypertension was performed according to established standards, aiming at blood pressure levels  $\leq 135/85$  mm Hg whenever possible, using restricted salt intake, and

appropriate drug therapy (avoiding drugs that inhibit the renin–angiotensin axis), at the discretion of the treating clinician. Protein intake was generally restricted to less than 1 g/kg/day based on appropriate dietary instructions given to the patients. The patients who received rhuEpo, also received oral iron supplements (100 mg of element iron /day) to maintain ferritin levels of  $\geq 150$   $\mu\text{g/L}$  and a transferrin saturation index  $\geq 20\%$ . Intravenous iron was not used. All patients were followed in the CKD outpatients clinic of the University Hospital of Ioannina, Greece. Written informed consent was obtained from all patients prior to participation in the study and the Hospital's Ethics Committee approved the study protocol. Randomization was done using a computerized sequence kept at the coordinating center at the University of Ioannina, Greece.

## Study design

Patients were randomized in one to one fashion to each treatment group between November 2000 and February 2002. Fifteen patients (group I) were received rhuEPO-alpha at a dose of 50 U/kg subcutaneously, once per week targeting at Hb levels 13 g/dL. For patients exceeding this target the dose of rhuEpo was down-titrated to 25 U/kg/week, or remained the same according to the discretion of the clinician. The others (group II) were not treated with rhuEpo until decrease of Hb levels below 9 g/dL.

In November 2002, the indication of subcutaneous rhuEPO-alpha administration in chronic renal failure patients was withdrawn because pure red-cell aplasia cases were reported [22]. Although no such adverse events had been recorded in any of the enrolled patients in our study, all patients were notified of this modification and subcutaneous rhuEPO-alpha was discontinued. Patients could then use an alternative form of rhuEPO (e.g. subcutaneous rhuEPO beta or darbepoietin) at the discretion of their treating physicians. The study was terminated 1 year after the recruitment of the last patient.

## Clinical and laboratory characteristics

Patients were seen at baseline and consequently monthly on an outpatient basis. The mean values of clinical and laboratory characteristics of the patients at baseline and after 12 months are presented in Table 1. Resting blood pressure and heart rate were obtained using standard methods. Blood samples were obtained after overnight fasting and the following laboratory parameters were recorded: Hb levels, serum creatinine, calcium ( $\text{Ca}^{+2}$ ), phosphorus, intact parathormone, albumin (ALB), and the lipid profile [Total cholesterol (T-cho), HDL-cholesterol (HDL-cho), Triglycerides (TG)]. LDL cholesterol (LDL-cho) was calculated by the Friedewald equation [23].

**Table 1** Baseline and 1 year clinical and laboratory characteristics of the 2 groups of patients

Parameters	Baseline		1 year	
	Group I (n=15)	Group II (n=16)	Group I (n=14)	Group II (n=13)
<b>Clinical</b>				
Age (years)	63.3±12.2	65.4±9.7	64.4±11.8	66.2±10.5
Gender (M/F)	7/8	10/6	7/8	10/6
Body weight (kg)	72.4±11.6	71.6±12.3	73.4±12.5	69.5±10.2
Body surface area (m <sup>2</sup> )	1.82±0.24	1.79±0.23	1.80±0.18	1.79±0.56
Systolic BP (mm Hg)	135.2±7.9	134.5±8.9	134.0±5.7	134.3±3.8
Diastolic BP (mm Hg)	80.9±6.5	81.1±9.1	79.0±6.4	80.6±6.5
Heart rate (beats/min)	63±11	76±13	71±12	80±15
<b>Antihypertensive medications</b>				
Calcium channel blockers	9	8	8	7
Centrally acting drugs	4	5	3	3
B-blockers	2	3	3	3
<b>Laboratory</b>				
Hb (g/dL)	10.1±0.6	10.4±0.5	13.6±1.0*	10.2±1.2
Creatinine clearance (ml/mg)	25.6±7.7	23.1±4.7	24.8±7.1	19.8±6.6*
Serum creatinine (mg/dL)	2.9±10.8	3.1±0.8	3.2±1.8	4.1±2.1*
Serum calcium (mg/dL)	9.1±0.5	9.4±0.6	9.0±0.5	9.2±0.6
Serum phosphorus (mg/dL)	3.9±0.9	3.9±0.8	4.1±1.0	4.2±1.6
Serum iPTH (pg/ml)	139.1±41.4	138.9±37.9	144.0±44.3	141.8±43.4
Serum albumin (g/dL)	3.8±0.4	4.0±0.4	3.9±0.4	3.8±0.4
Serum triglycerides (mg/dL)	135.6±41.5	153.2±48.7	151.6±53.6	128.9±37.4
Serum T-chol (mg/dL)	231.5±33.4	215.4±38.7	219.9±43.7	200.9±31.7
Serum LDL-chol (mg/dL)	160.2±37.9	141.8±26.3	151.6±53.6	128.4±37.4
Serum HDL-chol (mg/dL)	40.2±12.3	42.9±10.9	55.6±10.2*	43.5±6.7

