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Title Page

Title: A single bout of hybrid intradialytic exercise did not affect left-ventricular function in exercise-naïve dialysis patients: a randomized, cross-over trial

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Running Title: Intradialytic exercise and cardiac function

Abstract

Introduction: Cardiovascular diseases are the leading cause of mortality in end-stage renal disease (ESRD) patients, especially those receiving hemodialysis (HD) therapy. HD has many side effects that are related to patients' hearts; such as recurrent myocardial ischemia and global or segmental left-ventricular dysfunction, which is associated with intradialytic hypotension, long-term loss of systolic function, and high incidence of cardiovascular events and death. Systematic exercise training has a beneficial effect on measures of cardiovascular fitness and reducing cardiovascular risk factors in ESRD. Whether there is an acute benefit of exercise during HD on left-ventricular function is not well known. The current study aimed to investigate whether a single bout of hybrid (aerobic and resistance) intradialytic exercise could affect left-ventricular function during HD sessions.

Methods: Twenty-one exercise naïve and clinically stable HD patients participated in the study. All participants completed two different HD trials on two different days, separated by one week: (1) standard HD and (2) HD including a single bout of hybrid intradialytic exercise. Hybrid intradialytic training included the usual intradialytic cycling followed by resistance training using elastic bands and dumbbells. Echocardiographic assessment of left- ventricular function was completed before HD, half an hour before the end of HD, and 30 min after the end of HD.

Results: Cohort data for left-ventricular function indices were not different between trials and did not change across time in either the standard HD or HD plus exercise trial. Cohort data for the change in ejection fraction from baseline to during HD did mask considerable inter-individual variability (HD - 0±15; HD plus exercise (-2±20). Despite this, the variability was not mediated by the addition of intradialytic hybrid exercise.

Conclusions: A single bout of hybrid intradialytic exercise did not affect left-ventricular function during the HD therapy. It is important to determine whether chronic exercise training could beneficially affect left-ventricular function abnormalities often observed during the HD therapy.

Trial Registration Number: The study is registered at ClinicalTrials.gov (NCT01721551) as a clinical trial.

Keywords: exercise, echocardiography, ejection fraction, survival

Introduction

It is well known that patients undergoing hemodialysis (HD) have an increased risk of cardiovascular disease (CVD) [1, 2]. Cardiovascular events are a common cause of mortality in these patients [3]. Moreover, diabetes, hypertension, prolonged anemia, arterial calcification and electrolyte imbalance are some factors that could predispose to cardiovascular mortality in patients undergoing HD [4].

According to the literature, disordered cardiovascular physiology induced by the HD therapy can induce acute left-ventricular function abnormalities [5, 6]. These abnormalities include, among others, intradialytic myocardial stunning (acute sub-clinical regional wall motion abnormalities) and left-ventricular dysfunction, which may, over time could lead to irreversible fibrotic changes and chronic HF, arrhythmias, and sudden cardiac death (SCD) [6, 7].

Numerous studies have highlighted the many beneficial effects of exercise in HD patients, including the positive effect on cardiovascular risk factors. Specifically, intradialytic exercise has improved aerobic capacity and some indicators of SCD [8, 9], and seems to reduce the level of muscle wasting and improve self-reported and objective measures of physical function [10-12]. Still, dialysis efficacy (measured by the KT/V index) and quality of life (QOL) have shown improvement [13].

It's important to clarify the importance of sustaining intradialytic exercise approach in the improvement of both psychological and physiological aspects of cardiovascular health in this population [14]. In a recent study from Penny and colleagues, acute intradialytic aerobic exercise resulted in a significant reduction in myocardial stunning in the last 30 minutes of HD as measured by a number of regional wall motion abnormalities assessed by echocardiography, while left-ventricular ejection fraction remained unchanged [15]. These findings were confirmed in a more recent study from McGuire et al. where aerobic intradialytic exercise did not affect global cardiac function while myocardial stunning significantly reduced [16]. These results suggest that intradialytic aerobic exercise may be helpful in reducing myocardial stunning induced by hemodialysis therapy and its did not negatively affect cardiac function. Still, further research in diverse populations and by examining also other forms of exercise is needed to extract safer conclusions.

