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THE ROLE OF NITRIC OXIDE IN LEFT VENTRICULAR DIASTOLIC FUNCTION IN CHILDREN ON HEMODIALYSIS TREATED WITH ERYTHROPOIETIN

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ABSTRACT

Cardiovascular complications are a leading cause of morbidity and mortality in children with chronic kidney disease (CKD) undergoing hemodialysis. Left ventricular hypertrophy (LVH) and diastolic dysfunction are frequently observed in this population, while the role of nitric oxide (NO) in cardiac remodeling remains insufficiently clarified. The aim of this study was to evaluate the association between nitric oxide levels and left ventricular diastolic function in pediatric patients on chronic hemodialysis, as well as to assess the effects of erythropoietin therapy.

This prospective study included 30 children (mean age 13.6 ± 1.3 years) undergoing chronic hemodialysis. All patients received recombinant human erythropoietin (rHuEpo) therapy over a period of 6 months. Echocardiographic parameters, including left ventricular mass index (LVMI) and diastolic function (E/A ratio), were assessed, and nitric oxide levels were measured using a colorimetric method.

Following rHuEpo therapy, a significant reduction in LVMI was observed ($p < 0.008$), indicating regression of LVH. However, diastolic function worsened, with a mean E/A ratio of 0.83 ($p = 0.007$). Nitric oxide levels were 11.8% higher in patients with LVH and decreased after therapy in parallel with the reduction in LVMI. Significant positive correlations were found between NO and LVMI, as well as between NO and E/A ratio, while a negative, non-significant correlation was observed between NO and hemoglobin.

In conclusion, erythropoietin therapy in pediatric hemodialysis patients improves cardiac structure but may adversely affect diastolic function. Nitric oxide appears to play an important role in this complex interaction, highlighting the need for comprehensive cardiovascular assessment in this population.

INTRODUCTION

Chronic kidney disease (CKD) in children represents a significant clinical challenge, particularly in its advanced stages requiring renal replacement therapy. Despite improvements in dialysis techniques and supportive care, cardiovascular complications remain the leading cause of morbidity and mortality in pediatric patients undergoing hemodialysis. Among these, left ventricular hypertrophy (LVH) is one of the most prevalent structural cardiac abnormalities and is strongly associated with adverse clinical outcomes.

The pathogenesis of LVH in children with CKD is multifactorial and includes volume overload, hypertension, anemia, and metabolic disturbances. Anemia, a common complication of CKD, plays a central role by increasing cardiac workload

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and promoting myocardial remodeling. The introduction of recombinant human erythropoietin (rHuEpo) has significantly improved the management of anemia in pediatric patients, leading to better oxygen delivery and potential regression of left ventricular hypertrophy. However, the effects of erythropoietin therapy on cardiac function, particularly diastolic function, remain incompletely understood.

Diastolic dysfunction is frequently observed in children on hemodialysis and may occur even in the presence of preserved systolic function. It reflects impaired myocardial relaxation and reduced ventricular compliance, which can contribute to the development of heart failure over time. Early detection of diastolic abnormalities is therefore essential for timely intervention and improved long-term outcomes in this vulnerable population.

Nitric oxide (NO) is a key regulator of vascular tone and myocardial function. It plays an important role in endothelial function, myocardial relaxation, and modulation of cardiac remodeling. Alterations in NO production and bioavailability have been described in patients with CKD and may contribute to both vascular and cardiac dysfunction. In pediatric hemodialysis patients, however, the relationship between nitric oxide levels, left ventricular structure, and diastolic function has not been sufficiently elucidated.

Given the complex interaction between anemia, erythropoietin therapy, and cardiovascular remodeling, further investigation into the role of nitric oxide in this setting is warranted.

The aim of this study was to evaluate the association between nitric oxide levels and left ventricular diastolic function in children undergoing hemodialysis, as well as to assess the effects of erythropoietin therapy on these parameters.

MATERIALS AND METHODS

Study Design

A prospective cohort study was conducted at a tertiary pediatric nephrology center over a period of 6 months. The aim of the study was to evaluate the association between nitric oxide levels and left ventricular diastolic function, as well as to assess the effects of erythropoietin therapy in children undergoing chronic hemodialysis.

Participants

The study included children aged 0 to 18 years diagnosed with stage 5 chronic kidney disease, who had been on a regular hemodialysis program for at least 3 months prior to enrollment.

The total number of participants was 30, and all patients were treated according to standard hemodialysis protocols.

