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Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin <10 g/dL

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Background. Left ventricular hypertrophy (LVH) frequently complicates chronic renal insufficiency. Anemia is also common in these patients and may contribute to LVH.

Methods. We conducted an open-label interventional trial to evaluate the effect of recombinant erythropoietin (rhEPO) on left ventricular mass index (LVMI) in anemic patients with renal insufficiency. Adults with creatinine clearance 10 to 30 mL/min (nondiabetics) or 20 to 40 mL/min (diabetics) were recruited, and rhEPO was given to those with anemia (hemoglobin level <10 g/dL). Baseline and 6-month LVMI and LVH (LVMI >130 g/m^2 in men and >100 g/m^2 in women), hemoglobin levels, creatinine clearance, blood pressure, medications, and medical history were obtained. Forty anemic and 61 nonanemic control subjects were enrolled.

Results. Overall, the prevalence of LVH was 68.3% (95% CI 58.3-77.2), and entry hemoglobin level was the only significant predictor of baseline LVH (adjusted OR 0.69 per g/dL increase in hemoglobin, 95% CI 0.50-0.94). After 6 months, LVMI decreased in anemic patients receiving rhEPO (142 ± 56 vs. 157 ± 56 g/m^2) ($P = 0.007$), with an increase in hemoglobin (11.3 ± 1.9 vs. 9.1 ± 0.7 g/dL) ($P = 0.001$). There were no changes in LVMI or hemoglobin level among controls. After adjusting for confounders and change in hemoglobin, receipt of rhEPO was associated with a significant reduction in LVMI ($P = 0.01$).

Conclusion. Treatment with rhEPO was not independently associated with significant changes in blood pressure or renal function. LVH is a common finding in chronic renal insufficiency and is associated with lower hemoglobin levels. Treatment with rhEPO may decrease LVH in patients with severe renal insufficiency and anemia.

The incidence and prevalence of chronic kidney disease is increasing in the United States [1–3] and cardiovascular disease continues to be the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) [3–6] as well as those with severe chronic renal insufficiency not yet requiring dialysis [7–11]. Cardiovascular structural and functional abnormalities, especially left ventricular hypertrophy (LVH), frequently occur in patients with ESRD who are beginning maintenance dialysis [12, 13], with only 16% of these patients having normal echocardiographic findings at dialysis initiation [12]. LVH has been shown to be an independent risk factor for cardiovascular mortality in patients with ESRD [12, 14]. In patients with ESRD and a left ventricular mass index (LVMI) >125 g/m^2, 5-year survival is slightly more than 20% while among patients with ESRD and an LVMI <125 g/m^2, 5-year survival is 50% [14]. The presence of LVH is also an important risk factor for the development of chronic heart failure on maintenance hemodialysis [15]. The impact of chronic heart failure on survival in ESRD patients on renal replacement therapy is striking, as the presence of heart failure is associated with a higher adjusted risk of death compared with having known coronary heart disease in new ESRD patients [16]. There is now a greater appreciation that LVH occurs early in the course of kidney failure, commonly affecting patients with chronic renal insufficiency,

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and reduced hemoglobin level has been identified as an important risk factor for its development [12, 13, 17, 18]. Therefore, successful therapies that can reduce the development and progression of LVH among patients with advanced chronic renal insufficiency may help to reduce the associated high rates of cardiac morbidity and mortality in this population and is an emerging therapeutic target.

Correction of anemia with recombinant erythropoietin (rhEPO) has been associated with improvement of LVH in patients with ESRD receiving maintenance dialysis [19, 20], but relatively little is known about its effects in patients with advanced chronic renal insufficiency not yet requiring renal replacement therapy. We conducted a prospective trial to evaluate the impact of rhEPO on left ventricular echocardiographic parameters in patients with severe chronic renal insufficiency complicated by anemia. We hypothesized that receipt of rhEPO would be associated with an improvement in LVH in anemic patients with severe renal insufficiency.

