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Effect of Intradialytic Respiratory Muscle Training on Cardiopulmonary Efficiency in Hemodialysis Patients

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ABSTRACT

Background: The specific training of respiratory muscles may be a useful alternative for patients with chronic kidney disease because the conditioning and strengthening of respiratory muscles can delay the complications of loss of muscle mass.

The aim of the work: The study aim was to examine the effect of intra dialytic respiratory muscle training on cardiopulmonary efficiency in hemodialysis patients.

Patients and Methods: From both sexes, sixty patients with chronic kidney disease participated in this study. They were aged 48 to 60 years old. Patients were randomly assigned to two groups; Study and control groups. The study group (n=30) received a daily morning and evening 20-minute diaphragmatic breathing exercise and intra dialytic 10- minute respiratory muscle training (RMT) by Sonmol respiratory trainer device three times per week for 12 weeks. The control group (n=30) received a daily morning and evening 20-minute diaphragmatic breathing exercise alone. The patients' systolic blood pressure (SBP), diastolic blood pressure (DBP), two-minute walk test (2MWT), peak expiratory pressure (PEP), and left ventricular ejection fraction (LVEF) were assessed in both groups twice pre-study and after 12 weeks at the end of the study.

Results: A significant improvement in SBP, DBP, 2MWT, PEP, LVEF was documented within both groups, but the improvements of group A were higher than group B. Between-group analysis of post-values of outcomes showed a significant improvement in all outcomes at toward group A: PEP(cmH_2O) improved by 29.59 %, LVEF (%) improved by 8.5 %, 2MWT(meter) improved by 19.32 %, SBP (mmHg) improved by 4.79 %, DBP(mmHg) improved by 5.10 %.

Conclusion: This trial suggests that adding 12-week RMT to diaphragmatic breathing exercise maximizes the significant improvement of outcomes (PEP, LVEF, 2MWT, SBP, and DBP) gained from diaphragmatic breathing exercise.

Keywords: Respiratory Muscle Training; Diaphragmatic Breathing Exercise; Cardiorespiratory Fitness; Hemodialysis.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a decreased glomerular filtration rate, and increased excretion of urinary album in, or both. CKD is prevalent in Africa and sub-Sahara Africa with the prevalence of 15.8% and 17.7%, respectively in general population [1]. The global prevalence of CKD is at~10% of the general population, affecting > 800 million adults worldwide. The global increase in CKD is mainly driven by the increasing prevalence of diabetes, hypertension, obesity, and ageing. By 2040, chronic kidney disease is estimated to become the fifth leading cause of death globally [2]. Physical deconditioning, exercise tolerance, and cardiorespiratory fitness are all low in hemodialysis patients with late stages of CKD. Additionally, this patient group shows alterations in gas exchange, muscular function, and pulmonary mechanics. The build-up of interstitial fluid in the lungs is one of the primary causes of respiratory impairment in these patients [3]. One of the most prevalent symptoms of CKD that patients describe is dyspnea and decreased cardiovascular fitness. According to observational studies, up to 60% of people with end-stage renal disease (ESRD) receiving conservative therapy may have it. Though dyspnea is common, it has not been adequately treated, and diagnosing its underlying cause is frequently a challenging clinical issue [4].

Reduced pulmonary function may be caused directly or indirectly by circulating toxins from renal uremia or by increased fluid load, immune response, electrolyte imbalance, inadequate nutrition, and/or acid-base disruption. Increased bodily fluid is a severe and widespread issue that can lead to major consequences for Hemodialysis (HD) patients. ESRD patients on regular hemodialysis frequently have weight changes during the inter-dialytic period, which may be related to their increasing bodily fluid load. Pulmonary edema and pleural effusion may result from the increased fluid load and pulmonary capillary permeability; these anomalies may explain the decreased pulmonary normal functioning [5]. The high prevalence of dyspnea and its heavy burden on both the quality of life and prognosis in dialysis patients is driving the need for new novel approaches to achieve a deeper, systematic understanding and treatment of respiratory dysfunction in these patients and identify additional therapeutic opportunities to improve their care [6]. As a part of exercise conditioning in CKD patients, the specific training of respiratory muscles may be a useful alternative for patients with chronic kidney disease because the conditioning and strengthening of respiratory muscles can delay the complications of loss of muscle mass [7]. RMT reduces oxidative stress, which is the cause of HD patients' decreased cardiorespiratory fitness. The mechanisms through which RMT improves endothelial glycocalyx are unknown. However, endothelial glycocalyx damage is correlated with circulating noradrenaline and adrenaline. One explanation for this is that RMT reduces sympatho-adrenal activity, which is corroborated by a notable decrease in at-rest heart rate in trained HD patients, hence minimizing this damage [8].

