Reduction of functional cardiovascular reserve in the stages of chronic kidney disease

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SUMMARY

OBJECTIVE: Patients with chronic kidney disease (CKD) present reduced oxygen consumption at peak exercise (VO_2 peak). No studies have evaluated objective measures of the cardiovascular reserve, besides VO_2 peak and VO_2 at the anaerobic threshold (VO_2 AT), and compared these measures among ckd patients at different stages of the disease.

METHODS: Fifty-eight patients [pre-dialysis group (PD)=26, hemodialysis group (HD)=20, and post-kidney transplant group (KT)=12] were included. The following measures of cardiovascular reserve were obtained: 1) peak heart rate (HR); 2) peak systolic blood pressure (SBP); 3) VO_2 peak and % predicted; 4) VO_2 AT and % of predicted VO_2 ; 5) peak circulatory power; 6) ventilatory efficiency for the production of carbon dioxide (VE/VCO₂ slope); 7) oxygen uptake efficiency slope (OUES); and 8) recovery of gas exchange.

RESULTS: The VO_2 peak and VO_2 AT in the PD, HD, and KT groups were reduced to 86% and 69%, 70% and 57%, and 79% and 64% of the predicted value, respectively. Patients in the HD group had lower VO_2 peak (17.5±5.9 vs. 23.2±8.2 [p-value=0.036]) and VO_2 AT (14.0±5.2 vs. 18.3±4.7 [p-value=0.039]) compared to patients in the KT group. OUES was significantly lower in the HD group compared to the KT group (p-value=0.034). Age in the PD, HD, and KT groups and sedentary lifestyle in the KT group were predictors of VO_2 peak.

CONCLUSIONS: CKD patients presented a reduction in cardiovascular reserve regardless of the stage of the disease. However, hemodialysis patients presented a greater reduction of cardiovascular reserve when compared to post-kidney transplant patients.

KEYWORDS: Renal insufficiency, chronic. Exercise test. Kidney transplantation. Renal dialysis.

INTRODUCTION

The cardiopulmonary exercise test (CPET) is considered a standard reference in the evaluation of cardiopulmonary and metabolic responses to aerobic exercise in patients with cardiovascular diseases¹.

Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease². Complex changes in the cardiovascular system of CKD patients result in structural and functional changes that may lead

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to reduced tolerance to exercise and quality of life, increased morbidity, and finally, premature death³.

Exercise capacity depends on the health of the cardiovascular system in maintaining the transport of oxygen and carbon dioxide between the cellular and pulmonary systems⁴. A reduction in exercise capacity limits the range of physical activities a patient can perform. Several measures of the functional cardiovascular reserve, in addition to those traditionally used, can be obtained from a CPET and have been used to evaluate patients with heart failure^{5,6}.

Several studies have already demonstrated a reduction in the functional cardiovascular reserve through a reduction of oxygen uptake at peak exercise (VO2 peak) in CKD patients⁷⁻¹⁰. However, we are not aware of any previous studies that evaluated objective measures of the cardiovascular reserve, besides VO2 peak and VO₂ at the anaerobic threshold (AT), and compared these measurements among CKD patients at different stages of the disease. Therefore, the objective of this study was to evaluate measures of functional cardiovascular reserve in CKD patients at different stages of the disease [pre-dialysis (PD), hemodialysis (HD), and post-kidney transplant (KT)] and to determine the predictors of VO₂ peak in these groups of patients. We hypothesized that although these patients have CKD in common, measurements of functional cardiovascular reserve would be significantly different in the different stages of CKD. The knowledge of these changes and differences may guide the treatment and implementation of preventive measures for other diseases, especially cardiovascular ones, which may occur due to renal disease.

METHODSStudy design

A secondary analysis was carried out using the dataset of research performed with patients who were submitted to pre-dialysis treatment, hemodialysis, or kidney transplant under follow-up at the Nephrology Unit of the Charity Hospital of Ijuí-RS. The pieces of research were cross-sectional studies conducted between 2012 and 2014. The researcher responsible for the dataset approved its use.

Patients were included in this study if they were at least 18 years old and had all data from the evaluation protocol in the databases, which included complete clinical evaluation, laboratory analysis, and cardio-pulmonary testing.

Study population

A total of 241 patients were followed up at the Nephrology Unit of the Charity Hospital of Ijuí-RS and screened between 2012 and 2014. From this total, 72 patients were included in previous research, of which 58 had complete biochemical and exercise capacity data and, therefore, were analyzed in this study (Fig. 1).