METHODS

Study sample

From 1997 to 1999, members of the Spanish Group for the Study of Left Ventricular Hypertrophy in Predialysis Patients recruited patients from a consortium of university and community hospitals in Spain who were age 18 years or older; who had a Cockcroft-Gault creatinine clearance [21] of 10 to 30 mL/min in nodiabetics and 20 to 40 mL/min in diabetics (approximately stage 4 chronic kidney disease); [22] and who had not previously received rhEPO treatment. Kidney function was assessed on two separate occasions during consecutive months prior to enrollment into the study, and the Cockcroft-Gault–calculated creatinine clearance from these two measurements was averaged and this was used as the baseline creatinine clearance for the study. We used Cockcroft-Gault creatinine clearance to estimate underlying glomerular filtration rate (GFR) consistent with options recommended in recent national guidelines [22]. We excluded patients who had a functional vascular access, prior acute myocardial infarction, known valvular heart disease, significant cardiac arrhythmia, congestive heart failure, systemic conditions with potential myocardial involvement (e.g., amyloidosis, systemic lupus, or vasculitis), or uncontrolled hypertension. The demographic characteristics and baseline level of comorbidity of the patients enrolled are reflective of the general ESRD population in Spain [23].

Written informed consent was obtained for all patients and participating centers' institutional review boards approved the study.

Study design and follow-up

We conducted a prospective, open-label trial of the effects of rhEPO on LVH based on the presence or absence of anemia, defined as a hemoglobin level <10 g/dL at entry. At study entry, hemoglobin levels (g/dL) and LVMI by standard echocardiographic methods were assessed [24, 25]. Only eligible patients found to be anemic were treated with subcutaneous rhEPO, with the dose adjusted to achieve a hemoglobin level of 12 g/dL, as the study's steering committee and participating institutions' institutional review boards concluded that it was unethical to conduct a placebo-controlled study based on existing clinical practice guidelines. The mean dose of rhEPO used was 4100 ± 325 U/week. During the study, patients receiving rhEPO also received oral iron supplements to maintain serum ferritin levels of ≥ 150 μg/L and a transferrin saturation index $\geq 20\%$, intravenous iron was not used. None of the patients developed functional iron deficiency (ferritin <150 mcg/L or transferring saturation index of <20%). Follow-up was discontinued if patients received arteriovenous vascular access, initiated dialysis, died, or dropped out of the study, but no patients met these criteria.

The original planned duration of follow-up for the study was 12 months, with an interim analysis after 6 months of follow-up. As per the original protocol developed by the study steering committee and required by the institutional review boards of participating institutions, study was terminated based on findings of a positive effect associated with receipt of rhEPO at the 6-month follow-up evaluation.

Clinical and biochemical characteristics

At study entry, we collected information on relevant medical history, including diabetes mellitus, dyslipidemia, and cigarette (never, current, or former) and alcohol use (yes or no), and presumed etiology of renal disease (diabetes mellitus, glomerulonephritis, polycystic kidney disease, nephrosclerosis, interstitial disease, renovascular disease, other etiology, or undetermined). We also obtained data on targeted medical therapies, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta blockers, calcium channel blockers, alpha blockers, vasodilators, and other antihypertensive agents.

Baseline and 6-month measures of resting blood pressure, heart rate, and body mass index (kg/m^2) were obtained using standard methods. Local laboratories were used to measure hemoglobin level, Cockcroft-Gault creatinine clearance (mL/min) based on ambulatory serum creatinine concentrations, serum calcium and phosphorous, plasma parathyroid hormone level, serum albumin, and plasma lipoprotein levels [total

cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and low-density lipoprotein (LDL) calculated using the Friedewald equation [26]].

Of note, there were no differences between the groups with regard to nephrology care before entering the study or the subsequent number of medical visits during the study. All patients were seen in the clinic by the site investigator and a study coordinator at each visit.

Baseline characteristics

A total of 162 patients were assessed for possible eligibility, and 140 patients agreed to be screened. Of these, 101 patients met enrollment criteria and agreed to participate, with 50% being men and a mean age of 60.5 ± 14.4 years (range 21 to 85 years). Forty patients (40.0%) met criteria for anemia (hemoglobin <10 g/dL) at entry. At baseline, the only significant differences in clinical or treatment characteristics among anemic and nonanemic subjects were slightly lower creatinine clearance and higher serum phosphorus level in anemic subjects (Tables 1 and 2).

Outcome variables

The primary outcome of interest was within-person change in LVMI between study entry and the end of follow-up.