Although RMT is important to improve cardiopulmonary efficiency, no randomized controlled trial has been done to explore the efficacy of RMT on cardiopulmonary efficiency in hemodialysis patients. So, this study aimed to investigate this domain.

PATIENT AND METHODS

Design: A randomized controlled trial.

Settings: Patients were allocated from Nasser Specialized Hospital, El- Qalyubia Governorate, Egypt

Ethics: Before starting this study, prior informed consent of all the subjects was obtained and a clearance was gained from the institutional ethical committee of the Faculty of Physical Therapy, Cairo University (P.T.REC/012/005259). Helsinki guidelines were followed.

Sample size: To avoid a type II error, a preliminary power analysis was conducted by G*power software, the program used a power 80%. The left ventricular fraction (%) settled as the primary outcome this study. The effect size of the analysis of the G Power was 0.78. According to the G Power analysis, number of patients within every group was 27 patients. To prevent drop (estimated by 10% approximately) during the treatment program, three patients were added in every group (figure 1)

Inclusion criteria: Patients (n=60 from both sexes) suffering from CKD were included. Patients' body mass index (BMI) ranged from 30-35 Kg/m^2. Ages of patients ranged from 48-60 years old. They had left ventricular dysfunction with ejection fraction of left ventricle ranged from 41-49%, they were on hemodialysis (HD) 3 times per week from 1-3 years ago, and they were suffering from dyspnea with 3-5 on Modified Borg Dyspnea Scale which considered moderate to severe degree.

Exclusion criteria: The study's authors eliminated/excluded anyone with smoking or alcohol-abuse, cardiac diseases other than left ventricular dysfunction, pulmonary or liver diseases, neurological insults, diabetes, anemia, psychiatric complaints, blood pressure more than 140/90 mmHg, peripheral vascular diseases, pregnant or breast feeding females. Any patient who engaged in other studies or done exercise or respiratory programmes within the last 6 months preceding this study were excluded.

Randomization: A simple randomization was used to assign 60 participants into two groups: The study group and the control group, 30 per group were randomly assigned. An independent person selected a paper from a sealed envelope to determine the group assignment. The study group (n=30) received a deep diaphragmatic breathing exercise and respiratory muscle training for 12 weeks. The control group (n=30) received a deep diaphragmatic breathing exercise only for 12 weeks **(Figure 2)**.

Deep diaphragmatic breathing exercise (for both groups): Patient was ordered to sit or lay down comfortably according to personal comfortability without crossing arms or legs. The patient placed his palm of one hand on the abdomen, below the rib cage (on the epigastric area) and the second hand was placed in the middle of the chest. Then the researcher asked the patient to take deep breath from the nose slowly while relaxing the neck and shoulder muscles, and exhale slowly with a sigh from the mouth. The patient was told to imagine their stomach as an inflated balloon during the inhale. Thus, take a deep breath through the nose, place the hand on abdomen, which is lifted by stomach, and try to move the abdomen rather than shoulders when inhale or exhale. Patients in both groups received intradialytic deep diaphragmatic breathing exercise, for 12 weeks. There were 3 sessions weekly. Every 3-5 successive deep diaphragmatic breathing exercise are considered as one set. Every two sets were separated with 2 minutes of rest to avoid hyperventilation. The total session lasted20 minutes [9]. The session was supervised by the researcher 3 times weekly (during HD sessions). Moreover, the patients were order to apply this session daily at the evening in their home. Also, they were directed to apply this session in the morning of off days of HD.