Data collection and variables

Clinical and demographic data were recorded, including age, sex, CKD etiology, time of current treatment, weight, height, body mass index (BMI), and presence of cardiovascular risk factors [sedentary lifestyle, systemic arterial hypertension (SAH), diabetes mellitus (DM), alcoholism, and smoking]. The laboratory data of creatinine, urea, potassium, hemoglobin, and hematocrit were collected from recent hematological and biochemical tests whose values were recorded on the medical records of the patients who were registered in the databases.

The CPET or maximum incremental exercise test was performed on a treadmill (Imbrasport, Porto Alegre, Brasil), with the following ramp protocol: initial speed of 1 km.h⁻¹ and final speed of 6 km.h⁻¹; and initial inclination of 0% and final inclination of 10%. Exhausted gases were analyzed every 20 seconds through a gas analyzer (total metabolic analysis system, TEEM 100, Aero Sport, Ann Arbor, Michigan). Blood pressure was measured every 3 minutes with a sphygmomanometer. Heart rate (HR) was determined using the R-R interval from 12 electrocardiogram leads. The CPET variables were calculated as described by Dall'Ago et al. 11. In summary, the VO₂ peak was defined as the highest value achieved during the test for 20 seconds, and peak circulatory power was calculated as the product of VO2 peak and peak systolic blood pressure (peak SBP). The recovery kinetics of oxygen uptake (T_{1/2}VO₂) was evaluated as the time required for a 50% decrease from the VO₂ peak and calculated using the least-squares model, according to Dall'Ago et al.¹¹. The oxygen uptake efficiency slope (OUES) was calculated as the slope of the linear regression line between VO₂ and the logarithm of ventilation (VE)¹². The evaluation of ventilatory efficiency was calculated using the linear regression model relating the VE and carbon dioxide production (VCO₂) during the exercise. For this, data from the entire cardiopulmonary test were used, from the beginning to the peak of the exercise. The slope values of the VE/VCO₂ ratio line were used for the analysis of ventilatory efficiency. The first ventilatory threshold (also known as the anaerobic threshold) was determined by reviewing the gas exchange curves and was the heart rate in which the ventilatory equivalent for oxygen increases systematically without an increase in the ventilatory equivalent for carbon dioxide¹. The prediction equation of the maximal oxygen uptake (VO_2 max), proposed by Almeida et al.¹³ for the Brazilian population, was used. All patients continued taking their usual medication prescribed by their physicians.

Statistical analysis

Normality was measured using the Kolmogorov-Smirnov test. Depending on the distribution of the variable, continuous data were described through the mean and standard deviation or median and interquartile range and compared by ANOVA (Tukey) or Kruskal-Wallis test, as appropriate. Categorical variables were presented as a percentage and were compared by Chi-square test or Fisher's exact test, as appropriate.

The VO₂ peak (in mL.kg-1.min-1) adjusted for age and body mass index was the outcome variable of primary interest in this study and, therefore, was used as a dependent variable for regression modeling analyses. To identify important predictors of VO₂ peak, a sequence of regression modeling analyzes were performed. Patient data were analyzed separately to determine the variables that were predictive of the VO₂ peak within each group. Significantly different variables between groups were first analyzed in a univariate linear regression model. Then, those significantly associated in the univariate analysis (p-value<0.05) were included in a multiple linear regression model. All data were stored and analyzed in the Statistical Package for the Social Sciences (SPSS) software for windows v. 20.0. A significance level of 5% was adopted.