Baseline and 6-month follow-up transthoracic echocardiographic studies were performed by the same cardiologist, in a blinded fashion, at each participating center using standardized protocols. A separate echocardiographic cardiologist blinded to group and treatment status independently reviewed and evaluated all echocardiograms. Using standard methods, readings were taken in the lateral decubitus position using M-mode and Doppler techniques, including measurement of left ventricular ejection fraction and fractional shortening, as well as the waves from protodiastolic filling (E wave) and telediastolic atrial contraction filling (A wave) to calculate E-to-A ratio. Inter-ventricular septal thickness was measured, excluding the thickness of the right and left endocardium, along with left ventricular posterior wall thickness, excluding the thickness of the endocardium and epicardium-pericardium.

Left ventricular mass was calculated using the Devereux formula corrected for body surface area to determine LVMI [24]. A secondary outcome was the presence of echocardiographic LVH was based on the Framingham Heart Study criteria of LVMI >130 g/m^2 for men and >100 g/m^2 for women [25].

From previous quality control measures of the echocardiography laboratories used in this study, the intrarater variability for the cardiologists reading the echocardiograms in the study has been less than 5%. All echocardiograms were re-reviewed by a single cardiologist at a centralized location; and in the case of any discrepancies in the reviews by greater than 10%, the studies were submitted to a third cardiologist without any formal association with the study for review.

Statistical approach

Continuous variables are presented as means with standard deviations or medians, with comparisons between groups using Student *t* test or Mann-Whitney rank-sum test. Categorical variables were compared between groups using Pearson's chi-squared test.

We first performed multivariable logistic regression to identify independent correlates of having LVH at study entry among the entire cohort, with candidate variables including characteristics previously reported to be associated with LVH as well as those variables associated with LVH on bivariate analyses with a $P < 0.05$.

We performed analyses for within-person changes during follow-up to compare the change in LVMI among patients who received rhEPO versus that among control subjects, after adjustment for known correlates of LVH and any baseline differences between groups on bivariate analyses with a $P < 0.05$, except for 6-month hemoglobin or change in hemoglobin during follow-up which were hypothesized to potentially be causally related to any observed effect of rhEPO on left ventricular parameters. In the final model, we included 6-month hemoglobin or change in hemoglobin to assess whether this mediated the observed results by examining the change in the β coefficient. Finally, we also examined the association between rhEPO therapy and change in creatinine clearance using multivariable linear regression.

We also conducted comparisons between the treatment and control groups in the unadjusted rates of LVH at study entry and at the end of follow-up.

A two-tailed P value < 0.05 was considered statistically significant. All analyses were performed using Stata 8.2 (Stata Corporation, College Station, TX, USA).

Role of the funding source

The funding source provided financial support and study drug. However, the study design and all analyses were independently developed, conducted, interpreted, and reported by the study investigators.

RESULTS

Baseline LVH in anemic vs. nonanemic subjects

Overall, 68.3% (95% CI 58.3 to 77.2) of all subjects met criteria for echocardiographic LVH at study entry. The mean LVMI was significantly higher in anemic compared with nonanemic subjects; similarly, the prevalence of LVH was substantially higher among anemic compared with nonanemic subjects (87.5% vs. 55.7%, respectively)

Table 1. Baseline characteristics of subjects with chronic renal insufficiency stratified by baseline anemia status

Characteristic	Anemic subjects (hemoglobin <10 g/dL) ($N = 40$)	Nonanemic Subjects (hemoglobin ≥10 g/dL) ($N = 61$)	*P* value
Mean (SD) age *years*	59.5 (15.8)	61.1 (13.6)	0.58
Women%	60.0	44.3	0.12
Mean (SD) hemoglobin *g/dL*	9.1 (0.7)	12.1 (1.3)	<0.001
Mean (SD) creatinine clearance *mL/min*	17.3 (5.8)	21.7 (7.0)	0.002
Tobacco use%			0.93
Never	75.0	77.0	
Current	7.5	8.2	
Former	17.5	14.8	
Alcohol use%	5.0	1.6	0.33
Diabetes mellitus%	30.0	19.7	0.23
Dyslipidemia%	27.5	27.9	0.97
Presumed etiology of renal insufficiency %			0.46
Diabetes mellitus	25.0	18.0	
Glomeruloneprhitis	15.0	24.6	
Polycystic kidney disease	10.0	16.4	
Nephrosclerosis	10.0	14.8	
Interstitial disease	2.5	4.9	
Renovascular disease	5.0	1.6	
Undetermined	7.5	8.2	
Other etiology	25.0	11.5	
Medication %			
Angiotensin-converting enzyme inhibitor	45.0	50.8	0.56
Angiotensin receptor blocker	8.1	7.1	0.86
Diuretic	18.9	32.1	0.16
Beta blocker	2.7	14.3	0.06
Calcium channel blocker	57.5	47.5	0.33
Alpha blocker	21.6	10.7	0.15
Vasodilator	5.4	3.6	0.67
Other antihypertensive	8.1	8.9	0.89
Mean (SD) systolic blood pressure *mm Hg*	148 (21)	146 (19)	0.56
Mean (SD) diastolic blood pressure *mm Hg*	82 (11)	83 (9)	0.60
Mean (SD) heart rate *beats/min*	79 (10)	77 (13)	0.32
Mean (SD) body mass index kg/m^2	26.1 (3.3)	27.5 (4.5)	0.10