According to the literature, the combination of resistance and aerobic exercise could benefit many aspects of health and quality of life [17], however, the acute and chronic effect of this form of exercise on left-ventricular function during the HD therapy has not yet been evaluated. The present study aimed to investigate whether a single bout of hybrid intradialytic exercise could affect left-ventricular function during HD sessions in exercise naïve ESRD patients.

Methodology

Participants

Twenty-one exercise-naïve dialysis patients (no prior exercise training experience) were recruited from the HD unit of the University Hospital of Larisa (UHL). The inclusion criteria for the study were:lack of participation in any organized exercise activities, being on HD for at least three months with adequate dialysis delivery and with stable clinical condition demonstrated by their medical record. Exclusion criteria included: (1) absence of diagnosed neuropathies (2) presence of a catabolic state within 3 months prior to the start of the study, (3) cardiac diseases with NYHA score >3 and (4) inability or refusal to participate in the exercise program. None of the recruited patients were engaged in any systematic exercise training program.

The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, Greece (UHL). All patients gave their written informed consent prior to study participation. The study is registered at ClinicalTrials.gov (NCT01721551) as a clinical trial.

Study Design

This study was a randomized cross-over trial on hemodialysis patients. Patients were assessed under two different scenarios taking place one week apart on the same day of dialysis (2^{nd} dialysis session of the week): Scenario 1: standard HD (without exercise) and Scenario 2: HD including a single bout of hybrid intradialytic exercise composed of both the usual cycling aerobic training followed by resistance training.

Hybrid Intradialytic Exercise bout

The order of the two scenarios was randomly applied in all patients using a computer random number generator. In the second scenario, exercise was performed between the first and second hour of the dialysis using an adapted bicycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity (W) or using the borg scale between 14-16. Patients were instructed to cycle between 50-55 rpm for 45 min. The patients' maximum exercise capacity was determined using a modified version of the Åstrand Bicycle Ergometer test on a previous day one week apart. This test required from the patient to perform cycling in the supine position at 50 rpm while the intensity was increased by 10 watts every one minute until exhaustion. The resistance component of the hybrid training included exercises using resistance bands (TheraBand© professional Latex, AKRON, OH 44310, USA – Resistance from Green to Silver) and portable ankle weights and dumbbells for exercising large muscle groups. In particular, the resistance training consisted of the following exercises: i) resistance bands exercises: chest press, triceps extension, shoulder flexion, hip abductions, seated row; ii) ankle weights and dumbells exercises: knee extension, biceps curl, hip flexion, shoulder press, side shoulder raise, straight-legged raise. The hand of the fistula was excluded from any exercise. The intensity of the resistance training was assessed by the Borg RPE scale and set to be between 14-16 (medium to hard). All participants completed both scenarios without any adverse effects or significant complaints.

Hemodialysis procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) three times per week using high flux polysulfone dialyzers (Fresenius Polysulfone® High-Flux). The HD session lasted approximately 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 12-14 (g/dL).