Respiratory muscle training (for study group only): This training was performed after the end of deep diaphragmatic breathing exercise by 15 minutes in study group only during the session of HD. Patient was instructed to sit upright and relax. The researcher ensured that the indicator of resistance level was placed at level-1 for the button of inspiration or expiration resistance. This level resistance was fixed for all patients of study group during all sessions of 12-week RMT. Researcher placed the nose clip on the patient's nose. Patient held the breathing trainer. Patient sealed the mouthpiece well by fixing the lips around mouthpiece of the device. Patient inhaled rapidly for 3 seconds, short break (nearly 1-2 sec) then exhale slowly, relaxing his/her chest and shoulder while maintain exhalation for 6 seconds. Patients completed eight full breathing cycles in a minute. The next minute, they did not train and instead rested. Five repetitions of this 1:1 train-rest ratio were made for total ten minutes [7].

Outcomes: Patients' systolic blood pressure (SBP), diastolic blood pressure (DBP), two-minute walk test (2MWT, as a measure for patients' functional capacity), peak expiratory pressure (PEP), and left ventricular ejection fraction (LVEF) were assessed in both groups.

Blinding: The assessors of SBP, DBP, 2MWT, PEP, and LVEF in both groups did not know the details of deep diaphragmatic breathing exercise diet or respiratory muscle training.

Statistical analysis: The collected data were analyzed statistically test of normality; results are presented as mean ± standard deviation (SD). The difference was calculated as follows: - Difference = pre-assessment – post-assessment. The Shapiro-Wilk test was used to verify that the data were normal. To evaluate the homogeneity between groups, Levine's test for the homogeneity of variances was utilized. There was homogeneity of variance and a normal distribution of the data. To compare the subject characteristics (age) between groups, an unpaired t test was used. A chi squared test was utilized to compare the distribution of sexes. Paired T test was used to assess the significant changes of SBP, PEP, LVEF, DBP, and 2MWT within groups. Unpaired T test was used to assess the statistical differences of SBP, PEP, LVEF, DBP, and 2MWT between groups before or post treatment. Statistical analysis was performed through the statistical package for social studies (SPSS) version 23 for windows. All statistical tests were conducted with a significance level of $p < 0.05$.