\* $p < 0.001$  between baseline and 1 year for each group

The Hb values were determined by an automatic hematological analyzer (Coulter Counter). Serum creatinine and  $sCa^{+2}$  were assessed by photometric methods (Olympus AV 600, Olympus, USA), while sALB was measured by a photometric BCG method (Olympus AV 600, Olympus, USA). Intact parathormone was measured by a chemiluminescent immunoassay (Immulite 200, Diagnostica products, Los Angeles, CA, USA). Concentrations of T-chol and TG were determined enzymatically using an Olympus AV 600 clinical chemistry analyzer (Olympus Diagnostica, Hamburg, Germany). Our laboratory is currently participating in the Murex Clinical Chemistry Quality Assessment Programme. The coefficient of variation values in this program in the past 2 years ranged between 0.99 and 2.44% for cholesterol and between 1.73 and 3.36% for TG. HDL-chol was determined by a direct assay (Olympus Diagnostica, Hamburg, Germany).

#### Echocardiographic measurements

An echocardiographic examination was performed at baseline and after 12 months using a cardiac ultrasound unit (HD1 5000, Philips, USA) with a 2–3.5 MHz transducer in the M-mode and in the Doppler bidimensional model. Moreover,

Tissue Doppler Imaging (TDI) was performed in all patients. The same experienced operator performed all the echocardiographic studies being unaware of each patient's treatment.

All recordings and measurements were performed in accordance with the recommendations of the American Society of Echocardiography [24] using the average value of three measurements. The echocardiographic window used was obtained in the 3–4 intercostal space with the patient in the 30-degree decubitus position.

#### • M-mode measurements

Using the M-mode technique we assessed the following parameters: end-diastolic diameter of the left ventricular chamber, the inter-ventricular septum thickness and the thickness of the left ventricular posterior wall. Care was taken to avoid misalignment and angulation in obtaining measurements. Left ventricular mass was calculated from end-diastolic LV dimensions using the formula of Devereux et al [25]. The LV mass was adjusted for body surface area and expressed as LV mass index. The LV ejection fraction was determined by 2D echocardiography using the modified biplane Simpson's method.

#### • Doppler measurements

The diastolic filling of LV (LV inflow) was examined using Doppler echocardiography. The peak velocity of

early diastolic filling (E) and the peak velocity of atrial filling (A) were recorded and the E to A ratio (E/A) was calculated. The deceleration time of the E wave (DcT) was also measured. The index of global cardiac function Tei index, was also calculated using mitral inflow and ejection time assessed by conventional Doppler echocardiography [26].

- *TDI measurements*

Tissue Doppler Imaging (TDI) was also used to assess LV diastolic function. Pulse-wave diastolic velocities (early, Em; late, Am) were obtained from the apical 4-chamber view at the septal position of the mitral annulus. Gain settings were adjusted carefully, and the direction of longitudinal motion was aligned with the scan line direction. Signals were obtained from 3 end-expiratory cycles, and averages were made for the diastolic velocities.

### Statistical analysis

All analyses are based on intention-to-treat. Comparisons of discrete and continuous variables between groups were performed by the chi-square test with continuity correction and the t-test, respectively.

All data were analyzed using the SPSS 11.5 software (SPSS, Inc., Chicago, IL). All *p*-values are two-tailed. A *p* value <0.05 was considered statistically significant.

## Results

### Clinical parameters

The baseline clinical parameters were similar between the 2 groups (Table 1). No statistical significant difference was observed in body surface area, body weight and systolic and/ or diastolic blood pressure (Table 1).

### Laboratory parameters

The Hb values at baseline were similar between the two groups. At the end of the 12-month study period patients treated with rhuEpo (*n*=14, 1 patient had died due to myocardial infarction) had increased Hb levels while in the group II patients (*n*=13, 1 patient died due to myocardial infarction, and 2 due to septic shock) remained almost unchanged (Table 1). No patient in group II required erythropoietin administration according to our prespecified criteria (Hb <9 g/dl).

Moreover, the renal function as estimated by creatinine clearance remained unchanged in patients treated with rhuEpo, while a statistically significant reduction was noticed in group II patients (*p*<0.05) (Table 1). We did

not observe any significant differences with the exception of HDL-chol (Table 1).

### Echocardiography

At the end of the follow-up period an improvement in cardiac performance was demonstrated in patients treated with rhuEpo. Specifically:

- *M-mode parameters*

We observed a statistically significant reduction in left ventricular mass (LVM) index (*p*<0.01) accompanied by an increase of left ventricular ejection fraction (LVEF) (*p*<0.01) in group I patients (Table 2). In group II patients we observed an increase of LVM while the LVEF remained almost unchanged (Table 2). These changes showed a statistically significant difference between the 2 groups (Table 2).

