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The effect of intensive hemodialysis on pulmonary arterial pressure and left ventricular systolic function in patients with end-stage renal disease; a prospective clinical trial

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ABSTRACT

Introduction: End-stage renal disease (ESRD) requires hemodialysis or kidney transplantation for the patients to survive.
Objectives: The present study was conducted to examine whether intensive hemodialysis and hemoglobin (Hb) concentration correction can improve left ventricular (LV) function and pulmonary arterial hypertension in ESRD patients?
Patients and Methods: This prospective clinical trial was designed to examine patients referring to public hospitals in Ahvaz, Iran, in 2016-2017. All the patients treated with intensive hemodialysis for two months were included in the study. The Hb concentration was corrected by the subcutaneous injection of erythropoietin at the dose of 50-150 IU/kg three times per week.
Results: Thirty-one ESRD patients with high pulmonary arterial pressure participated in this study. After the intervention, blood Hb levels increased significantly in the ESRD patients from 9.20±1.39 g/dL to 10.96 ± 1.01 g/dL ($P<0.0001$). Pulmonary arterial pressure decreased significantly from 53.52 ± 10.63 mmHg to 43.32 ± 10.92 mm Hg ($P<0.0001$). Left ventricular ejection fraction increased significantly based on the visual assessment and Simpson's method (2D echocardiography) from 41.06 ± 10.76 to 43.00 ± 11.28 and 46.26 ± 13.72 to 48.36 ± 13.90, respectively ($P<0.0001$). Absolute value of two dimensional global longitudinal strain (GLS) increased significantly from 13.99 ± 5.05 to 15.14 ± 5.32 ($P<0.0001$) after the intervention.
Conclusion: Intensive hemodialysis for two months resulted in a significant increase in Hb concentrations, improved the LV systolic function and decreased pulmonary hypertension in ESRD patients.
Trial registration: The trial protocol was approved in the Iranian Registry of Clinical Trials (identifier: IRCT20180212038705N1, https://www.irct.ir/trial/29593; Ethic code: IR.AJUMS.REC.1396.911).

Implication for health policy/practice/research/medical education:
In our prospective clinical trial on 31 patients with high pulmonary arterial pressure, we found intensive hemodialysis for two months resulted in a significant increase in Hb levels in patients and a decrease in pulmonary arterial pressure.
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Introduction

End-stage renal disease (ESRD) requires hemodialysis or kidney transplantation for the patients to have a proper quality of life (1). According to the United States Renal Data System (USRDS) reports released in 2015, there were approximately 500 000 cases of ESRD receiving hemodialysis treatment and more than 40% had received kidney transplantation (2).

Pulmonary hypertension (PHT) is a progressive disorder that leads to cardiovascular, pulmonary and

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systemic diseases and other complications with a significant morbidity and mortality (3). Pulmonary arterial hypertension (PAH) is characterized by right ventricular (RV) dysfunction and increases pulmonary artery pressure, thus resulting in the malfunction of the left ventricular (LV) myocardium (4). Screening for PAH among patients undergoing hemodialysis is therefore vital (5,6). Compared to conventional hemodialysis, intensive hemodialysis could be associated with better survival rates and improved physical and mental health and quality of life (7,8).

Anemia is an independent predictor of renal dysfunction (such as ESRD) and poor erythropoietin production (9). Anemia may also have a positive correlation with cardiovascular disorders such as pulmonary arterial pressure, right ventricular hypertrophy, RV failure and premature death (9,10).

Objectives

The present study was conducted to examine whether intensive hemodialysis and hemoglobin concentration correction can improve LV function and pulmonary arterial pressure in ESRD patients.

Patients and Methods

Study design

In this prospective clinical trial, the inclusion criteria consisted of giving informed consent, Patient with ESRD, age over 18 years and systolic pulmonary artery pressure (sPAP)> 40 mm Hg. The exclusion criteria consisted of having pulmonary parenchymal and vascular diseases, such as acute or chronic pulmonary thromboembolism and chronic obstructive pulmonary disease, serum ferritin levels less than 200 ng/mL, transferrin saturation less than 20% and valvular heart diseases such as flail leaflet of the mitral valve, a recent myocardial infarction and an acute illness altering hematocrit levels, such as acute bleeding or acute infection.