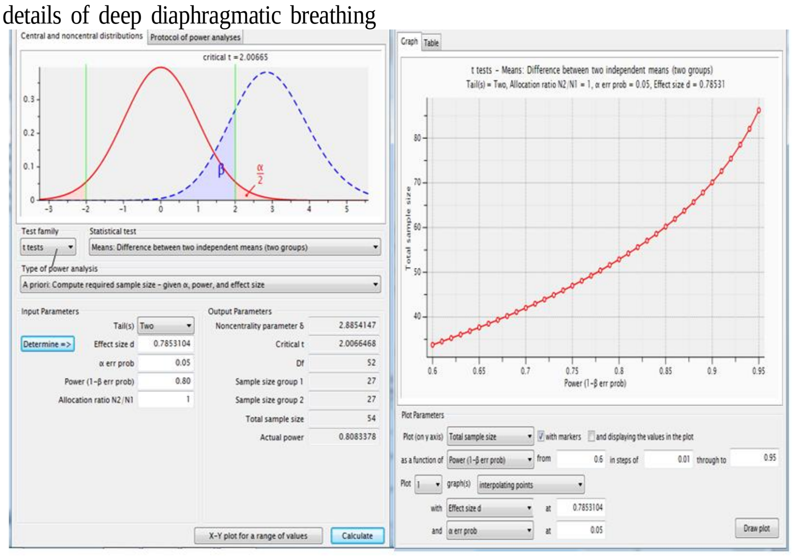

Figure (1): J-power of study

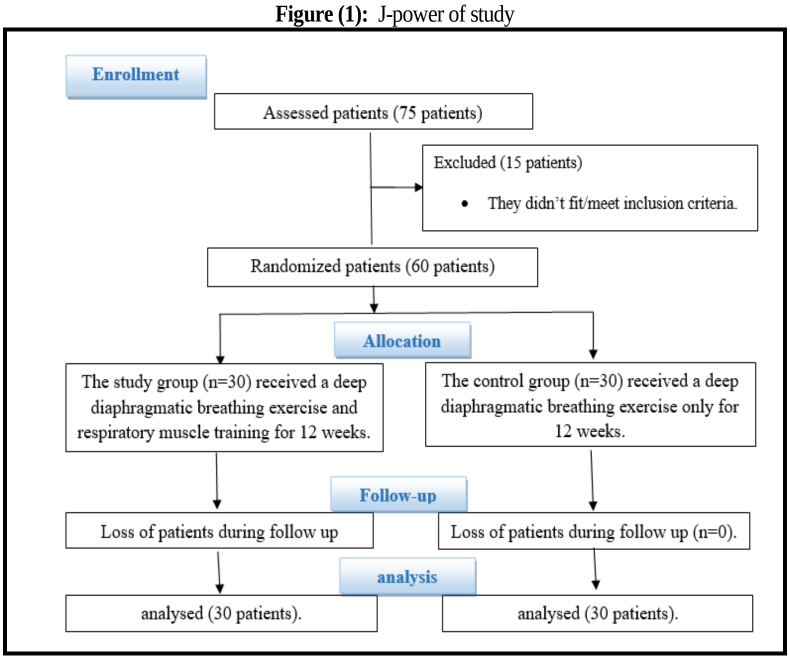

Figure (2): Flow chart of patients

RESULTS

Table (1) showed that there was no intra-group significant difference between participants' main characteristics (age, BMI, and sex distribution). Table (2) did not show between-group pre-treatment significant difference in PEP, LVEF, 2MWT, SBP, and DBP. A significant improvement in PEP, LVEF, 2MWT, SBP, and DBP was documented within both groups, but the better level of improvement was detected in the study group. Post-treatment between-group comparison of all outcomes indicated a significant improvement in the direction of the study group.

Table [1]: The data (basic/demographic) before initiating the assigned interventions for HD patients.

Data	Group of deep diaphragmatic breathing exercise plus Respiratory muscle training	Group of deep diaphragmatic breathing exercise	P value
Age (years)	55.36±3.67	54.06±3.63	0.173
Body mass index (kg/m^2)	25.39±2.40	26.34±2.59	0.146
Sex distribution	17 women: 13 men	16 women: 14 men	0.438

All data are expressed as mean±SD; Sex distribution is tested via Chi square test. All p values are non-significant.

Table (2): Outcome of HD patients.

Outcomes	Group of deep diaphragmatic breathing exercise plus Respiratory muscle training	Group of deep diaphragmatic breathing exercise	P value (between both groups)
PEP (cmH$_2$O)			
Before the trial	74.33±17.35	66.33±16.29	**0.071**
After the trial	96.33±22.04	75.33±18.14	**<0.001***
P value (within both groups)	<0.001*	<0.001*	
LVEF (%)			
Before the trial	45.86±2.34	45.10±2.66	**0.242**
After the trial	95.40±9.90	46.63±3.36	**<0.001***
P value (within both groups)	<0.001*	<0.001*	
2MWT(meter)			
Before the trial	154.56±20.28	145.86±16.57	**0.074**
After the trial	184.43±21.07	163.36±18.47	**<0.001***
P value (within both groups)	<0.001*	<0.001*	
SBP(mmHg)			
Before the trial	128.36±5.11	130.30±5.44	**0.162**
After the trial	122.20±4.51	126.83±5.14	**<0.001***
P value (within both groups)	<0.001*	<0.001*	
DBP(mmHg)			
Before the trial	84.30±2.97	84.60±2.82	**0.690**
After the trial	80±3.33	82.33±3.06	**0.007***
P value (within both groups)	<0.001*	<0.001*	

SD: Standard deviation; *: patients' P value is significant (P < 0.05).

DISCUSSION

Results showed a significant improvement in all outcomes in both groups but the improvements of group A were higher than group B. Between-group analysis of post-values of outcomes showed a significant improvement in all outcomes at toward group A. RMT is characterized as a wonderful exercise that strengthens the respiratory muscles by applying significant load to them. RMT strengthens the respiratory muscles and increases the amount of oxygen that enters the bloodstream with each breath. Stronger respiratory muscles make it easier to accomplish essential respiratory activities by delaying or eliminating respiratory muscle exhaustion **(10)**.