- *Doppler parameters*

We did not observe any significant alterations in conventional Doppler parameters in group I patients (Table 2). On the other hand, a significant increase of E and E/A, and a decrease in DT parameter was evident in untreated patients (Table 2). A significant difference in the values of E, A, DT between the 2 groups was evident (Table 2).

- *TDI parameters*

The assessment of diastolic LV performance using novel techniques (TDI) disclosed some remarkable changes. Particularly, we observed an increase in Em/Am ratio in group I patients while in group II the E/Em ratio was increased (Table 2). Statistically significant differences between the 2 groups were noted in the Em/Am, and in the E/Em ratio (Table 2).

- *Tei index*

Finally, an improvement of global (systolic and diastolic) cardiac function, as assessed by the Tei index, was demonstrated in group I patients (Table 2).

## Discussion

In the present study, we observed a significant decrease of LVM and an improvement of systolic and diastolic cardiac performance in patients with CKD stage 3 or 4 who were treated with rhuEpo. To the best of our knowledge, no study to date has examined modern echocardiographic indexes evaluating both systolic and diastolic LV function in this setting. Moreover, in this population a decline of renal function was evident in patients who did not receive rhuEpo.

Renal anemia, uremia, secondary hyperparathyroidism and other factors favor promote the development of LVH

**Table 2** Baseline and 1 year echocardiographic parameters of the 2 groups of patients

Parameters	Baseline		1 year		Normal values
	Group I (n=15)	Group II (n=16)	Group I (n=14)	Group II (n=13)	
<b>Systolic function</b>					
LVM (g/m <sup>2</sup> )	143.8±64.8	131.8±36.4	116.5±34.9*	155.6±51.6***	≤125 g/m <sup>2</sup> (M), ≤100 g/m <sup>2</sup> (F)
LVEF (%)	61.9±10.8	67.5±0.9	70.5±7.6*	63.4±9.3**	64–83%
<b>Diastolic function</b>					
E (cm/s)	60.8±16.3	63.0±16.4	62.6±12.8	78.6±12.9***	62±14
A (cm/s)	83.6±13.8	91.7±18.7	78.9±21.3	97.4±24.7**	59±14
E/A	0.75±0.24	0.70±0.20	0.87±0.35	0.84±0.22*	1.1±0.3
DT (ms)	240.9±81.9	247.7±78.6	233.9±98.6	166.9±45.1***	210±36
<b>Systolic/diastolic function</b>					
Em (cm/s)	5.8±1.8	5.8±1.0	6.7±1.7a	5.7±1.5	10.9±0.5
Am (cm/s)	10.0±1.8	10.0±1.6	9.8±1.8	10.7±2.4	12.3±0.4
Em/Am	0.59±0.18	0.60±0.16	0.71±0.21*	0.56±0.18**	>1
E/Em	10.9±3.2	11.1±3.5	9.7±2.4	14.8±5.2***	<9
Tei index	0.40±0.19	0.48±0.16	0.35±0.12*	0.51±0.18**	<0.40

\* $p < 0.01$  between baseline vs. 1 year for each group

\*\* $p < 0.05$  group A vs. group B at the end of the study

[27, 28]. Moreover, renal anemia correlates significant with the LVM in dialysis patients [28] and the relative risk of LVH is increased (duplicated) for every 1 g/dL decrease of Hb level [29]. Although there is evidence for the association between Hb levels and LVM in CKD, the underlying causality has been questioned [18].

Our results support the findings of previous studies evaluating patients with CKD stage 3 or 4. In these studies the mean decrease of LVM was 14–42 g/m<sup>2</sup> reported at 12-month and at least 6-month follow-up periods [13, 14, 16]; thus our finding of a mean decrease in LVM of 27 g/m<sup>2</sup> after 12 months of rhuEpo therapy are in agreement with the above mentioned studies. Furthermore, a recent study showed that treatment with rhuEpo can prevent further progression of LVH in CKD patients with mild to moderate anemia [17]. On the other hand, another study of patients with CKD stage 3 or 4 did not show a significant change of LVM over 2 years using rhuEpo, although there appeared to be a decrease in LVM in the subgroup with LVH at study entry [15]. In this context, 2 further studies failed to demonstrate that correction of anemia with Epo ameliorates or delays LVH in this setting [18, 19]. Different study designs and populations may account for these disparities. Importantly, 2 recent randomized controlled trials failed to show that complete correction of anemia favours better clinical cardiovascular outcomes [19, 30]. Increased blood pressure, thrombosis, vasoconstriction, blood viscosity, ventricular afterload, and oxidative stress have been proposed as potential mechanisms for this apparent paradox and might offset the benefits of improved myocardial and peripheral oxygenation [31]. However, it should be acknowledged that a considerable

proportion of patients in these studies had a history of heart failure while the underlying etiology and the ejection fraction (EF) were not reported. Thus, it is believed that the findings are inconsistent and point to the need for adequately powered clinical outcome trials [32].