Therapeutic intervention, clinical and laboratory

All the patients were treated with intensive hemodialysis for two months. They received hemodialysis four times a week after reaching dry weight. The mean hemoglobin (Hb) before taking erythropoietin and after Hb correction was measured and recorded at the end of the study (i.e. two months later). Hemoglobin concentration was corrected by the subcutaneous injection of erythropoietin at the dose of 50-150 IU/kg three times per week.

Standard echocardiography and strain analysis by speckled tracking method

Two-dimensional echocardiography examination was performed for all the patients, including the two-dimensional method, color Doppler study and tissue Doppler echocardiography (global longitudinal strain by the speckle tracking method), using Vivid E9 ultrasound system (USA, GE Ultrasound) before and after the intensive hemodialysis. Transthoracic echocardiography was performed to determine the LV systolic function using the biplane Simpson's method at least three times, and the mean value was calculated for each patient. Other echocardiographic parameters, including PAP and LV diastolic function, were recorded for all the patients and global longitudinal strain (GLS) was measured by the 2D method. GLS using speckle tracking echocardiography offline analysis with 2D speckle tracking software was performed for the evaluation of LV GLS. Apical 4, 3 and 2 chamber views were selected (Figure 1). The longitudinal strain was calculated based on the entire traced LV contour (Figure 2). GLS by 2D STE, strain's curves (Figure 3) and a bull's eye map of each segment (Figure 4) were finally determined. Tricuspid valve regurgitation velocity was measured through the apical four chamber view using continuous wave Doppler echocardiography. sPAP was then calculated according to the modified Bernoulli equations, as follows:

$$PASP = 4 \times (Tricuspid\ regurgitation\ jet\ velocity)^2 + (Estimated\ right\ atrial\ pressure)$$

In this study, a sPAP above 40 mm Hg was defined as a criterion for the presence of PHT.

Left ventricular systolic dysfunction was defined as LVEF<50%. Left ventricular diastolic function (LVDD) was evaluated according to diastolic guidelines (Impaired relaxation; early mitral inflow peak velocity/ late mitral inflow velocity (E/A)< 0.8, deceleration time (DT) >240 ms and Early mitral inflow peak velocity/early diastolic mitral annular velocity (E/e' at the septal annulus) <0.8, pseudo-normal pattern: (E/A = 0.8-2, DT = 160-240 ms and increased E/e') and restrictive pattern; (E/A >2, DT <160 ms and increased E/e' at the septal annulus).

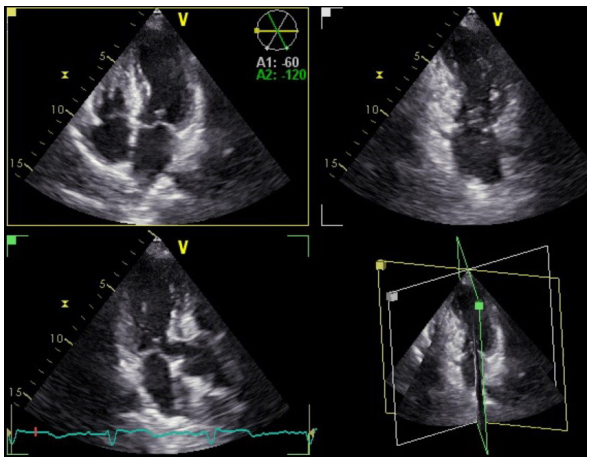

Figure 1. Two-, three- and four-chamber views for evaluation of longitudinal strain.

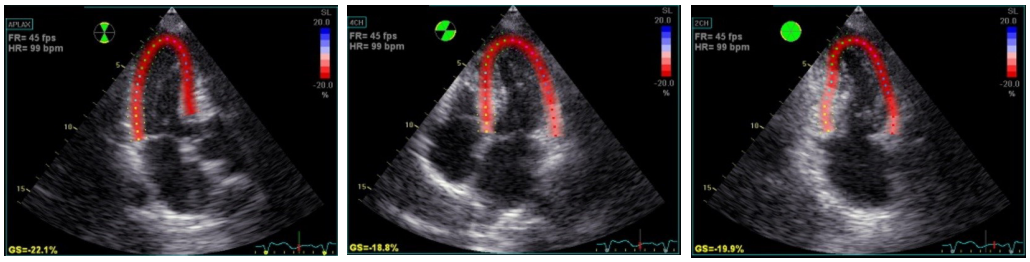

Figure 2. LV contour was traced in all three views for evaluation of longitudinal strain.