Echocardiography

Echocardiographic scans were performed using an iE33 echocardiographic system (Philips Medical Systems, Andover, MA, USA). All image acquisitions were made with the subject lying in the left lateral decubitus position using a 2.5 MHz transducer. Echocardiographic assessment was completed at 3 timepoints: before the initiation of the HD session, half an hour before the end of HD session, and 30 min after the disconnection of the patient from the HD machine. For each patient, ≥ 3 consecutive beats were analyzed in each scan, and the mean value was used in the subsequent statistical analysis. All echocardiograms were performed by the same experienced echocardiographer. For the recording of HR, a single lead ECG inherent to the echocardiographic system was used. Left ventricular dimensions were determined from 2-dimensional guided M-Mode images according to the recommendations of the American Society of Echocardiography (ASE) for chamber quantification, [18] using the parasternal long-axis acoustic window. LV mass was calculated from M-Mode traces at the level of mitral valve and determined in g by using the recommended ASE formula. LV mass index was calculated by dividing LV mass by body surface area (using the DuBois and DuBois formula) and height [19] to minimize effects of age, gender, and overweight status [18]. For the assessment of LV diastolic function, the transducer was applied apically (4-chamber view) whilst a pulsed wave Doppler sample volume (4 mm) was located at the tips of the mitral valve leaflets. Doppler gain, pulse repetition frequency, and high-pass filter were all adjusted in order to maximize the signal to noise ratio. The following parameters were evaluated: early peak flow velocity (E), late peak flow velocity (A); thus the ratio of E to A was calculated. The primary outcome variable was ejection fraction (EF) and change in ejection fraction (ΔEF) from baseline to intervention. Ejection fraction was calculated using the biplane Simpson's method from 2-dimensional apical 2- and 4- chamber orientation to evaluate the patient's systolic function. Tissue Doppler velocities were assessed at the basal septum, using pulsed-wave tissue Doppler imaging. The sample volume (2 mm) was placed at the basal septum at the level of the mitral annulus ring in parallel to the longitudinal movement of the septum. The high-pass filter was bypassed, and gains were set to a minimal value to obtain the best signal to noise ratio. Peak systolic (S') as well as early diastolic (E') and peak late diastolic (A') myocardial tissue velocities were assessed and the E'/A' ratio was calculated. In addition, the conventional Doppler E to tissue Doppler E' ratio (E/E') was calculated. The data acquired were analyzed online and the person responsible for echo data analysis was blinded to treatment scenarios.

Blood Chemistry

Routine monthly laboratory results were recorded including c reactive protein, ferritin, iron, hematocrit, KT/V and hemoglobin (Table 1). The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

Comorbidity

The Charlson Comorbidity Index (CCI) was used to calculate the prognostic comorbidity in the current study. The CCI foresees a 10-year survival in patients with multiple comorbidities. The higher the score, the greater the number of comorbidities is, which subsequently worsen the 10-year survival [20].

Statistical analysis

Baseline characteristics of the two HD sessions were compared using unpaired t-tests. Two-way (time X scenario) repeated measures analysis of variance (ANOVA) was used to examine the effect of both sessions on the examined parameters. Difference between any 2 groups was tested using Bonferroni post-hoc test. Delta-changes (from baseline to the end of the intervention) for the examined variables were evaluated via unpaired t-tests. The results are expressed as mean ± SD. All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, Chicago III). Differences were considered significant when $P \leq 0.05$.

Results

After screening 78 dialysis patients, twenty-one patients fulfilled the study criteria and enrolled in the study (see Table 1, Fig 1). No differences were observed for any variable at baseline before the initiation of dialysis between the two scenario days. Echocardiographic indices of LV structure at baseline between the two different scenario days are presented in Table 2.

LV loading and functional data across both trials are presented in Table 3. Pre-dialysis LVIDd values were not different between the two trials. There was a significant main effect for time as LVIDd was reduced by 2-3 mm in both trials during dialysis with a return to baseline during recovery ($p=0.03$, Table 3).

The EF did not change across both trials (Table 3, Figure 1). Similarly, the change in EF from baseline to peak dialysis was not different from zero, although some individual variability was noted (Table 3, Figure 2). In addition, S'velocity showed a significant main effect for time, with an increase during dialysis and recovery in both trials compared to baseline ($p=0.04$,Table 3, Figure 3).

Indices of diastolic function are also presented in Table 3. There was a significant main effect of time for the E ($p=0.01$), A ($p=0.02$), and A'velocities ($p<0.05$). Data for E velocity were reduced during dialysis compared to baseline in both trials, with only a partial return recovery at the post-dialysis assessment. The same pattern was observed for A velocity, with absolute changes being slightly smaller ($p<0.05$). Data for A' velocity increased slightly at post- assessment when compared to baseline and during dialysis time-points ($p<0.05$). All other variables did not change across in either time point (Table 3).