Table 2. Baseline laboratory and echocardiographic measures stratified by baseline anemia status

Characteristic	Anemic subjects (hemoglobin <10 g/dL) ($N = 40$)	Nonanemic subjects (hemoglobin ≥10 g/dL) ($N = 61$)	*P* value
Selected laboratory measures			
Mean (SD) serum calcium *mg/dL*[a]	9.0 (0.9)	9.0 (1.7)	0.85
Mean (SD) serum phosphorus *mg/dL*[a]	5.0 (0.8)	4.2 (0.7)	<0.001
Median (interquartile range) plasma parathyroid hormone *pg/mL*[b]	180 (93–289)	112 (65–250)	0.19
Mean (SD) serum albumin *g/L*[c]	4.2 (0.6)	4.4 (0.7)	0.08
Mean (SD) total cholesterol *mg/dL*[d]	200 (41)	216 (44)	0.10
Mean (SD) high-density lipoprotein cholesterol *mg/dL*[e]	42 (10)	49 (17)	0.04
Mean (SD) low-density lipoprotein cholesterol *mg/dL*[f]	159 (40)	165 (48)	0.63
Mean (SD) triglycerides *mg/dL*[g]	134 (59)	148 (65)	0.30
Baseline echocardiographic measures, mean (SD)			
Left ventricular mass index g/m^2	157.0 (55.7)	131.2 (42.7)	0.01
Interventricular septal thickness *mm*	11.6 (2.4)	10.7 (2.8)	0.08
Left ventricular posterior wall thickness *mm*	10.8 (2.1)	10.5 (2.4)	0.57
Left ventricular ejection fraction%	60.7 (10.2)	60.4 (11.0)	0.89
Left ventricular fractional shortening%	37.0 (7.8)	36.8 (8.5)	0.91
E-to-A ratio	0.93 (0.35)	0.90 (0.41)	0.72

E to A ratio is measurement of left ventricular ejection fraction and fractional shortening, as well as the waves from portodiastolic filling (E wave) and telediastolic atrial contraction filling (A wave).

[a]In 34 anemic and 56 nonanemic patients with available data.
[b]In 32 anemic and 52 nonanemic patients with available data.
[c]In 37 anemic and 58 nonanemic patients with available data.
[d]In 35 anemic and 56 nonanemic patients with available data.
[e]In 30 anemic and 50 nonanemic patients with available data.
[f]In 29 anemic and 50 nonanemic patients with available data.
[g]In 34 anemic and 55 nonanemic patients with available data.

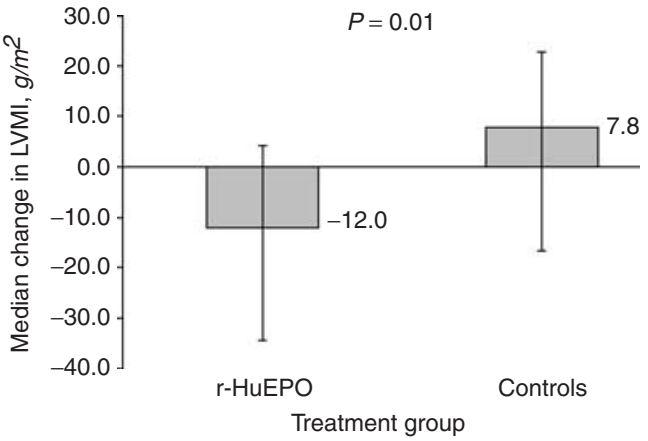

Fig. 1. Median change in left ventricular mass index over a 6-month follow-up period comparing anemic patients who received recombinant human erythropoietin (r-HuEPO) with nonanemic control subjects. Error bars represent interquartile ranges.