The most significant respiratory muscle, the diaphragm, has a positive impact on expiratory forced volume and capacity when its strength is increased. Also, the chronic adaptation of the pulmonary system to exercise is related to decreased muscle stiffness, improved nerve conduction velocity, improved contractile activity, increased metabolic enzyme activity in respiratory muscles, and increased elasticity of the lungs and chest wall. These viewpoints can help to explain them. PEP, a measure of expiratory muscular strength, is elevated, according to four additional findings **(11)**. Strengthening the respiratory muscles may potentially have an effect on cardiorespiratory fitness. The vagal regulation of the heart and cardiorespiratory coupling/fitness is arguably the most common observation of RMT **(12)**.

The purpose of respiratory workouts is to increase oxygenation and ventilation. Lower respiratory frequency may arise from increased air entering the lungs due to increased lung compliance during respiratory exercise. When oxygen requirements are met, tolerance to the exercise rises, improving physical capacity **(13)**. This exercise may help to explain improved LVEF following respiratory training. In patients with LVD, deep breathing exercises can reduce chemoreceptor sensitivity and enhance cardiac autonomic modulation. In addition to lowering pulmonary pressure and pulmonary edema, this exercise will raise the LVEF. The regulation or modification of the cardiopulmonary reflex may result in an enhanced ventilator mechanism **(14)**.

In agreement with the presented results, regular application of respiratory muscle training in CKD patients significantly improved patients' expiratory muscle strength and physical functioning **(15)**.

According to our findings, PEP dramatically increased in patients with ESRD following respiratory training conducted at home using an inspiratory-expiratory system for a total of five minutes of precise breathing exercises (8 breaths per minute) separated by one minute of rest, twice daily on days when dialysis was not performed, for a total of four weeks, with the air resistance gradually increasing **(7)**. In agreement with the presented findings, diaphragmatic breathing exercise or incentive spirometer training for 8 weeks in Egyptian HD patients who aged 55-65 years old significantly improved their 6MWT **(16)**. In addition, involving HD patient in 8-week RMT during HD session significantly improved their PEP, blood pressure, and 6MWT **(8)**. Furthermore, the twice daily application of intra dialytic inspiratory muscle training in HD patients (n=12) for 8 weeks significantly improved their PEP and six-minute walk test **(17)**.

Consistent with us, the application of respiratory muscle training either by incentive spirometer or by inspiratory muscle trainer in HD showed a significant improvement in physical functioning and respiratory muscle strength [18]. Also, inspiratory muscle training as a part from12-week intra dialytic multicomponent exercise program that constituted from aerobic and resistance exercise thrice weekly showed a significant improvement in patients' 6MWT, PEP [19]. In addition, regular performance of deep breathing exercise for 30 minutes thrice weekly in patients with LVD significantly decreased patients' SBP and DBP [13]. Furthermore, application of inspiratory muscle training for 12 weeks in HD patients significantly improved their peak expiratory flow [20].

Heart rate and arterial pressure oscillations reflect both autonomic neuronal fluctuations and mechanically generated central blood volume variations that accompany respiration. Since there is currently no known mechanism that explains the effect shown following deep breathing training or RMT, the possible explanations for the current findings are purely conjectural. While it is impossible to rule out adaptations in the brain stem's cardiovascular and respiratory control regions, the most likely explanation is that modifications in the activation and relaxation of respiratory muscles may have contributed to the rise in heart rate variability in order to promote enhanced vagal modulation of the heart, which in turn improved LVEF and blood pressure [21].