On the other hand, the mechanisms of improvement of left ventricular performance after rhuEpo administration are not clear. Erythropoietin is increasingly recognized as an agent with favourable pleiotropic effects on the cardiovascular system, apart from erythropoiesis [33–35]. Several direct beneficial effects of rhuEpo have been proposed, including inhibition of myocardial cell apoptosis and favorable cardiac remodeling [36], phosphatidylinositol 3'-kinase (P13k)/Akt-mediated protection of cultured myocytes from hypoxia-induced apoptosis [37] and improved left ventricular function and decreased apoptosis following ischemia/reperfusion (I/R) injury in the myocardium [38, 39]. Another operating mechanism could be the increased neovascularization leading to increased capillary density [40]. The value of this mechanism in improving LV performance has been recently demonstrated in a rat model of post-myocardial infarction heart failure [41].

Patients with anemia seem to have normal conventional indices of diastolic function because of a pseudo-normalization phenomenon which is a result of increased preload. TDI has been demonstrated to provide relevant additive information about left ventricular systolic and diastolic performance. Most importantly, mitral annular velocities derived from TDI seem to be less load dependent than conventional mitral inflow variables [42]. In addition, it has been shown that the ratio of the peak early diastolic mitral inflow velocity over the peak early diastolic annulus



velocity (E/Em) allow an accurate estimation of filling pressures in different subsets of patients [43].

Tei index combines systolic and diastolic time intervals and it has been demonstrated to predict the prognosis of patients with idiopathic dilated cardiomyopathy and cardiac amyloidosis [26, 44]. Thus, these newer cardiac markers (Tei index and E/Em ratio) are stronger predictors of future cardiac events than conventional parameters of systolic and diastolic cardiac performance [45].

Our population had no evidence of heart failure with conventional parameters, but the E/Em ration ( $\geq 10$ ) was consistent with diastolic dysfunction, whereas the Tei index ( $>0.35$ ) indicated a global cardiac (systolic and diastolic) impairment. Our results showed that the administration of rhuEpo retarded the progression of heart failure as expressed by the E/Em and Tei indices, while in patients not treated a progression of cardiac dysfunction was noted.

It could be therefore concluded that correction the renal anemia, along with control of blood pressure and volume status, might favourably affect cardiac geometry and structure as well as systolic/diastolic function in patients with advanced CKD.

The correction of renal anemia using rhuEpo may have benefits that extend beyond the effects on LVH and cardiac function. Small studies demonstrated benefits of Hb normalization on sleep [46], exercise capacity and well being [47, 48] and quality of life [49] in dialysis patients. Moreover, the use of rhuEpo in predialysis patients (CKD stage 3 or 4) has been reported to be associated with favourable effects on serum creatinine and creatinine clearance in randomized control studies [20, 49]. Potential mechanisms of preserved renal function include the correction hypoxia of tubular cells, and the attenuation of apoptotic processes [20].

Our results are in agreement with the above mentioned studies; although two recent studies showed that the progression of renal failure was not retarded in patients treated with rhuEpo [15, 16]. This disagreement is possibly due to the inclusion of a significant number of subjects with diabetes mellitus in the latter studies.

Finally, we observed a significant increase in the HDL cholesterol levels in the treated group. This favourable antiatherogenic effect could be attributed to the anti-inflammatory activity of rhuEpo as well as to the improvement in tissue oxygenation owing to correction of anemia [50].

#### Limitations

We believe that our study adds to the clarification of the role of rhuEpo in cardiac performance. However, some limitations should be mentioned. *Firstly*, the study population was relatively small. *Secondly*, it is unclear whether our

findings are operative in patients with other stages of CKD. *Thirdly*, we performed measurements of Em only in the septal wall. During the study period this measurement was considered of equal value compared to the lateral mitral annular position. Only recently, some papers indicate that the assessment of lateral mitral annular velocities by TDI may be a little bit better for the evaluation of left ventricular filling pressures. *Finally*, in the majority of patients the cause of CKD was unknown. However, in many patients seen in our center the size of the kidneys (small size—shrunk kidneys) and the presence of increased echogenicity did not permit the performance of renal biopsy.

#### Conclusions

In conclusion, the administration of rhuEpo in CKD patients with renal anemia seems to have beneficial effects on cardiac performance and structure. Further studies with larger populations and longer follow-up are needed in order to elucidate the impact of this strategy on the LV systolic and diastolic function.

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