($P = 0.001$). There were no other significant differences in other echocardiographic parameters between groups at baseline (Table 2).

Correlates of LVH

In the entire sample, only hemoglobin level was an independent predictor of LVH at baseline. After adjustment for potential confounders including age, gender, etiology of renal disease, diabetes mellitus, tobacco use, body mass index, baseline systolic and diastolic blood pressure, and use of ACE inhibitors or beta blockers, a higher hemoglobin level was associated with a lower likelihood of having LVH (adjusted OR 0.69 per g/dL increase in hemoglobin, 95% CI 0.50 to 0.94). Of note, at baseline and at the end of follow-up, there were no significant differences among those subjects with documented LVH in the proportion of the eccentric versus concentric LVH in either group (data not shown).

EPO and changes in LVMI

At 6 months, hemoglobin level was increased compared with baseline levels in subjects receiving rhEPO (11.3 ± 1.9 vs. 9.1 ± 0.7 g/dL, respectively) ($P < 0.001$), but not in control subjects (11.9 ± 1.5 vs. 12.1 ± 1.3 g/dL, respectively) ($P = 0.06$).

Among patients treated with rhEPO, mean LVMI was significantly lower at 6 months compared with baseline (142.0 ± 55.7 vs. 157.0 ± 55.7 g/m^2, respectively) ($P = 0.007$). However, there was no significant change in mean LVMI at 6-month follow-up compared with baseline among nonanemic controls (137.1 ± 50.6 vs. 131.2 ± 42.7 g/m^2, respectively) ($P = 0.23$) (Fig. 1).

At 6 months of follow-up, the prevalence of echocardiographic LVH was lower but not significantly different than at baseline among anemic subjects receiving rhEPO (75.0% vs. 87.5%, respectively) ($P = 0.31$), while the prevalence of LVH was significantly higher among nonanemic controls at the end of follow-up compared with baseline (59.0% vs. 55.7%, respectively) ($P = 0.02$). Interestingly, in comparing across groups, the prevalence of LVH was not significantly different at the end of follow-up (75.0% in anemic subjects vs. 59.0% in controls) ($P = 0.10$).

We found no significant differences at 6 months compared with baseline for left ventricular ejection fraction in anemic patients treated with rhEPO (61.2% ± 8.6% vs. 60.7% ± 10.2%, respectively) ($P = 0.74$) or control subjects (61.6% ± 10.7% vs. 60.4% ± 11.0%, respectively) ($P = 0.39$). Of note, there were no significant changes at 6 months in E-to-A ratios, interventricular septal thickness, or left ventricular posterior wall thickness in either group (data not shown).

After adjustment for potential differences in age, gender, baseline hemoglobin level, baseline LVMI, diabetes status, etiology of renal disease, body mass index, ACE inhibitor use, beta blocker use, baseline and change in systolic and diastolic blood pressure, baseline and change in creatinine clearance, and baseline and change in left ventricular ejection fraction, we found that receipt of rhEPO was associated with a significant decrease in LVMI ($\beta = -33.8$, $P = 0.01$) over the 6-month follow-up. Finally, neither adding in the final hemoglobin level at 6 months or the 6-month change in hemoglobin level to the model significantly affected the observed association between rhEPO and LVMI.

EPO, change in blood pressure, renal function, and laboratory values

There were no significant changes at 6-month follow-up compared with baseline in mean systolic blood pressure (146 ± 18 vs. 148 ± 21 mm Hg, respectively) ($P = 0.54$) or diastolic blood pressure (81 ± 9 vs. 82 ± 11 mm Hg, respectively) ($P = 0.85$) in anemic subjects who received rhEPO. Similarly, there were no significant changes 6 months compared with baseline in systolic blood pressure (144 ± 15 vs. 146 ± 19 mm Hg, respectively) ($P = 0.46$) or diastolic blood pressure (82 ± 11 vs. 83 ± 9 mm Hg, respectively) ($P = 0.70$) in control subjects.