Ethical issues

The study was in accordance with the Declaration of Helsinki and its later amendments. This paper was extracted from the residential thesis of Forough Darabi, at the department of internal medicine and advanced echocardiography ward of Ahvaz Jundishapur University of Medical Sciences. This prospective clinical trial was approved by the ethics committee of the Ahvaz Jundishapur University of Medical Sciences (# IR.AJUMS.REC.1396.911). All the participants were informed about the study aims and procedures. Informed consent process was performed for all the patients. The trial protocol was also approved in the Iranian Registry of Clinical Trials (identifier: IRCT20180212038705N1, https://www.irct.ir/trial/29593).

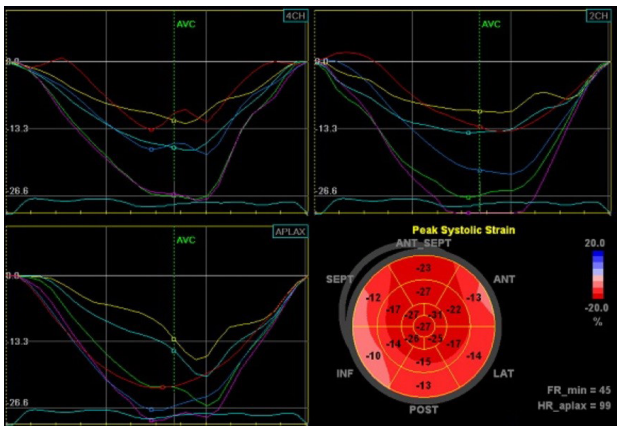

Figure 3. Bull's eye map and strain curves.

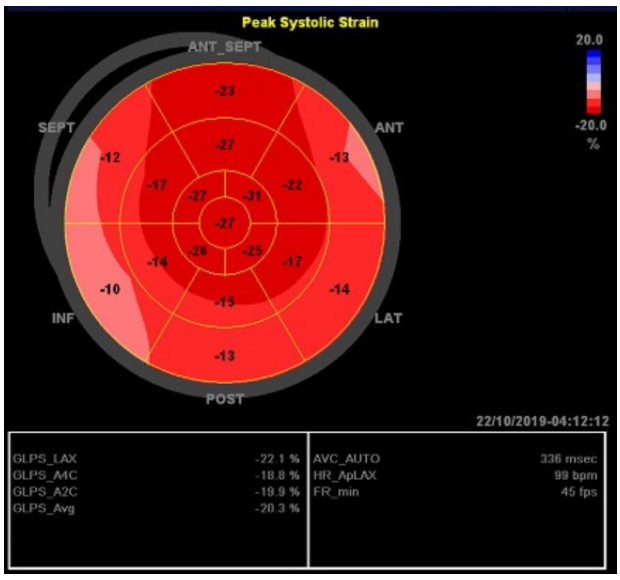

Figure 4. Bull's eye map with average global longitudinal strain (GLS) of 2, 3 and 4 chamber views.

Statistical analysis

After collecting the data, descriptive statistics including mean, standard deviation and frequency were measured. Depending on the normality of the distribution of the quantitative variables, the independent t-test or Mann-Whitney test was used, and in the case of the qualitative variables, the chi-square test was used to compare the mean of the variables between the two groups. A *P* value less than 0.05 was considered statistically significant. All the analyses were performed in SPSS 20 for Windows.

Results

Intensive dialysis and Hb correction were carried out for the 31 ESRD patients with high PAH (Figure 5). The mean age of the participants was 54.68 ± 14.85 (range 29 to 85) years. The mean duration of the disease was 3.45 ± 2.42 (range 1 to 9) years and the duration of dialysis was 3.43 ± 2.26 (range 1 to 9) years.

The most commonly used medication was erythropoietin (93.5%). Table 1 presents the other baseline characteristics of the patients.

Plasma Hb levels increased significantly after the intervention ($P<0.0001$). Additionally, at the end of the intervention, ferritin levels decreased significantly compared to the baseline (Table 2).

The PAP levels decreased significantly in the ESRD patients after the intervention ($P<0.001$). After the completion of the intervention, LVEF values increased significantly ($P<0.001$). In addition, the absolute value of GLS (using the 2D method) increased significantly after the intensive dialysis ($P<0.001$; Table 2).