To meet the demands of prolonged physical activity, RMT delays diaphragm exhaustion, increases the intensity of respiratory muscle exertion required to activate the metaboreflex, and improves cardiorespiratory efficiency [22]. In patients with left ventricular dysfunction (LVD), RMT can postpone the onset of diaphragmatic fatigue. This can lessen the blood flow required by the respiratory muscles during exercise, increase ventilator efficiency, and/or decrease the recruitment of accessory respiratory muscles. Patients with LVD may have greater ventilatory sensitivity to central and peripheral chemoreceptor stimulation, which can lead to sympathetic vaso-constriction and reduced blood flow to the skeletal muscles during exercise. Thus, whole-body aerobic exercise training can reduce the sympathetically induced vasoconstriction that diaphragm exhaustion may cause in limb muscles. RMT may also postpone the onset of diaphragm fatigue by enhancing the strength and endurance of the ventilatory muscles. This could reduce sympathetic activity, improve peripheral muscle perfusion, and increase functional capacity [23]. Parallel to the presented results, the results of a systematic review involved 11 articles about efficacy of RMT in ESRD patients reported that, as a non-pharmacological therapy, respiratory muscle training can efficiently improve maximal expiratory pressure in patients with CKD and is safe for such populations [24]. The presented results were confirmed by **Pellizzaro *et al.*** [25] who mentioned that involving HD patients in RMT program significantly improved the patients' PEP, 6MWT.SBP, DBP, and inspiratory muscle strength. **El-Deen *et al*.** [26] stated that using an inspiratory muscle trainer for 12 weeks is a useful therapeutic strategy to increase the strength of the respiratory muscles (maximal inspiratory and expiratory pressures) in hemodialysis patients from Egypt.

In a systematic review that discussed the effect of RMT on patients with chronic renal failure on dialysis, IMT with a fixed load significantly improves 6-MWT and respiratory muscle strength (inspiratory and expiratory muscles) [17], so the results of this systematic review were consistent with our results. The application of IMT in HD patients for 12 weeks in the study conducted by **Elsisi et al.** [27] showed similar findings to ours because they reported a significant improvement in HD patients' peak expiratory flow after this form of training.

Involving four clinical trial, the systematic review which aimed to assess the effect of RMT (applied from 8-10 weeks) on PEP and 6-minuye walk test in HD patients was consistent with the presented results because it showed a significant improvement in the two variables [28]. Furthermore, despite the non-significant increase in blood pressure and LVEF, RMT was linked to a large improvement in exercise capacity in LVD patients with low aerobic capacity, which is partially consistent with the data presented [29]. In partial agreement with us, respiratory muscle strength significantly improved after 5-week inspiratory muscle training in CKD patients, but, opposite to us, their 6-minute walk test did not significantly improved may be due to the small number of trained HD patients (n=14 patients) and the short period of training for 5 weeks only [30]. Also, in a partial agreement with the presented results the presented results, significant improvement in 6MWT and office systolic blood pressure were reported after 3-month slow breathing retraining in heart failure patients but their LVEF did not significantly improved [31]. In addition, despite improvement of physical functioning, respiratory muscle strength of HD patients in the study conducted by **Campos *et al*.** [32] opposed our results because it did not show a significant improvement after a program of inspiratory muscle training may be due to the small number of participants.

Opposite to the presented results, a systematic review which included four trials assessed effect of inspiratory muscle training on respiratory muscle strength and functional capacity did not find a detectable effect of inspiratory muscle training on the two variables may be due to the different levels of applied intensity during the IMT in HD patients [33].

The current study's findings contradicted those of **Lamberti *et al.*** who demonstrated that no significant alterations were observed in the 6 MWT following two months of breathing exercises with hemodialysis patients. Conversely, after four weeks of respiratory training by a respiratory trainer that included both expiratory and IMT, 6MWT did not significantly improve in individuals with end-stage renal illness. The non-significant improvement in 6MWT could be attributed to the small number of trained patients [7]. Opposite to us, 6-MWT did not significantly changed after IMT in health older adults may be sue to the short duration of training (8 weeks) [34].

Limitations: Tracking long-term follow-up to the outcomes of the trial was a limitation of performed assessments that must be considered in future trials.

Conclusion: This trial suggests that adding 12-week intra dialytic RMT to deep diaphragmatic breathing exercise increases the gained improvements in PEP, LVEF, 2MWT, SBP, and DBP in HD in patients.

Conflict of Interest: None

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