Original Article

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TANAFFOS

Cardiopulmonary Exercise Test Parameters among Dialysis Patients with End-Stage Renal Disease

Alireza Eslaminejad [1], Seyed Mehran Marashian [1], Mohammad Hadi Tajik Jalayeri [2], Fatemeh Yassari [1]

[1] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Department of Pulmonary Medicine, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Correspondence to: Yassari F
Address: Chronic Respiratory Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: fa.yassari@gmail.com

Background: The current study aimed to assess some parameters of the cardiopulmonary exercise test (CPET) among end-stage renal disease patients who underwent dialysis. The ultimate goal is to improve disease management to achieve optimal quality of life and exercise capacity in this group of patients.
Materials and Methods: Through a cross-sectional design, the current study enrolled 46 dialysis patients by simple sampling between Jan 2019 and Jan 2020. Some CPET parameters such as AT, VO_2, VO_2/kg, SPO_2, minute ventilation CO_2 production/O_2 consumption ratios (VE/VCO_2 and VE/VO_2, respectively), O_2 pulse, heart rate reserve (HRR), breathing reserve (BR) and end-tidal carbon dioxide pressure ($PETCO_2$) were focused.
Results: Although a limited sample size, the current study showed that VO_2/Kg, VE/VCO_2, $PETCO_2$, and SPO_2 are the main parameters affected by dialysis as expected.
Conclusion: The current study suggests using cardiopulmonary rehabilitation for all chronic medical conditions such as chronic kidney disease and end-stage renal disease that increase the rate of metabolic acidosis.

Keywords: End-stage renal disease; Cardiopulmonary exercise test; Dialysis; VO_2/kg, $PETCO_2$

INTRODUCTION

Chronic kidney disease (CKD) is not a rare medical condition in the global population. It involves 12% of adults, globally in the United States while 4.7 are at stages 3-5 (1). In 2009, the prevalence of CKD (stages 3-5) was 14.9% in Iranian individuals ≥ 20 years of age (1). However, Bouya et al. reported it 15.14% in Iran in 2018 affecting females 1.7 times more than males (2). Two well-known risk factors for CKD, hypertension and diabetes mellitus, are dangerously prevalent in our population in Iran. So, it seems to be necessary for policymakers to pay attention to elderly people, females, obese individuals, and people who suffer from dyslipidemia (1,2). Mousavi et al. explained that more than 32,000 Iranians underwent renal replacement therapy (RRT) in 2007 due to ESRD which means just less than 436 per million population (pmp). The incidence of ESRD in Iran experienced a sharp increase from 13.82 pmp in 1997 to 63.8 pmp in 2006 (3).

The cardiovascular and respiratory systems are the most involved organs in CKD. Lungs and kidneys work together to make stability in acid-base balance in the body. Many CKD complications result from an alteration in body volume, plasma oncotic pressure, metabolism in bone and minerals, concomitant heart failure, and impaired immune function which could finally increase the risk of pulmonary edema, fibrinous pleuritis, pericardial effusion, pulmonary calcification, sleep apnea, anemia, and dialysis-related hypoxemia. Each of these complications may affect the quality of life and exercise capacity (4). This is worth mentioning that studies showed that the most frequent cause of death in CKD is cardiovascular problems regardless of the primary cause of CKD or the cause of increasing disease stage from mild to severe (5-7).

Wallin et al. showed that vascular stiffness and self-reported physical activity were significantly lower in stages 4-5 of CKD compared with stages 2-3 (8). They reported significantly lower peak workload, exercise time, heart rate reserve, peak systemic oxygen delivery, and heart rate recovery two minutes after their cycle exercise ended when compared to non-dialysis stages 4-5 and 2-3 of CKD with healthy people. They also found lower hemoglobin and stroke volume in stages 4-5 of CKD who did not take beta blockers in comparison with healthy individuals. Moreover, peak workload was strongly related to the systemic oxygen delivery factors, peak HR, and hemoglobin level. Their results also revealed that aerobic exercise capacity in non-dialysis CKD decreases gradually with increasing disease severity (8). In line with previous studies, there has been an association found between a reduction in exercise capacity and a decline in muscle strength, cardiovascular function, and physical activity (9). This finding indicates that there is a potential link between severity and abnormal exercise response in kidney disease.