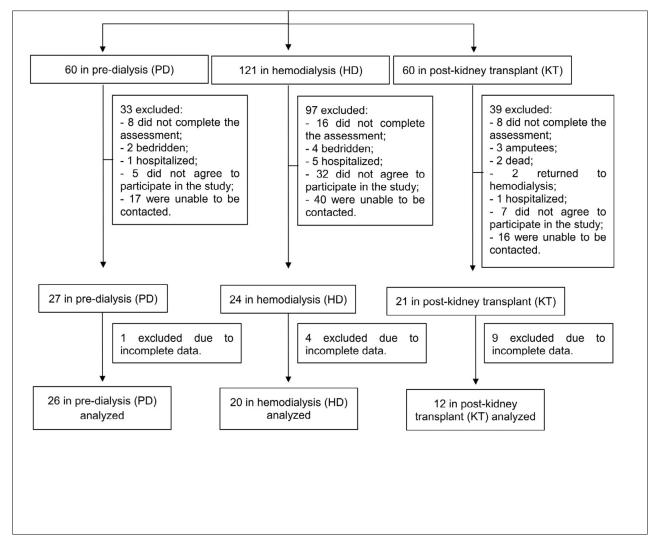


FIGURE 1

RESULTS

Characteristics of the patient population

Fifty-eight patients were included in this study. The characteristics of these patients are shown in Table 1. The CKD patients of the three groups had similar (a) sociodemographic and clinical characteristics: age (p-value=0.202), sex (p-value=0.526), BMI (p-value=0.790), time of CKD (p-value=0.084); and (b) prevalence of comorbidities such as: hypertension (p-value=0.340), DM (p-value=0.768), smoking (p-value=0.237), and alcoholism (p-value=0.146).

Biochemical data differed significantly between the PD, HD, and KT groups (Table 1). Creatinine and urea levels were higher in patients in the HD group when compared to patients in the PD group (p-value<0.001; p-value=0.005) and KT group (p-value<0.001; p-value<0.001), respectively. Additionally, creatinine and urea levels were higher in patients in the PD group when compared to patients in the KT group (p-value=0.050; p-value=0.012), respectively. Potassium was significantly higher in the PD group when compared to the HD (p-value=0.050) and KT (p-value=0.042) groups. Hemoglobin and hematocrit levels were lower, and

consequently the percentage of patients with anemia was higher in the HD group when compared to the PD (p-value=0.001; p-value=0.001) and KT groups (p-value<0.001; p-value<0.001).

Functional cardiovascular reserve

Metabolic data of the CPET for the three groups are presented in Fig. 2. When compared to patients in the KT group, patients in the HD group had lower VO_2 peak (17.5±5.9 vs. 23.2±8.2 [p-value=0.036]), corresponding to 70.5% vs. 79.5% of the predicted VO_2 peak, and VO_2 AT (14.0±5.2 vs. 18.3±4.7 [p-value=0.039]), corresponding to 56.7% vs. 63.7% of the predicted VO_2 peak. Patients in the PD group presented lower peak circulatory power values when compared to those in the HD group (p-value=0.002). The OUES was significantly lower in the HD group when compared to the KT group (p-value=0.034).

Independent predictors of VO₂ peak

The increase in age was negatively associated with VO_2 peak in patients in the PD group (b=-0.13; p-value=0.034), HD group (b=-0.33; p-value=0.002), and KT group (b=-0.66, p-value=0.011). A sedentary

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION IN THE DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE

Variables	PD (n = 26)	HD (n = 20)	KT (n = 12)	p-value
Age, years	61.2 ± 16.3	56.2 ± 11.3	53.3 ± 8.6	0.202
Males, n (%)	17 (65.4)	14 (70.0)	10 (83.3)	0.526
BMI, kg.m ⁻²	27.8 ± 4.3	26.8 ± 4.3	27.4 ± 5.3	0.790
Treatment time ^a , months	12.0 [5.5 – 36.0]	36.0 [14.5 – 50.2]	31.0 [20.5 – 207.5]	0.084
Comorbidities, n (%)				
SAH	23 (88.5)	15 (75.0)	11 (91.7)	0.340
DM	13 (50.0)	8 (40.0)	6 (50.0)	0.768
Sedentary lifestyle ^b	21 (80.8)	17 (85.0)§	5 (41.7)‡	0.015*
Smoking	4 (15.4)	1 (5.0)	0 (0.0)	0.237
Alcoholism	8 (30.8)	7 (35.0)	0 (0.0)	0.146
Biochemical parameters				
Creatinine, mg.dL ⁻¹	3.2 ± 1.5†	9.3 ± 2.5§	1.5 ± 0.3‡	<0.001*
Urea, mg.dL ⁻¹	106.6 ± 43.3†	160.1 ± 46.4§	55.3 ± 15.0‡	<0.001*
Potassium, mEq.L ⁻¹	8.8 ± 11.7†	5.2 ± 0.8	4.4 ± 0.4‡	0.004*
Hemoglobin, g.dL ⁻¹	12.3 ± 2.1†	9.7 ± 1.6§	13.8 ± 1.5	<0.001*
Hematocrit, %	37.6 ± 6.0†	29.8 ± 5.0§	41.7 ± 4.6	<0.001*
Anemia ^c , n (%)	13 (50.0)†	20 (100.0)§	4 (33.3)	<0.001*