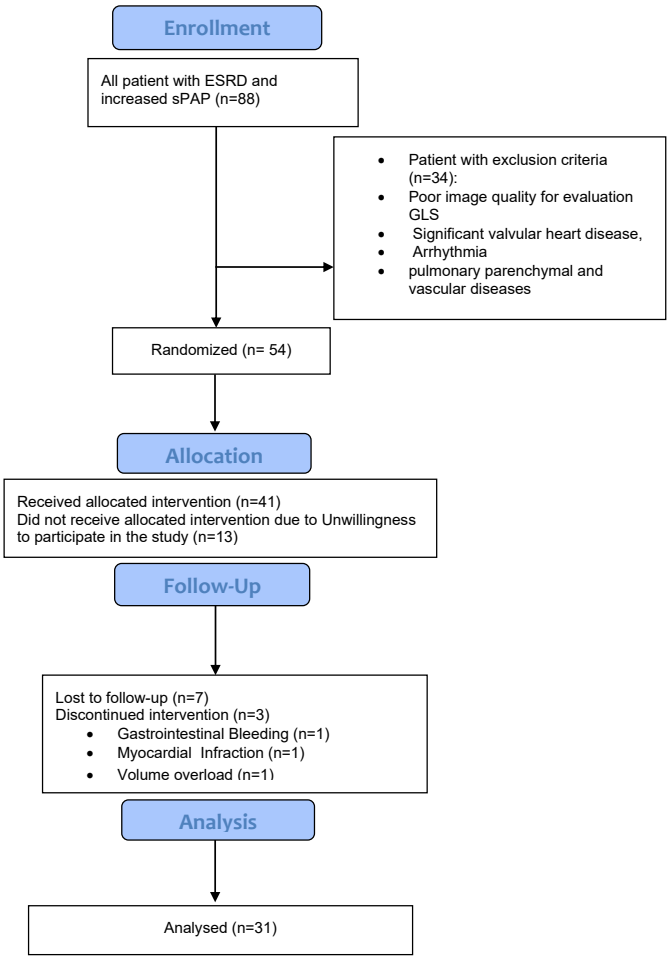

Figure 5. Flowchart of the study.

Discussion

Cardiovascular disease remains the leading cause of mortality in renal transplantation and ESRD patients (11,12). PHT is defined as an increase in one of the factors affecting pulmonary vascular resistance that may be considered an independent risk factor involved in the death of hemodialysis patients (13,14). Although anemia causes several abnormalities in chronic kidney disease, including erythropoietin production deficiency, reduced erythrocyte survival and uremic accumulation, it is also proposed as a significant risk factor for cardiovascular diseases with adverse outcomes (15,16). Walker et al demonstrated a close relationship between cardiovascular pathology and anemia in patients with elevated serum creatinine (17). Correcting anemia and maintaining Hb levels in the standard range using erythropoiesis stimulating agents are very important for managing these patients (18-20). Although intensive hemodialysis may be associated with an increased risk of clinical problems (21,22), many studies have reported that intensive hemodialysis can improve cardiac mass and decrease intradialytic hypotension with favorable clinical outcomes (7,8,23,24).

The results of the present study showed that Hb levels increased significantly in patients after two months of intensive hemodialysis (four days per week) and erythropoietin administration. This intervention also reduced PAP significantly and improved cardiac function in ESRD patients. The improvement of cardiovascular function after Hb correction with erythropoietin and intensive hemodialysis has formerly been reported in some other studies. Chan et al showed that nocturnal hemodialysis, which is an emerging mode of intensive hemodialysis, improved uremic clearance, Hb levels and hematopoietic progenitor cell function significantly in patients with ESRD (20). In a similar study by Nehus et al, cardiac function improved after beginning intensive hemodialysis in pediatric patients with ESRD (25). At the beginning of the present study, Hb concentrations were higher than 11 g/dL in 12.26% of the patients, while 62.29% had normal Hb concentrations, which indicates the effectiveness of the intervention.

