Renal Replacement Therapy

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Six-minute walk test may be a reliable predictor of peak oxygen uptake in patients undergoing hemodialysis

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Abstract

Background Cardiorespiratory fitness seems to play an important role in the general health of patients undergoing hemodialysis (HD). However, the prediction of peak oxygen uptake ($\dot{V}O_{2peak}$) in a clinical setting is not widely adopted for these patients.

Objectives Evaluate the agreement and reliability between directly and indirectly $\dot{V}O_{2peak}$ measurements in patients undergoing HD.

Methods This is a cross-sectional study with patients undergoing HD that performed a cardiopulmonary exercise test (CPET) with 5/10 watts incremental load in each minute using a cycle ergometry to directly evaluate the $\dot{V}O_{2peak}$, and the 6-min walk test (6MWT) in a 30-m corridor to indirect measures it. Both tests were performed on a midweek non-dialysis day. Bland–Altman analysis of agreement limits was used with direct and indirect $\dot{V}O_{2peak}$ values. Intraclass correlation coefficient (ICC) and Cronbach's Alpha was used to evaluate the reproducibility and reliability between direct and indirect $\dot{V}O_{2peak}$ values.

Results Twenty-six patients (54.4 ± 14.5 years, 53.8% of male) were evaluated. The $\dot{V}O_{2peak}$ direct mean obtained through CPET was 15.91 ± 5.26 (ml/kg/min), while the indirect mean obtained through 6MWT was $\dot{V}O_{2peak}$ of 14.89 ± 4.21 (ml/kg/min). There was a strong positive correlation between both $\dot{V}O_{2peak}$ values ($r = 0.734$; $p < 0.001$). The Bland–Altman analysis demonstrated that the methods agreed with each other ($p = 0.103$). Also, the ICC (0.829) and Cronbach's Alpha (0.846) showed excellent reproducibility and reliability.

Conclusions 6MWT is a reliable tool for estimating $\dot{V}O_{2peak}$ in patients undergoing HD.

Keywords Chronic kidney disease, Cardiopulmonary exercise test, Six-minute walk test, Oxygen uptake, Hemodialysis

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Introduction

Patients with chronic kidney disease (CKD) may experience physical deconditioning due to a high sedentary behaviour and impairments of musculoskeletal, cardiopulmonary, and cardiovascular systems caused by the hydroelectrolytic imbalance, and the subclinical pro-inflammatory state [1–3]. The fatigue symptoms commonly seen in a patient with CKD are exacerbated by the hemodialysis (HD) treatment and impact the physical deconditioning [4]. In the long term, it may deteriorate cardiorespiratory fitness and increase the risk of mortality due to the high incidence of cardiovascular events [5–7].

Cardiorespiratory fitness is accurately evaluated by peak oxygen uptake (VO_{2peak}) [8]. The VO_{2peak} reflects the greatest oxygen-carrying capacity of the blood, oxygen extraction at the tissues, and oxygen uptake by the musculoskeletal system [5, 7, 8]. Patients undergoing HD commonly show lower cardiorespiratory fitness and VO_{2peak} than healthy individuals [9]. Peak oxygen uptake values ≤ 17.5 ml/min/kg have been previously associated with lower survival in patients undergoing HD, indicating the clinical importance of evaluating cardiorespiratory fitness in this population [6].

Generally, the most popular clinical tests to evaluate cardiorespiratory fitness are the cardiopulmonary exercise test (CPET) and the 6-min walk test (6MWT) [10, 11]. The CPET is the gold standard method to assess functional impairment related to cardiorespiratory health and provides a direct VO_{2peak} measurement. However, advanced and high-cost equipment is required, as well as a special room for sudden medical emergencies. Moreover, a specialized team must be present [8]. Thus, simple, widely available, reliable, and economically feasible tests to routinely evaluate cardiorespiratory fitness in the clinical setting are necessary, such as the 6MWT.

The 6MWT is a field widely tool applied in different populations, such as patients with CKD, for functional capacity measurement. Its performance demands a 30-m corridor and portable equipment to evaluate blood pressure, oxygen saturation (SpO_2), and heart rate (HR) [12]. Therefore, 6MWT appears to be a low-cost and easy-application test to indirectly estimate cardiorespiratory fitness and may be done more frequently than the CPET test in the clinical routine of patients undergoing HD [11].