The unadjusted rate of progression of renal insufficiency was greater in treated subjects compared with control subjects (median change in creatinine clearance −3.4 vs. −1.3 mL/min, respectively) ($P = 0.005$), but rhEPO was not significantly associated with change in renal function after adjustment for diabetes status, etiology of renal disease, and baseline creatinine clearance among subjects. There was no change in medication use or laboratory values at follow-up. No adverse events were

reported among patients receiving rhEPO during the study period.

DISCUSSION

Among adults with advanced chronic renal insufficiency, we found that reduced hemoglobin level is associated with increased odds of having echocardiographic LVH and administration of rhEPO in anemic (hemoglobin <10.0 g/dL) patients with severe renal insufficiency reduced LVMI after 6 months of therapy, even after accounting for the change in hemoglobin level, compared with untreated non-anemic controls. LVH affected more than two thirds of our sample overall at baseline, and was substantially more frequent in patients with hemoglobin <10.0 g/dL (88%) compared with those with hemoglobin of ≥10 g/dL (56%) at study entry, despite similar levels of renal dysfunction as estimated by Cockcroft-Gault creatinine clearance. Our study suggests that short-term treatment with rhEPO in anemic patients with severe chronic renal insufficiency not yet requiring dialysis may reduce LVMI, without any clinically significant detrimental effects on blood pressure or renal function during the 6-month follow-up.

Our study is one of the largest interventional studies reported to date to evaluate the impact of rhEPO on LVMI in patients with chronic renal insufficiency, with longitudinal comparisons between anemic and nonanemic subjects with similar degrees of renal dysfunction at entry. Our findings support and materially extend results of two previously published studies evaluating a total of 20 patients with severe renal insufficiency not yet requiring renal replacement therapy that showed a beneficial effect of rhEPO on LVH [27, 28]. In these studies, mean decreases in LVMI of 14 g/m^2 [27]and 41 g/m^2 [28], respectively, were reported at 12-month and at least 6-month follow-up periods; thus, our finding of a mean decrease in LVMI of 12 g/m^2 after 6 months of rhEPO therapy among anemic subjects is of the magnitude expected given our study design. Interestingly, a recent study of patients who had Cockcroft-Gault–calculated creatinine clearance of 15 to 50 mL/min plus higher entry hemoglobin levels (11 to 13 g/dL for men and 11 to12 g/dL for women) did not show a significant change in LVMI over 2 years using epoetin a to maintain hemoglobin levels at either 12 to 13 g/dL or 10 to 11 g/dL, although there appeared to be a decrease in LVMI in the subgroup with LVH at study entry [29]. The latter subgroup findings are consistent with our results, although 88% of our anemic subjects had LVH at entry compared with 30% of subjects in the study by Roger et al [29], suggesting that rhEPO may be most beneficial in the setting of established LVH. The lower prevalence of LVH noted by Roger et al compared with our study may have been due to enrollment of younger patients with more preserved levels of renal function and higher hemoglobin levels [29]. Other studies of patients with comparable severity of renal dysfunction have observed a similar prevalence of LVH [13]. Our results, taken in conjunction with these previous studies on the effects of EPO on LVH suggest that patients who benefit most from EPO therapy are those with lower hemoglobin levels (<10 g/dL) and those with preexisting LVH.

Why use of rhEPO would improve left ventricular parameters is not completely clear, although emerging evidence provides several possible explanations. In our study, rhEPO treatment increased hemoglobin by approximately 2 g/dL as expected, which would augment oxygen-carrying capacity, assuming no change in cardiac output. However, we found that the beneficial association of rhEPO on reducing LVMI persisted after adjustment for change in hemoglobin level during follow-up. EPO is increasingly recognized as playing as playing diverse roles in the cardiovascular system outside of erythropoiesis [30–32]. Several direct beneficial effects of rhEPO have been proposed, including inhibition of myocardial cell apoptosis and favorable cardiac remodeling [33–36], phosphatidylinositol 3′-kinase (PI3K)/Akt-mediated protection of cultured myocytes from hypoxia-induced apoptosis [37–39], and improved left ventricular function and decreased apoptosis following ischemia/reperfusion (I/R) injury in the myocardium [37, 39–42]. EPO does not appear to act through influencing sympathetic nerve activity or cardiopulmonary baroreceptor sensitivity [43]. Our results are consistent with the hypothesis of direct beneficial effects of EPO on the myocardium, although the mechanisms for these actions remain unclear.