Discussion

In this study, we investigated the effect of a single bout of combined aerobic and resistance intradialytic exercise (hybrid exercise) on left-ventricular function during HD therapy in exercise-naïve patients. The primary outcome of the present study was that a single bout of hybrid intradialytic exercise did not affect left-ventricular function, including LVEF differently than HD without exercise. Exercise during HD should be considered as a safe non-pharmacological approach associated with many benefits and therefore the HD patients should be encouraged to participate in systematic intradialytic exercise programs.

It is well known that cardiovascular diseases are the primary cause of mortality and morbidity in the HD population [2]. Hemodialysis is a life-saving treatment for ESDR patients; however, it has been associated with several cardiac abnormalities [5, 6]. Therefore, it is very important for the patients' overall health and quality of life to overcome HD-therapy complications on cardiac function.

Published evidence reveals that long-term intradialytic aerobic exercise can improve cardiac function [9]. A study performed by Momeni and colleagues (2014) aimed to examine the effect of a 3-month intradialytic exercise program on echocardiographic indices in HD patients and found that cardiac systolic and diastolic function indices were improved after the exercise intervention [21]. Specifically, researchers found an improvement of left ventricular ejection fraction (LVEF), diastolic function and mitral valve minimum pressure in HD patients after a 3 months of exercise intervention [21]. However, it should be mentioned that other studies contradict these results. Deligiannis and colleagues (1999) concluded that that supine sub-maximal intradialytic exercise improved the LVEF and maximal oxygen consumption [22] while another study resulted in an increase of cardiac output and decreasing of relative blood volume after an intradialytic exercise program [23]. In the study of Penny and colleagues, it was shown that a single bout of intradialytic aerobic exercise was associated with a reduction in HD-induced myocardial stunning, as revealed by the reduction in the presence of regional wall motion abnormalities (RWMAs) assessed with echocardiography [15].

To our knowledge, only few studies have examined the effect of intradialytic exercise on cardiovascular function in HD patients and especially at the time that the patients were receiving the hemodialysis therapy and none using a combination regime with aerobic and resistance. It seems that our study is only the third attempt to investigate the acute effect of intradialytic exercise on cardiac function during the HD therapy in these patients after the recent work by Penny and colleagues [15] and McGuire and colleagues [16] . However, this the first study aiming to investigate the combined effect of aerobic and resistance training (also called hybrid exercise training) on left—ventricular function in a single bout in exercise training-naïve patients. The findings of the present study reveal that a single bout of hybrid intradialytic exercise does not affect left-ventricular function. The changes observed in several echocardiographic parameters of left-ventricular function wre similar in both trials (with or without exercise during HD). Therefore, the current findings add to the literature by introducing a very promising and effective exercise training approach such as hybrid exercise training [17] as a safe and well-tolerated by the patients method, which is did not negatively affect cardiac function during HD therapy. It's was assumed that the resistance component of the hybrid training may played a role in stressing a bit further the myocardium of the HD patient (taking into account also that they were exercise- naïve), inducing various abnormalities in echocardiographic parameters of cardiac function of the left ventricle. We highlight the fact that both the previous two aerobic exercise studies and the current (hybrid exercise) study show that exercise is overall not a harmful regime for HD patients showing no difference in LVEF. Consequently, it is important to determine in future studies whether long-term exercise training could affect the myocardial stunning often appeared during HD as well as myocardial function in general. According to the literature, long term exercise training beneficially affect cardiovascular health in the HD population [22, 24]; however, the effect on myocardial stunning remain unexplored.

Finally even the majority of previous studies concerning intradialytic exercise have shown a beneficial effect not only in the cardiovascular system [11] but also on aspects related to body composition [25], dialysis efficacy [26] and QOL in HD population [27-29] there are many practical burdens to the clinical staff related to the incorporation of intradialytic exercise into routine clinical practice.