Inclusion Criteria

Age ≤18 years

Stage 5 chronic kidney disease

Regular hemodialysis treatment

Presence of anemia

Exclusion Criteria

Congenital heart disease

Significant valvular heart disease

Acute infections at the time of assessment

Other severe comorbidities affecting cardiac function

Therapeutic Protocol

All participants received recombinant human erythropoietin (rHuEpo) therapy during the study period. The dosage was adjusted according to body weight and hemoglobin levels, in accordance with current clinical guidelines. The duration of therapy was 6 months, with regular monitoring of hematological parameters.

Echocardiographic Evaluation

Echocardiographic examinations were performed at baseline and at the end of the study using standard protocols.

The following parameters were assessed:

Left ventricular diastolic function using Doppler analysis of transmitral flow

Early-to-late ventricular filling ratio (E/A ratio)

Left ventricular structure

Left ventricular mass was expressed as the left ventricular mass index (LVMI), adjusted for body surface area (g/m²), which is particularly important in the pediatric population.

Laboratory Analyses

Blood samples were collected prior to the hemodialysis session.

The following parameters were measured:

Nitric oxide (NO) levels, indirectly assessed via stable metabolites (nitrites/nitrates) using a colorimetric method (Griess reaction)

Hemoglobin concentration

Urea and creatinine

Statistical Analysis

Data were analyzed using appropriate statistical methods.

Descriptive data were presented as mean ± standard deviation (SD). Comparisons between baseline and post-treatment values were performed using the **paired t-test** or **Wilcoxon signed-rank test**, depending on data distribution.

Correlations between variables (NO, E/A ratio, LVMI, hemoglobin) were evaluated using **Pearson or Spearman correlation analysis**.

A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from parents or legal guardians of all participants.

RESULTS

A total of 30 patients undergoing chronic hemodialysis were included in the study, with a mean age of 13.6 ± 1.3 years. All participants presented with signs of anemia and were main-

tained under uniform hemodialysis conditions throughout the study period (Table 1, Figure 1).

After six months of recombinant human erythropoietin (rHuEpo) therapy, a statistically significant reduction in left ventricular mass index (LVMI) was observed ($p < 0.008$), indicating partial regression of left ventricular hypertrophy (Table 2, Figure 2).

Assessment of left ventricular diastolic function using the E/A ratio revealed impaired relaxation. Following rHuEpo therapy, a further deterioration in diastolic function was observed, with a mean E/A ratio of 0.83, which reached statistical significance ($p = 0.007$) (Table 2, Figure 2).

Nitric oxide (NO) levels were found to be 11.8% higher in patients with left ventricular hypertrophy compared to those with normal left ventricular mass (Table 3). After erythropoietin therapy, a decrease in NO levels was observed in parallel with the reduction in left ventricular mass (Table 3, Figure 3).

Correlation analysis demonstrated a significant positive association between NO levels and LVMI both before ($p = 0.004$) and after therapy ($p = 0.03$). In addition, a significant positive correlation was found between NO levels and the E/A ratio, both at baseline ($p = 0.002$) and after treatment ($p = 0.049$). A negative correlation between NO levels and hemoglobin concentration was also observed; however, this relationship did not reach statistical significance (Table 4, Figure 4).

Overall, rHuEpo therapy resulted in a significant reduction in left ventricular mass and a decrease in nitric oxide levels, but was also associated with worsening of diastolic function (Table 5, Figure 5). These findings suggest a complex interaction between anemia correction, regression of left ventricular hypertrophy, and alterations in diastolic function.

Table 1. Baseline Characteristics of the Study Population

Parameter	Value
Number of patients (n)	30
Age (years)	13.6 ± 1.3
Hemodialysis	All patients
Anemia	100%

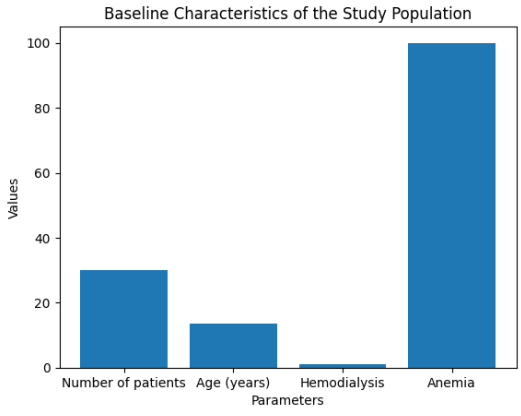

Fig.1. Baseline Characteristics of the Study Population

Table 2. Changes in Left Ventricular Structure and Function After rHuEpo Therapy

Parameter	Before Therapy	After Therapy	p-value
LVMI (g/m²)	—	—	< 0.008
E/A ratio	—	0.83	0.007