Since metabolic disorders are associated with ESRD, hemodialysis might cause a significant reduction in

Table 1. Baseline characteristics of patients

Variables	Number (%)
Age (year)[a]	54.68 ± 14.85 (29-85)
Gender/Female	16 (51.6)
BMI (kg/m²)	
18-20	8 (25.8)
20-25	17 (54.8)
25-30	6 (19.4)
Other illness	
DM	15 (48.4)
HTN	24 (77.4)
Smoking	9 (29.0)
Duration of ESRD (year)[a]	3.45 ± 2.42 (1-9)
Duration of hemodialysis (year)[a]	3.43 ± 2.26 (1-9)
History of drug use	
CaCO3	25 (80.6)
Nephrovit	15 (48.4)
Sevelamer	20 (64.5)
Erythropoietin	29 (93.5)
Valsartan	22 (70)
Amlodipine	8 (25.8)
Lasix	11 (35.5)
Insulin	15 (48.4)

[a] Data are expressed as mean ± SD (Min-Max).
Note: BMI, body mass index; DM, diabetes mellitus; HTN, Hypertension.

Table 2. Para-clinic and echocardiographic data of patients (pre-intervention and post-intervention

Variables	Patients		*P* value*
	Pre-intervention	Post-intervention	
Hb (g/dL)	9.20 ± 1.39 (6.70-11.80)	10.96 ± 1.01 (9.00-13.50)	0.0001
Cr (mg/dL)	7.40 ± 2.34 (4.10-13.00)	5.61 ± 1.81 (3.10-10.30)	0.005
Ferritin (ng/mL)	358.11 ± 183.21 (200-800)	256.27 ± 148.71 (100-570)	0.0001
PAP (mm Hg)	53.52 ± 10.63 (40-85)	43.32 ± 10.92 (25-76)	0.0001
LVEF% (by visual assessment)	41.06 ± 10.76 (18-53)	43.00 ± 11.28 (18-55)	0.0001
LVEF % (Simpson method)	46.26 ± 13.72 (20.0-65.0)	48.36 ± 13.90 (20.00-73.00)	0.0001
GLS (3D)	13.99 ± 5.05 (6.5-24.0)	15.14 ± 5.32 (7.0-26.0)	0.0001
TR valve problems			
Mild	4 (12.90 %)	9 (29.03 %)	0.074
Moderate	21 (67.74 %)	19 (61.29 %)	
Moderate to severe	5 (16.13 %)	3 (9.68 %)	
Severe	1 (3.23 %)	0	
LVDD			
Impaired relaxation	3 (9.7 %)	8 (25.8 %)	0.006
Pseudo-normal pattern	20 (64.5 %)	17 (54.8 %)	
Restrictive pattern	8 (25.8 %)	6 (19.4)	

Note. ESRD: end-stage renal disease; Hb: hemoglobin; Cr: creatinine; PAP: pulmonary arterial pressure; LVEF: Left ventricular ejection fraction; GLS, global longitudinal strain; TR: Tricuspid valve regurgitation; LVDD: Left ventricular diastolic dysfunction.
All the variables are presented as mean ± standard deviation (Min-Max).
P values ≤ 0.05 are considered significant.

end-systolic and end-diastolic LV volumes, systolic and diastolic blood pressure and increases in LV torsion and ejection fraction (24,26,27). Chen et al showed that LV longitudinal strain using 3D speckle tracking and global function is superior in hemodialysis compared to non-hemodialysis patients (28). The results of current study also showed improvements in cardiac function and systolic and diastolic parameters of the left ventricle after intensive dialysis. A significant increase was reported in LVEF and also in GLS according to the echocardiographic findings. At the end of the intervention, diastolic LVDD also improved significantly compared to the beginning of the study.

In general, regular echocardiographic evaluation along with other effective therapies, such as intensive hemodialysis, is important for the early identification of cardiac involvement in patients with LV dysfunction and high PAP.

Conclusion

The results of this study showed that intensive hemodialysis for two months results in a significant increase in Hb levels in patients and a decrease in PAP. In addition, the evaluation of ventricular function showed significant improvements in LVEF, GLS and LV diastolic function. The treatment regimen, however, did not have any significant effects on tricuspid regurgitation and other heart valve abnormalities. As a result of the regimen used, intensive hemodialysis and Hb correction with erythropoietin can be used to reduce pulmonary hypertension, increase serum Hb, and improve cardiac function in ESRD patients.

Limitations of the study

In the present study, PAP was measured using non-invasive Doppler echocardiography without direct invasive measurements (e.g. right heart catheterization). Some studies using invasive methods, however, have shown a correlation between sPAP measurements by Doppler echocardiography (29,30).

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Authors' contribution

Design of the work: NA, SAH. Data collection, design and preparation of the figures: NA, FD, SAH. Data analysis and interpretation: NA and MM. Drafting the article: NA and FD. Critical revision of the article: NA, SAH and MM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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