The purpose of this study was to evaluate certain parameters of the cardiopulmonary exercise test (CPET) in ESRD patients who underwent dialysis. The aim was to improve disease management and help these patients achieve optimal quality of life and exercise capacity.

MATERIALS AND METHODS

Participants

In this cross-sectional study, 46 patients were enrolled by simple sampling between January 2019 and January 2020. They had been under dialysis for at least three months and had at least one cardiopulmonary exercise test result as a routine workup while on dialysis.

All the patients were at stages 4-5 of CKD. They were older than 15 and all of them participated in the study after giving their verbal consent. People with the inability to complete cycle ergo-spirometry, low O_2 saturation (< 88%), malignant hypertension (or >200/120mmHg), uncontrolled respiratory failure or pulmonary hypertension, and medical conditions affecting patients' orientation to obey the orders during the test were excluded. The current study focused on the parameters of CPET in this group of patients and also tried to find any correlation between those parameters and demographics as well as habits like smoking.

Cardiopulmonary exercise test (CPET)

We used the "RAMP" protocol considering incremental tests to symptom-limited maximum regarding ATS statement for CPET. Before starting the test, blood pressure and heart rate were checked at rest and in a supine position after a physical examination by the same pulmonologist. Then, participants were instructed to cycle firstly at the speed of 60 rpm to be continued until exhaustion. Heart rate and QRS wave shape and changes, especially ST-T segment were monitored via continuous 12-lead electrocardiography to be in normal and safe range. The quality of the test was defined regarding "good effort criteria" based on the ATS guideline in 2001. Some parameters were more focused on by this study such as AT, VO_2, VO_2/kg, SPO_2, minute ventilation CO_2 production/O_2 consumption ratios (VE/VCO_2 and VE/VO_2, respectively), O_2 pulse, heart rate reserve (HRR), breathing reserve (BR), and end-tidal carbon dioxide pressure ($PETCO_2$). AT or anaerobic threshold addresses the point of changing aerobic exercise into anaerobic metabolism used in suggesting exercise capacity (ExCap) in each individual.

CPET termination occurs when the patient has fatigue, faintness, confusion, pallor, dyspnea, or pain, especially chest pain with ischemic changes in ECG as well as second or third degree of heart block during the test or recorded systolic blood pressure >240 mmHg and/or diastolic blood pressure >110 mmHg. Participants with a fall in systolic blood pressure >20 mmHg or O_2 saturation fall to < 81% were directed to terminate the test before taking urgent actions to bring them back to a stable situation.

Statistical analysis

Demographics, physical findings, ECG, and CPET results were recorded before using SPSS for the analysis. The chi-square test was used for analyzing qualitative variables while the t-test was used for quantitative ones. A confidence interval of 95% besides type one error of 0.05 and a significance level of < 0.05 was chosen to achieve the power study of 0.8.

Ethics

By excluding complicated cases and early termination of CPET in problematic cases, the investigators tried to prevent instability in participants while all the participants could quit the study whenever they wished with no penalty or limitation. CPET is a routine for all patients who are referred for dialysis at least once during their hemodialysis program and there was no extra charge for the patients. All participants were informed about their CPET results with a final diagnosis that the pulmonologist of the study reported.

RESULTS

In total, 46 patients with ESRD enrolled in the study including the youngest with 18 and the oldest with 75 years of age. The mean age was 44.63±14.42 years while 50% of the participants were younger than 47. Among the participants, 35 were male and 11 female. Smokers made up 23.9% of the patients and 35 (76.1%) did not smoke. In 45 cases, the cause of renal disease was clear among which 14 (31.1%) reported hypertension and 12 (26.7%) had diabetes mellitus. BMI was an average of 24.07±4.54 for all participants while the minimum was 17.76 against 36.57 for the maximum. The diagnosis of cardiopulmonary exercise test was clear for 43 including CHF or deconditioning + hyperventilation in 16 (34.78%) followed by deconditioning or early termination due to fatigue each in 11 (23.9%) while 5 (10.9%) terminated the test early due to hyperventilation alone. No correlation was found between age, sex, BMI, and the cause of CKD and the CPET diagnosis for the participants.

In terms of CPET results, the mean AT was 35.46±10.12 with the range of 12-58, and 30 (65.2%) of the patients had AT<40 whilst 16 (34.8%) had AT≥40. However, there was no correlation between AT (lower and higher than 40) and the cause of chronic kidney disease.