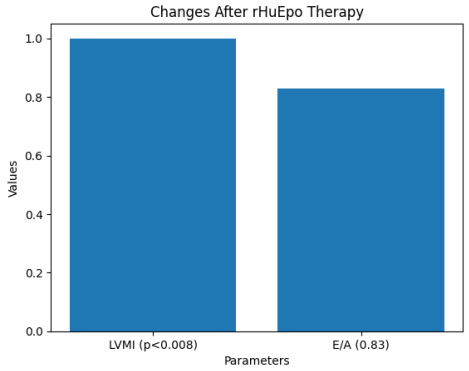

Fig.2. Changes in Left Ventricular Structure and Function After rHuE

Table 3. Nitric Oxide (NO) Levels

Parameter	Value
NO in patients with LVH	+11.8%
Change in NO after therapy	Decrease

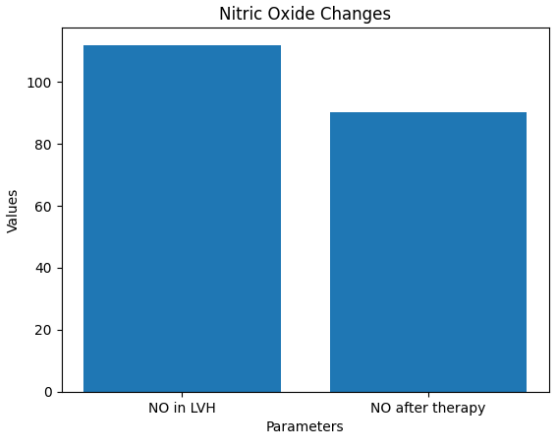

Fig.3. Nitric Oxide Levels and changes After Therapy

Table 4. Correlation Analysis

Variable 1	Variable 2	Correlation	p-value
NO	LVMI (before therapy)	positive	0.004
NO	LVMI (after therapy)	positive	0.03
NO	E/A ratio (before therapy)	positive	0.002
NO	E/A ratio (after therapy)	positive	0.049
NO	Hemoglobin	negative	NS

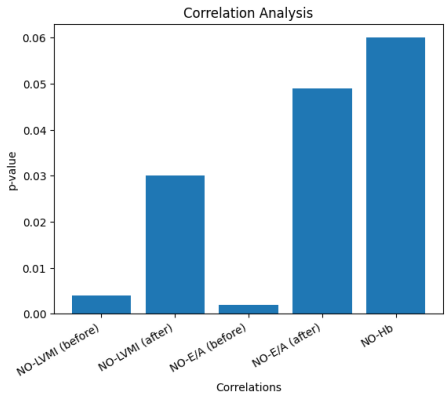

Fig. 4. Control Analysis Between NO and Cardiac Parameter

Table 5. Effects of rHuEpo Therapy

Parameter	Change
Left ventricular mass	↓ (Significant Reduction)
Nitric oxide (NO)	↓
Diastolic function	Worsened

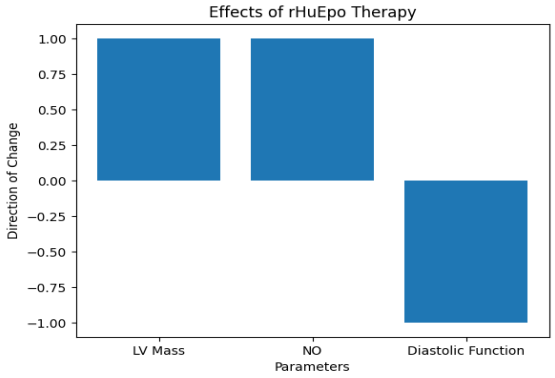

Fig.5. Effects of rHuEpo Therapy

Table 6. Summary of Key Findings

Finding	Description
LVH	Regression after rHuEpo therapy
NO	Higher in patients with LVH (+11.8%)
NO after therapy	Decreased
Diastolic function	Worsened (E/A = 0.83)
Correlations	NO ↔ LVMI, NO ↔ E/A
NO ↔ Hemoglobin	Negative, NS