The present study has some obvious strengths and weaknesses that need to be acknowledged. The fact that the participants represent a diverse population (age, dialysis vintage and gender) as well as were exercise-naïve (not prior experience on intradialytic exercise training) is considered as one of the uniqueness and strengths of the current study since it gives a pragmatic approach on to what happens to HD patients when they first exposed into exercise stress. In addition, the nature of the exercise bout, which combined both aerobic and anaerobic elements (hybrid), is considered another strength following the global trends in exercise rehabilitation training. Another important aspect of the current study is the fact that the hybrid type of training showed no side effects and no changes in their current cardiovascular state, presenting the first shreds of evidence of safety for the patients to be involved. Regarding the weaknesses identified in the current study, the low number of participants seems to be the most important because it could have affected the outcomes of the study, even though this number is higher than the majority of the published articles dealing with the effects of acute intradialytic exercise on cardiac function HD issue. Second, the intensity of the exercise was fixed between 13-16 level of the Borg scale, while other more intense protocols could have shown different results.

In conclusion, in the current study, we found that a single bout of moderate-intensity intradialytic aerobic and resistance exercise had no significant effect on cardiac function compared to HD without exercise. This adds to pre-existing literature suggesting that such exercise is safe and well-tolerated in people on hemodialysis. Considering the documented benefits of intradialytic exercise to physical function, quality of life and overall health, participation in such exercise should be encouraged in individuals receiving chronic hemodialysis therapy.

DECLARATIONS

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Conflicts of interest/Competing interests

The authors declare no conflicts of interest.

Ethics approval

The study was approved by the Human Research and Ethics Committee of the University of Thessaly (634, 10/10/2012) and performed under ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

All patients gave their written informed consent prior to study participation.

Consent for publication

YES

Availability of data and material

All data and materials of this study are available upon request.

Authors'contributions

SSG, performed the literature review, data acquisition and analysis, draft and revise the first version.

CDG, overviewed the data analysis, performed clinical examination of the participants and draft and revised the various version;

CK, performed statistical analysis, updated the literature review, draft and revised the various version

KG, performed ecordiography analysis and consultation, contribute to statistical and power analysis, and draft and revised the various version;

PZ, recruit patients, performed medical examination, participated in the study design and data analysis and revised the various versions of the paper;

TE participated in patients recruitment, data acquisition and analysis, draft and revised the various version;

IS participated in the study design, assist in literature review and statistical kai power analysis and draft and revised the various version;

GKS conceive the project idea, participated in the study design, overview the whole process of the experiments and analysis and draft all versions of the paper.

All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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Table 1. Basic characteristics of the participants

Variables	Values
N	21
Female/Male	4/17
Age (yr)	56±19
Weight (kg)	77.8±18.5
Height (m)	1.69±0.10
BMI (kg/m^2)	27.1±6.2
Months in dialysis	40±44
WHR	1.02±0.12
CRP(mg/dL)	3.2±4.2
HCT	34.8±3.8
KT/V	1.2±0.6
Hb(g/dL)	12.8±1.2
Iron(μg/dL)	65.3±48.5
Ferritin (ng/mL)	1121.2±942.7
CCI	6.5±2.2

All data are mean ± SD. BMI, body mass index; WHR, waist to hip ratio; CRP, C Reactive Protein; HCT, hematocrit; Hb, hemoglobin; KT/V, Dialysis efficiency; CCI, Charlson Comorbidity Index