PD: pre-dialysis group; HD: hemodialysis group; KT: post-kidney transplant group, BMI: body mass index; CKD: chronic kidney disease; SAH: systemic arterial hypertension; DM: diabetes mellitus. a: Treatment time, months: this variable refers to the time of conventional treatment through the use of medication in the PD group, the time of hemodialysis treatment in the HD group, and the time since kidney transplant for the KT group. b: The patient was considered sedentary if he/she reported not performing any physical activity at least 3 times a week for at least 30 minutes. c: Anemia was defined according to World Health Organization criteria (hemoglobin <13 g.dl-1 in men and <12 g.dl-1 in women). Values for categorical variables are presented as frequency (percentage); values for continuous variables are presented as mean ± standard deviation or median [interquartile range]; the p-value exact calculated by the Tukey test or Kruskall-Wallis test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. *p-value <0.05. †p-value = 0.05 when compared to the PD and HD groups (Mann-Whitney test or Fisher's exact test). ‡p-value = 0.05 when compared to the PD and KT groups (Mann-Whitney test or Fisher's exact test). \$p-value = 0.05 when compared to the PD and KT groups (Mann-Whitney test or Fisher's exact test).

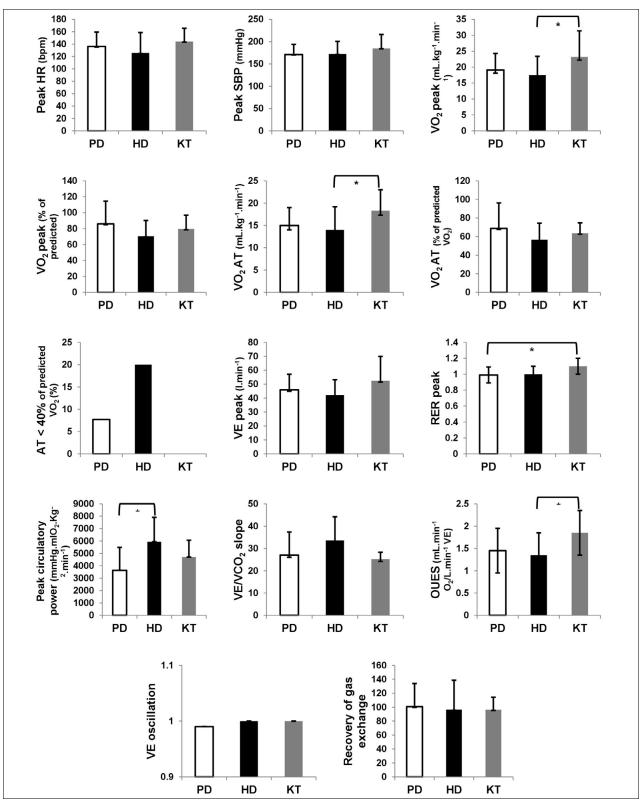


FIGURE 2

lifestyle was negatively and significantly associated with VO_2 peak in patients in the KT group (b=11.63, p-value= 0.007), but not in the PD (b=-1.85, p-value=0.487) and HD (b=-2.67, p-value=0.483) groups. The analysis of the multiple linear regression model for the KT group was performed. In the post-kidney

transplant patient population, the constant VO_2 peak was 54.59 mL.kg⁻¹.min⁻¹ (adjusted R²=0.76; p-value<0.001). Higher age (b=-0.51 [95% CI=-0.85 – -0.18], p-value=0.007) and sedentary lifestyle (b=-9.28 [95% CI= -14.83 – -3.72], p-value=0.004) were significant predictors of lower VO_2 peak.

DISCUSSION

To our knowledge, this is the first study to evaluate measures of functional cardiovascular reserve in CKD patients and their association with the stages of kidney disease. Studies involving objective measures of the functional cardiovascular reserve are common for patients with heart disease^{5,6}, but for CKD patients, such studies are rare. In this study, we detected that VO₂ peak and VO₂ AT in pre-dialysis, hemodialysis, and post-kidney transplant patients were reduced to 86% and 69%, 70% and 57%, and 79% and 64% of the predicted value, respectively. A previous study has shown that reduced VO2 peak and VO2 AT values were associated with an increased risk of premature death in CKD patients¹⁴. The present study further demonstrated that these parameters were significantly reduced in patients in the HD group compared to patients in the KT group. Other findings were that a) patients in the PD group had lower values of circulatory power when compared to those in the HD group, and b) OUES was significantly lower in the HD group when compared to the KT group.