As shown in Table 1, VO_2% of the predicted value was 49.17±13.48 at its average which contained between 12 and 85 liter per minute. This was while VO_2/kg was 16.12±5.08 at average value which was between 3.4 and 29.3 ml/min/kg. The study could not find any relationship between VO_2% and neither the cause of ESRD nor smoking behavior. VO_2% showed no relationship with overall BMI and BMI<18 or BMI>30. VE/VCO_2 had a mean ± SD of 36.44±6.25 with a range between 27 and 54 while 23 (50%) of the participants reported VE/VCO_2≥34. The study found an overall correlation between VE/VCO_2 and the cause of CKD (P value=0.019). However, when categorized into lower and upper 34, VE/VCO_2 did not correlate with the cause of CKD, although diabetes mellitus cases were more in the latter category.

Table 1. CPET findings for the participants

	Mean ± SD	Min	Max
AT	35.46±10.12	12	58
VO_2%	49.17±13.48	12	85
VO_2/kg(ml/min/kg)	16.12±5.08	3.4	29.3
VE/VCO_2	36.44±6.25	27	54
VE/VCO_2 slope	34.12±7.74	23.4	52
SPO_2	93.82±3.80	85	99
$PETCO_2$	28.96±3.11	21	36
SPO_2 rest	94.87±1.98	91	99

AT: Anaerobic Threshold, VO_2: Oxygen Consumption, VCO_2: Carbon Dioxide Production, VE: Minute Ventilation, SPO_2: Oxygen Saturation, $PETCO_2$: Pressure of End-Tidal Carbon Dioxide

VE/VCO_2 slope was also evaluated for any correlation with CKD cause but no desirable result was found. For breathing reserve (BR), the mean ± SD was reported to be 50.72±19.46, and 50% of the patients had BR>52.5 but no relationship was found between smoking and the cause of CKD in this regard. The values related to SpO_2 and $PETCO_2$ are presented in Table 1. This is worth disclosing that SpO_2, SpO_2 at rest, and $PETCO_2$ at rest correlated with the cause of CKD among our participants (P value= 0.01, 0.034, and 0.027, respectively). $PETO_2$ had no relationship with the cause of CKD (Table 2).

Table 2. Correlation between cause of CKD and CPET parameters

	Cause of CKD
AT	0.580
VO_2%	0.149
VO_2/kg(ml/min/kg)	0.291
VE/VCO_2	*0.019
VE/VCO_2 slope	0.131
SPO_2	*0.010
$PETCO_2$	*0.027
SPO_2 rest	*0.034

AT: Anaerobic Threshold, VO_2: Oxygen Consumption, VCO_2: Carbon Dioxide Production, VE: Minute Ventilation, SPO_2: Oxygen Saturation, $PETCO_2$: Pressure of End-Tidal Carbon Dioxide. * $P<0.05$.

Concerning systolic blood pressure (SBP), although hypertension was the main cause of CKD in 31.1% of our participants and the mean of peak SBP=192.02 and SBP at rest=138.24, no correlation was found between the values of SBP in the current study and the cause of CKD during our analysis (Table 2).

DISCUSSION

The current study aimed to find any characteristics of cardiopulmonary exercise tests and the causes of chronic kidney disease among a group of patients who were referred to our hospital for dialysis for more than three months. Four parameters of CPET were found to be correlated with the main cause of CKD including VE/VCO_2, SPO_2, SPO_2-rest, and $PETCO_2$ at rest. The most common causes of CKD were hypertension and diabetes mellitus. Hypertension has been known as not only the cause of CKD but also a complication of it. Studies also showed that diabetes mellitus is a main cause of CKD. Some believe that certain populations may have a tendency to CKD including elderly individuals, early-onset DM in youth, obese individuals, some specific ethnicities, and people in low/middle-income societies. These risk factors are usually seen in DM and may show a correlation with the mentioned conditions.