Figure 1. Flow of participants through the study

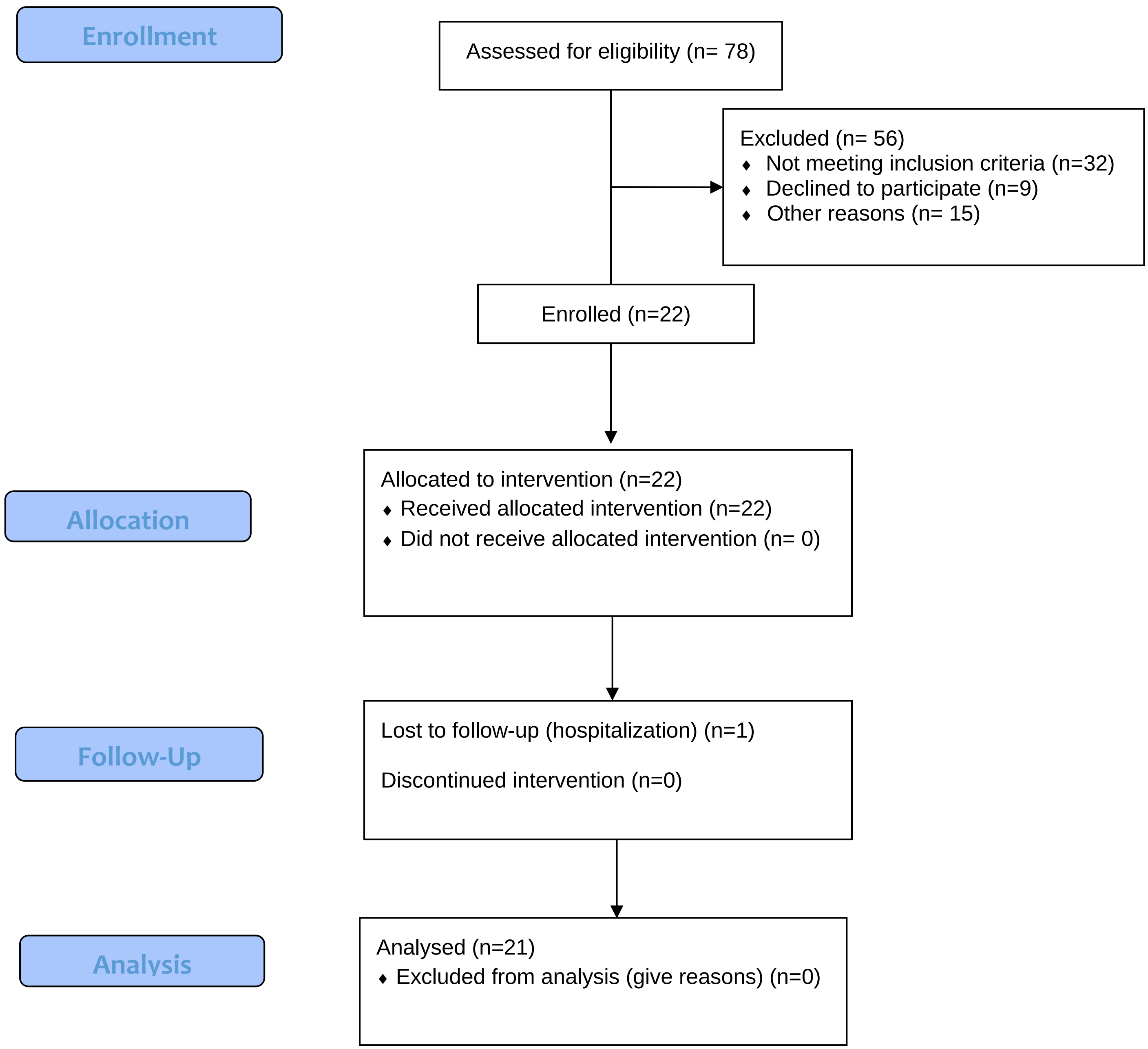


Table 2. Echocardiographic indices of LV structure at baseline between the two different trial days

Parameter	Scenario	Values	p value
IVSTd (mm)	No Exercise	12 ± 2	0.443
	Exercise	11 ± 2	
LVPWTd (mm)	No Exercise	11 ± 2	0.952
	Exercise	12 ± 3	
LVmass (g)	No Exercise	57 ± 9	0.283
	Exercise	55± 15	
LVmass/BSA (g/m^2)	No Exercise	31 ±4	0.289
	Exercise	29 ± 8	
LVmass/height(g/m$^{[2.7]}$)	No Exercise	14 ± 4	0.277
	Exercise	14 ± 4	

All data are mean ± SD. IVSTd, interventricular septum thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LV, left ventricle; BSA, body surface area.

Table 3. Echocardiographic data for loading, systolic and diastolic function at baseline, during and post dialysis in the two scenarios.