OUES and circulatory power are variables which are evaluated less frequently than other traditional indices. Reduced OUES values^{5,15} and circulatory power^{16,17} predict a worse prognosis in heart disease. Despite the great potential of these variables for clinical evaluation¹⁶⁻¹⁸, we did not find its use in the population of CKD patients, so our data are pioneering and can serve as a comparison for future studies. When comparing our OUES data with those from another population that also had a chronic limiting disease, such as patients with heart failure (1.96 ml.min⁻¹)⁵, our patients performed worse regardless of the stage of CKD; only the KT group had slightly similar values.

 ${
m VO_2}$ peak, ${
m VO_2}$ AT, and OUES were significantly better in post-kidney transplant patients, confirming their better exercise capacity when compared to patients in the HD group. These findings corroborate the literature that shows that kidney transplant is the only treatment that offers better survival compared to other renal replacement therapies. A successful kidney transplant reduces the risk of cardiovascular mortality when compared to maintaining dialysis therapy 14,19,20. A recent study has demonstrated an improvement in the survival of patients with reduced functional cardiovascular reserve after kidney transplant 14.

Although ${\rm VO_2}$ peak, ${\rm VO_2}$ AT, and OUES were better in the post-kidney transplant patients, all the other

measures of the functional cardiovascular reserve were not significantly different from the patients in the PD and HD groups. This evidences that the improvement in exercise capacity is not complete, and that it depends on other factors such as the adoption of a healthy lifestyle with regular practice of exercise. For the KT patients, a sedentary lifestyle was a significant independent predictor of lower VO₂ peak. Physical training has been shown to improve VO₂ peak in patients undergoing long-term hemodialysis²¹.

Comparable reduced VO_2 peak values (18.8 mL.kg⁻¹.min⁻¹)¹⁰; (18.5 mL.kg⁻¹.min⁻¹)²¹; (18.6 mL.kg⁻¹.min⁻¹)⁷ were documented in previous studies in CKD patients undergoing hemodialysis, but other measures of the cardiovascular reserve were not available for comparison^{7,22}. A comparison with data from Sietsema et al. ^{7,22} reveals that our patients' hemoglobin levels were lower (11.2 and 11.8 g.dL⁻¹), although the dialysis time was similar (41.5 and 32.0 months). Our patients were older and had a higher BMI, which may result in a lower VO_2 peak; however, the VO_2 peak was comparable across studies.

The hemoglobin levels of patients in our study were lower (11.8 g.dL⁻¹) when compared to the study of Ting et al. ¹⁰, despite dialysis time (32.0 months), age (53.3 years), and BMI (27.2 kg.m⁻²) being similar. This study evaluated other objective measures of cardiovascular reserve such as VO $_2$ peak (73.4% of predicted), VO $_2$ AT (11.2 mL.kg⁻¹.min⁻¹), VO $_2$ AT (43.9% of predicted VO $_2$), VE/VCO $_2$ slope (29.3), and HR peak (132.8 bpm), which were also relatively similar to those found in our study; however, our HD patients presented worse performance, except in VO $_2$ AT.

Patients in the studied HD group presented a higher prevalence of anemia and significantly lower hemoglobin and hematocrit levels when compared to patients in the PD and KT groups. It is known that the presence of anemia in CKD is determined by different factors such as relative erythropoietin (EPO) deficiency, iron deficiency, inflammation, hyperparathyroidism, blood loss, decreased half-life of red blood cells, and deficiency of folic acid and vitamin B12²³.

Creatinine and urea are markers traditionally used to characterize the impairment of glomerular function. In our study, the values of these two markers for all three groups support the values of erythrocyte parameters since the greater the renal damage, the lower the EPO production, and consequently, the lower the erythrocyte production leading to an anemic state²⁴. Thus, even using recombinant

human erythropoietin, hemodialysis patients present a greater degree of anemia, and a greater degree of functional impairment. Pre-dialytic patients still have higher hemoglobin concentrations due to better renal integrity. Patients after renal transplantation, due to the production of the grafted organ, are able to produce a greater amount of EPO and, therefore, have higher hemoglobin levels.