Cardiopulmonary exercise test has been raised through the recent decade to objectively assess the function of circulatory and respiratory systems as well as body metabolism which are main factors of quality of life and physical exercise capacity. Chronic kidney disease is also one of the issues correlated to exercise capacity intolerance which was assessed by the current study. The most important parameter is VO_2/Kg/min which was lower than the predicted values in 100% of our participants and its range showed only 3(6.5%) VO_2/Kg values equal to or more than 25ml/min/Kg. This may show the severity of impaired cardiopulmonary capacity in ESRD compared with a healthy population. Kirkman et al. figured out that CPET could reveal subclinical cardiopulmonary intolerance in non-dialysis CKD patients (10). They compared CKD patients with healthy participants and found lower peak VO_2 and higher VE/VCO_2 slop among which the latter was even lower than what we reported (32±0.8 *vs.* 36.44±6.25). Comparing stages 2-5 of CKD, Faria et al. showed an indirect linear correlation between VO_2/Kg and the stage of the disease in a comparison with healthy people (11). Interestingly, their patients had no different spirometry findings compared to healthy people but heart rate reserve (HRR) also differed between the studied groups. It is inevitable to believe that the VO_2 peak is known as a promising predictor of survival among patients who suffer from kidney disease at the end stage as Yang et al. pointed out in 2017 (12). Wallin et al. believed that not only systemic factors like low peak heart rate and hemoglobin, but also peripheral factors such as microcirculation dysfunction, mitochondrial dysfunctions, and muscle mass loss may affect VO_2 peak and consequently exercise capacity (8). These are factors usually involved in hypertension and diabetes mellitus which, in turn, play a key role in renal failure. This was later confirmed by Lim et al.(13) when they compared exercise capacity before and after kidney transplantation in 253 participants to show VO_2 max improvement after transplantation as well as Pei et al. (14) who addressed aerobic exercise and rehabilitation to improve cardiopulmonary function.

From our participants, 50% showed VE/VCO_2 ≥34, especially in DM. Sprick et al. evaluated the exercise capacity of three groups of ESRD, hypertensive and healthy people to show that there was impaired muscle functional sympatholysis (FS) among ESRD patients which is, in turn, due to low oxygen tissue saturation index (TSI) (15). However, metabolic acidosis in CKD and consequently in ESRD was raised by Sprick et al. in an article published in 2019 concluding that low serum bicarbonate may increase blood pressure but reduce muscle interstitial PH to cause fatigue earlier during exercise (16). A study by Fellstorm et al. revealed that AT<40, which means a higher rate of early metabolic acidosis, was associated with more left ventricular mass on echocardiography and also excess mortality among ESRD cases waiting for transplantation. More than 65% of our participants had AT<40 and their mean AT was 35.46 which was less than the survivors reported by Fellstorm et al. Although they could not evaluate the role of age and diabetes but, they considered low AT and previous history of renal transplantation as the two independent main risk factors for all-cause mortality in ESRD patients (17).

Our study also found a correlation between $PETCO_2$ and the cause of ESRD which had DM and HTN equally as the main causes to increase it and almost no other causes of ESRD had $PETCO_2$≥29. This may address the very low $PETCO_2$ among dialysis patients compared to healthy people as well as the fact that these results are not generalizable due to the limited sample size in the current study. We expected very low levels of $PETCO_2$ in DM-or HTN-related renal failure but primary renal problems like glomerulonephritis may affect $PETCO_2$ more than systemic conditions like DM and HTN. We also found a correlation between SPO_2 and the cause of ESRD which showed less O_2 saturation than 95% in hypertensive patients while Diabetic patients showed significant SPO_2≥95% in two-thirds. The same result was obtained for SPO_2-rest too.

To the best of our knowledge, there is no research work to study cardiopulmonary exercise tests in a population of dialysis patients with a comparison between all CPET parameters and the main suggested causes of ESRD. It is worth mentioning that a great number of physicians focus just on medications and some dietary recommendations that are supported by medical texts and have no attention to rehabilitation aspects which are nowadays the case of debate and controversy. However, the current study may suggest encouraging ESRD patients to help themselves by appropriate exercise as cardiopulmonary rehabilitation since just less than 60% of the participants were diagnosed with deconditioning. Although, they may be strongly resulted from muscular weakness, hyperventilation and fatigue could be improved by a great range through cardiorespiratory rehabilitation. .

CONCLUSION

Despite a limited sample size, the current study showed that VO_2/Kg, VE/VCO_2, $PETCO_2$, and SPO_2 are the main parameters affected by dialysis as expected; through a multifactorial mechanism which is not too hard to explain. The current study suggests using cardiopulmonary rehabilitation for all chronic medical conditions such as CKD and ESRD that increase the rate of metabolic acidosis. It is worth working with a larger population to achieve comprehensive management of ESRD on dialysis and provide optimal quality of life for patients.

Conflicts of interest

There are no conflicts of interest.

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