Parameter	Scenario	Baseline	During HD	Post
Preload				
LVIDd (mm)	No Exercise	47±6	45±6*	46±5
	Exercise	46±6	43±5*	45±5
Systolic Function				
EF (%)	No Exercise	51 ± 8	54±8	50±10
	Exercise	50 ± 12	53±9	49±13
Δ EF (peak	No Exercise		2.26 ± 9.5	
dialytic stress)	Exercise		5.74 ± 13.18	
S' (m/s)	No Exercise	0.08±0.01	0.11±0.02*	0.11±0.02
	Exercise	0.09±0.02	0.11±0.02	0.11±0.02
Diastolic Function				
E (m/s)	No Exercise	0.87±0.26	0.62±0.13*	0.70±0.16
	Exercise	0.88±0.18	0.64±0.11*	0.73±0.12
A (m/s)	No Exercise	0.92±0.37	0.82±0.35*	0.84±0.34
	Exercise	0.93±0.31	0.78±0.32*	0.80±0.32
E/A	No Exercise	1.00±0.34	0.85±0.32	0.94±0.38
	Exercise	0.97±0.19	0.93±0.29	1.04±0.41
E' (m/s)	No Exercise	0.09±0.02	0.08±0.02	0.09±0.03
	Exercise	0.09±0.02	0.09±0.03	0.08±0.03
A'(m/s)	No Exercise	0.09±0.02	0.08±0.02*	0.09±0.02
	Exercise	0.09±0.02	0.09±0.02	0.10±0.02
E'/A'	No Exercise	1.12±0.50	1.03±0.48	1.06±0.54
	Exercise	1.01±0.40	1.04±0.46	0.84±0.40
E/E'	No Exercise	10±5	9±5	8±3
	Exercise	11±5	8±3	10±5

*All data are mean ± SD. Δ , delta, EF, ejection fraction, S', annular systolic tissue velocity, E, transmitral doppler early diastolic wave; A, transmitral doppler atrial diastolic wave; E/A, ratio of E and A wave peak velocities; E', annular early diastolic myocardial velocity; A', annular late diastolic myocardial velocity; E'/A', ratio of early to atrial diastolic myocardial velocity; E/E', ratio of transmitral blood flow velocity to tissue doppler velocity. *Significant main effect of time*

Figure 1. Ejection Fraction (EF%) at baseline, during, and post dialysis with and without the implemented exercise session.

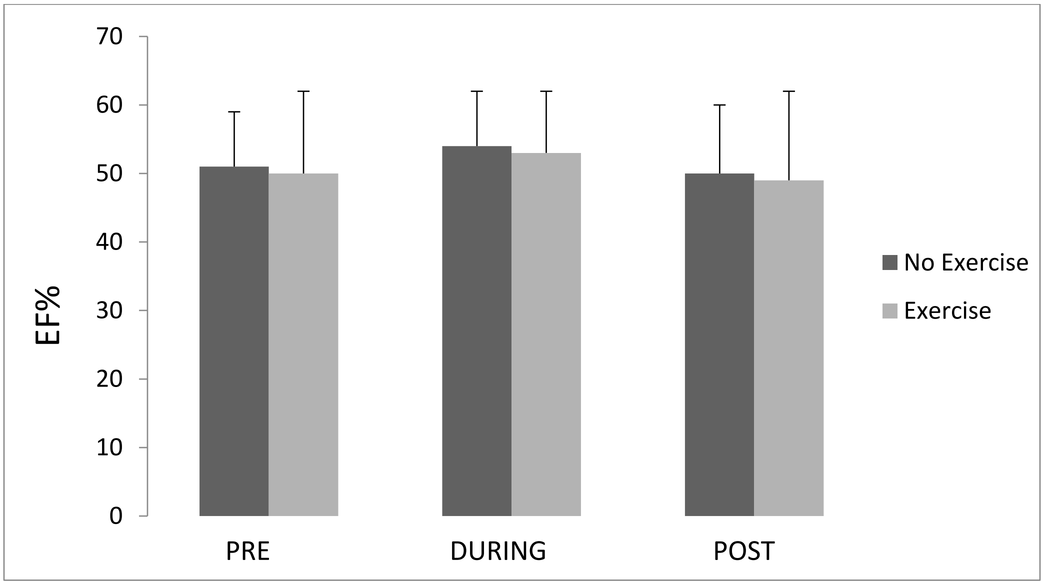


Figure 2. ΔEF (peak dialytic stress) during dialysis with and without the implemented exercise session.