Hemoglobin and iron are involved in the processes of releasing oxygen to tissues, so they may affect exercise capacity. A recent study in patients with heart failure observed a significant reduction in exercise capacity in parallel to reduced hemoglobin levels, and in patients with anemia and iron deficiency, exercise capacity was significantly lower than in patients with isolated anemia or iron deficiency²⁵. We observed a significant difference in hemoglobin levels between the PD, HD, and KT groups, and in the VO, peak and VO, AT between the HD and KT groups. However, in a subgroup analysis, we did not observe a significant difference in VO2 peak between patients with and without anemia (p-value=0.390); additionally, there was no correlation between hemoglobin levels and VO₂ peak (r=0.189; p-value=0.250) and VO₂ AT (r=0.174, p-value=0.290). This evidences that in this population, regardless of the CKD stage, anemia did not significantly affect the measures of cardiovascular reserve and was not a predictor of VO₂ peak.

This study is characterized by the initial exploration of measures of functional cardiovascular reserve in CKD patients and by comparing these measures between the different stages of the disease. Like any study, it has some limitations. First, although the literature indicates that measures of the functional cardiovascular reserve are prognostic markers in patients with heart failure, the cross-sectional nature and relatively small sample size of the present study did not allow us to expand the prognostic utility of both indices. Therefore, further prospective evaluations in this population are required to use these measures as prognostic markers.

CONCLUSIONS

Our study shows that patients with CKD present a reduction of functional cardiovascular reserve regardless of the stage of the disease they are in. However, hemodialysis patients presented a greater reduction of cardiovascular reserve when compared to post-kidney transplant patients. Since a sedentary lifestyle was an independent predictor of the lowest VO_2 peak in post-kidney transplant patients, the importance of physical training to improve functional cardiovascular reserve is emphasized, especially in these patients.

Authors' contributions

Schneider J designed the study, analyzed the data, and wrote the manuscript. Fontela PC reviewed the analysis of the data and the manuscript and provided intellectual content of critical importance to the work described. Frizzo MN, Franz LBB, and Oliveira OB reviewed the manuscript. Winkelmann ER designed the study, reviewed the analysis of the data, and wrote the manuscript. All authors approved the final version of the manuscript.

RESUMO

OBJETIVO: Pacientes com doença renal crônica (DRC) apresentam redução no consumo de oxigênio no pico do exercício (VO_2 pico). Nenhum estudo avaliou medidas objetivas da reserva cardiovascular, além do VO_2 pico e do VO_2 no limiar anaeróbio (LA), e comparou essas medidas entre pacientes com DRC nos diferentes estágios da doença.

MÉTODOS: Cinquenta e oito pacientes [grupo pré-diálise (PD)=26, grupo hemodiálise (HD)=20 e grupo pós-transplante (PT)=12] foram incluídos. As seguintes medidas da reserva cardiovascular foram obtidas: 1) frequência cardíaca (FC) pico; 2) pressão arterial sistólica (PAS) pico; 3) VO₂ pico e % do predito; 4) VO₂ LA e % do VO₂ predito; 5) potência circulatória pico; 6) eficiência ventilatória para a produção de dióxido de carbono (VE/VCO₂ slope); 7) eficiência ventilatória para o consumo de oxigênio (Oues); 8) recuperação das trocas gasosas.

RESULTADOS: O VO_2 pico e o VO_2 LA nos grupos PD, HD e PT foram reduzidos para 86% e 69%, 70% e 57%, e 79% e 64% do valor previsto, respectivamente. Pacientes do grupo HD obtiveram VO_2 pico (17,5±5,9 vs. 23,2±8,2 [p=0,036]) e VO_2 LA (14,0±5,2 vs. 18,3±4,7 [p=0,039]) mais baixo, comparado aos pacientes PT. A Oues foi significativamente menor no grupo HD comparado ao grupo PT (p=0,034). Idade nos grupos PD, HD e PT, e sedentarismo no grupo PT foram preditores do VO_2 pico.

CONCLUSÃO: Pacientes com DRC apresentam redução da reserva cardiovascular independentemente do estágio da doença. No entanto, pacientes em hemodiálise apresentam uma redução mais acentuada da reserva cardiovascular quando comparados aos pacientes pós-transplante.

PALAVRAS-CHAVE: Insuficiência renal crônica. Teste de esforço. Transplante de rim. Diálise renal.

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