Use of EPO for normalizing hemoglobin levels has been reportedly associated with potential adverse effects on blood pressure as well as serum creatinine levels [44]. During a 6-month treatment period, we found neither significant changes in systolic or diastolic blood pressures nor any changes in the use or type of antihypertensive therapies. In addition, while Cockcroft-Gault creatinine clearance decreased at a faster crude rate among patients receiving rhEPO compared with controls, this difference was no longer significant after controlling for potential confounders. In fact, previous investigators have suggested that treatment of anemia with erythropoietin in chronic kidney disease may, in fact, be associated with a slower progression of renal failure [45–47], which was not observed in our study. In these previous studies where EPO treatment was associated with a slower progression of disease, subjects with diabetes mellitus were either excluded or were enrolled in relatively modest numbers [45–47]. Our study population included a significant number of subjects with diabetes, with the group having anemia and receiving rhEPO having somewhat

more diabetics than the control arm, although the difference was not statistically significant (30.0% vs. 19.7%, respectively) ($P = 0.23$). Given the known rapid progression of diabetic nephropathy, this may have masked possible beneficial effects of EPO on renal function in our study. Additionally, as a requirement of the steering committee and institutional review board in the institution where the research was conducted, data were analyzed at an interim 6-month follow-up period and the trial terminated, if a significant benefit were found. In previous studies demonstrating that EPO appeared to beneficial on slowing progression of renal disease, this effect was noted at 12 to 36 months of follow-up [45–47].

As an open-label, nonrandomized trial, we cannot completely exclude effects of residual confounding or cointervention in evaluating the impact of rhEPO. Yet, while small differences existed between anemic and nonanemic subjects in baseline renal function that may help to explain the presence and severity of anemia between groups, there were no significant differences in relevant patient characteristics, comorbidities, or other relevant therapies at baseline or during follow-up. While our study did not address the effects of rhEPO on clinical cardiovascular events or functional status (e.g., New York Heart Association Class for heart failure symptoms), LVH is well-established as a potent risk factor for cardiovascular death in patients with renal disease [14]. Finally, our study was also unable to determine the specific reasons for the beneficial effect observed with receipt of rhEPO therapy in the setting of advanced chronic renal insufficiency and anemia.

CONCLUSION

LVH is a common complication in chronic renal insufficiency, and lower hemoglobin level is associated with an increased risk of LVH. Short-term treatment with rhEPO in patients with severe chronic renal insufficiency complicated by anemia and LVH was associated with a reduction in LVMI. Our results are in agreement with and extend previous studies on the effects of EPO [27, 28]. The magnitude of change in LVMI obtained in our study, if sustained, could lead to the reversal of LVH in mild cases and may have a demonstrable impact on cardiac mortality if it can be achieved in a large at-risk population such as those with chronic renal insufficiency. Indeed, a recent study by Khan et al [48] shows that pre-ESRD treatment with EPO is associated with decreased mortality on dialysis. Given the potential implications of our findings to the growing chronic renal insufficiency population, future randomized trials of the effect of treating to different target hemoglobin levels with rhEPO on cardiovascular and other relevant outcomes in patients with chronic renal insufficiency and LVH are needed.

Appendix. Members of the Spanish Group for the Study of Left Ventricular Hypertrophy in Pre-dialysis Patients

Hospital	Members
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H. Universitario de Canarias	Víctor Lorenzo, Margarita Rufino Delgado, Fundaciûn Jiménez Díaz, Belén Marrûn, and Carlos Caramelo Díaz
H. La Paz	José Luis Miguel Alonso
H. Clínico San Carlos	Francisco Coronel and Jose Antonio Herrero
H. Son Dureta	Antonio Morey and Rosario Bernabeu
H. Lluís Alcanyís	Juan Carlos Alonso and Florencio Sigenza
H. Josep Trueta	Martí Vallës Prats and Josep Maria Bronsoms
H. General Albacete	José Portolés
H. General Asturias	Julio Herrera and Pedro Vidau
H. Candelaria	Jesus Chaín and Fernando Moujir
H. Bellvitge	Alberto Martínez Castelao and Francesc Moreso
H. Teruel	Juan José Bellvis and Antonio Gascûn
H. del Aire	Emilio González Parra and Miguel Rodeles del Pozo
H. Torrecardenas	Maria Dolores del Pino
H. Princesa de Espaóa	Francisco Fernandez

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