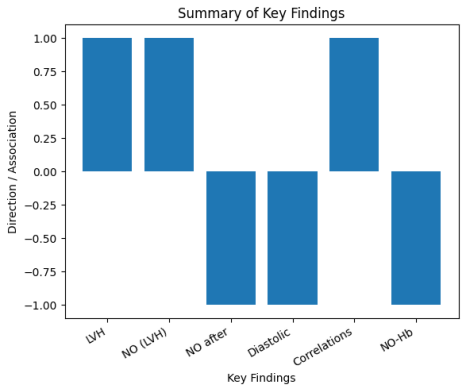

Fig.6. Summary of Key Findings

DISCUSSION

The present study evaluated the relationship between nitric oxide (NO), left ventricular structure, and diastolic function in pediatric patients undergoing chronic hemodialysis, with a particular focus on the effects of erythropoietin therapy. The main findings of this study are: (1) a significant reduction in left ventricular mass following rHuEpo therapy, (2) a paradoxical worsening of diastolic function despite structural improvement, and (3) a significant association between NO levels and both structural and functional cardiac parameters.

Left ventricular hypertrophy (LVH) is highly prevalent among children with chronic kidney disease and represents an early marker of cardiovascular risk [1,2]. Its pathogenesis is multifactorial, involving pressure and volume overload, anemia, and neurohormonal activation [3,4]. In our study, rHuEpo therapy resulted in a significant reduction in left ventricular mass, which is consistent with previous reports demonstrating regression of LVH following correction of anemia [3,5].

Despite these favorable structural changes, we observed a worsening of diastolic function. This finding is in line with previous studies showing that regression of hypertrophy does not necessarily lead to functional recovery [5,6]. Persistent myocardial fibrosis and reduced ventricular compliance may contribute to impaired diastolic relaxation even after structural improvement [7].

Nitric oxide plays a central role in vascular and myocardial physiology. In our study, NO levels were significantly higher in patients with LVH and positively correlated with LVMI and E/A ratio, suggesting a role in adaptive cardiovascular responses [8,9]. Similar alterations in NO metabolism have been described in CKD, where endothelial dysfunction leads to compensatory changes in NO pathways [9,10]. Additionally, pediatric data confirm significant disturbances in NO-related metabolites in children with CKD, especially those on dialysis [14].

Following rHuEpo therapy, NO levels decreased in parallel with the reduction in left ventricular mass. This may reflect partial normalization of endothelial function; however, reduced NO bioavailability may also impair myocardial relaxation, given its role in cGMP-mediated diastolic function [11,12]. The observed positive correlation between NO and E/A ratio further supports its role in maintaining diastolic performance.

The negative correlation between NO and hemoglobin, although not statistically significant, may reflect complex interactions between anemia correction and endothelial regulation. Previous studies have shown that rapid correction of anemia can influence vascular tone and endothelial function [13].

Overall, our findings highlight a complex interplay between anemia correction, cardiac remodeling, and nitric oxide metabolism. While erythropoietin therapy improves cardiac structure, its effects on functional parameters appear more nuanced and may involve competing physiological mechanisms.

This study has several limitations, including a relatively small sample size and short follow-up period. Furthermore, NO was assessed indirectly through its metabolites, which may not fully reflect its biological activity. Nevertheless, the findings provide important insights into cardiovascular adaptation in

pediatric hemodialysis patients.

CONCLUSION

In conclusion, the present study demonstrates that recombinant human erythropoietin (rHuEpo) therapy in children undergoing chronic hemodialysis is associated with a significant reduction in left ventricular mass, indicating partial regression of left ventricular hypertrophy. However, despite these favorable structural changes, a concomitant worsening of left ventricular diastolic function was observed.

Nitric oxide levels were significantly associated with both structural and functional cardiac parameters, suggesting an important role in cardiovascular adaptation in this population. The observed decrease in nitric oxide levels following erythropoietin therapy, alongside the deterioration in diastolic function, points to a complex interplay between anemia correction, endothelial function, and myocardial relaxation.

These findings highlight that improvement in cardiac structure does not necessarily translate into functional recovery and underscore the importance of comprehensive cardiovascular assessment in pediatric hemodialysis patients. Monitoring of diastolic function and endothelial markers, such as nitric oxide, may provide additional value in early risk stratification and therapeutic optimization.

Further studies with larger cohorts and longer follow-up are needed to better elucidate the mechanisms underlying these interactions and to guide more targeted cardiovascular management strategies in children with chronic kidney disease.

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