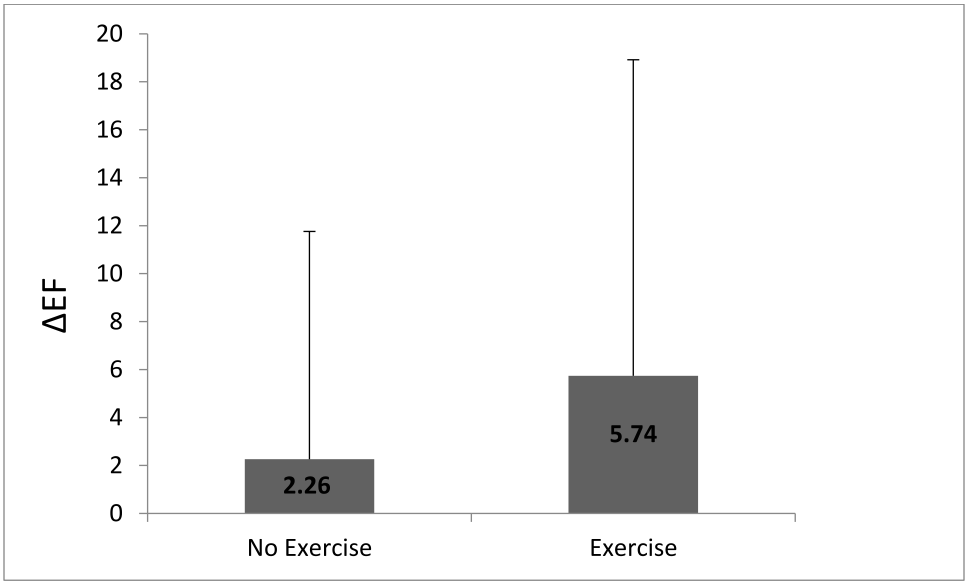
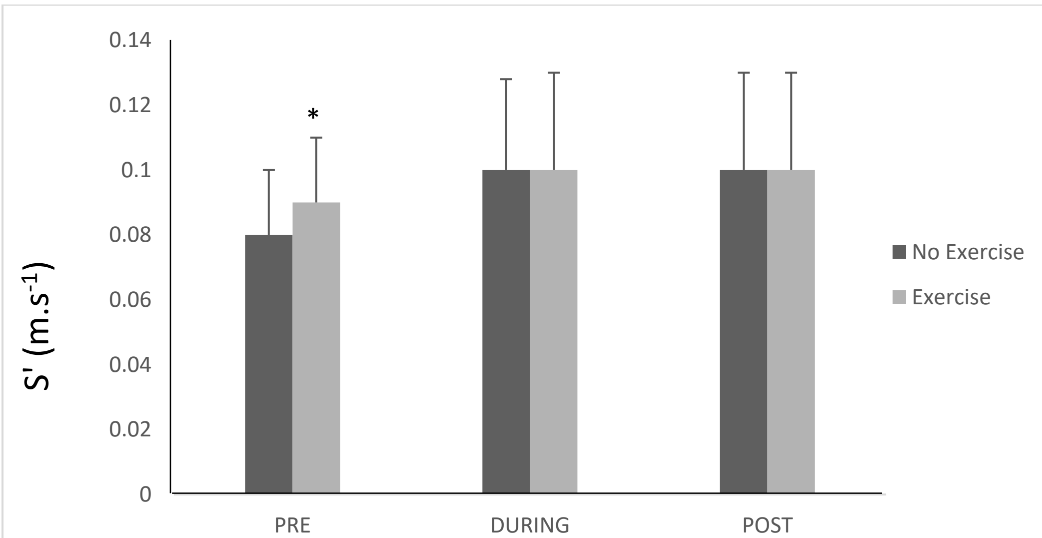


Figure 3. Annular systolic tissue velocity (S') at baseline, during, and post dialysis with and without the implemented exercise session.



** Significant main effect of time.*