The main difference between both tests is that CPET is a lab test that provides maximum exercise exertion, directly measuring the VO_{2peak}, whereas the 6MWT is a field submaximal exercise test that indirectly estimates VO_{2peak} by the distance walked [13]. Despite that, indirect evaluations of VO_{2peak} in patients undergoing HD in clinical setting is not widely adopted. Therefore, this study aimed to evaluate the agreement and reliability between directly and indirectly VO_{2peak} measurements in patients undergoing HD.

Methods

This is a cross-sectional study that enrolled patients with CKD from two HD centres in Porto Alegre, Brazil (Division of Nephrology of Hospital de Clínicas de Porto Alegre—HCPA and Instituto de Doenças Renais—IDR), who were invited to participate from September 2016 to August 2019. This study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (40,167,014.3.0000.5327), and it was conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent.

All eligible patients had been diagnosed with CKD ≥ 6 months, undergoing HD > 3 months, clinically stable (absence of any hospitalization in the last 30 days), ≥ 18 years old, and did not suffer from any musculoskeletal impairment such as sequelae by stroke or walking damage, and had a serum haemoglobin level ≥ 10.0 g/dl (100 g/l). Patients who had acute myocardial infarction within 3 months, an inflammatory process in treatment with anti-inflammatory or antibiotics drugs in the last 30 days, decompensated coronary artery disease, symptomatic peripheral arterial disease, and lower-limb arteriovenous fistula, arteriovenous grafts, or tunnelled catheter due to the unknown risk were not eligible. All patients performed CPET and 6MWT to be included in the analysis.

Cardiopulmonary exercise test

The CPET was performed by a trained physiotherapist and physician in a cycle ergometer to directly evaluate the VO_{2peak} (ml/kg/min). It has been applied an incremental load protocol with 5 or 10 Watts (W) per minute [8]. The incremental load protocol was defined by the authors respecting the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) [8] guidelines and according to CKD cause. Those with suspicion of hypertension as CKD cause were submitted to a 5 W incremental due to possible hemodynamic and cardiovascular acute adverse events. Patients with other CKD causes had a 10 W increase protocol.

CPET was performed at Vmax® Encore metabolic cart system (CareFusion, San Diego, California, USA) using a gas analyzer. The patients used a 10-lead electrocardiogram cardiosoft (V1, V2, V3, V4, V5, V6, RL, RA, LL, LA) to evaluate the heart electrical function and to measure the HR and maximum HR percentage ($\%HR_{max}$) and were also monitored during the whole CPET through pulse oximetry to obtain SpO_2, and a manual sphygmomanometer in the non-fistulated arm to obtain blood pressure.

The HR, $\%HR_{max}$, and SpO_2 were constantly registered, and the systolic blood pressure (SBP), diastolic blood pressure (DBP), dyspnea perception, and lower limb fatigue (i.e., evaluated by a Borg CR10 Scale) were monitored every one-minute [8, 14].

Patients were verbally encouraged before and during the whole CPET to obtain a maximum physiological exertion (respiratory exchange ratio [RER] > 1.0) [8, 15]. CPET consisted of 4 phases: (a) three-minute rest in which was verified the absence of hyperventilation; (b) a warm-up unloaded cycling (0 W for 2-min); (c) an incremental phase of exercise every minute (5/10 W—cycling rate at 60–65 revolutions per minute) until the patient reaches volitional exhaustion (RER > 1.0) or the test is terminated by the physician. If the subject did not reach an RER > 1.0, they were encouraged to continue the test; d) an active recovery unloaded (0 W for 1 min).

If necessary, CPET was interrupted as suggested by the ATS/ACCP under the supervision of a physician [8]. In the end, HR, $\%HR_{max}$, SpO_2, SBP, and DBP delta values were registered.

Six-minute walk test

6MWT was performed using a standard protocol according to ATS guideline [12]. It was performed in a 30-m corridor with signs every three-meter and delimitated by cones. Immediately before the test's beginning and after its end, HR and SpO_2 were evaluated through pulse oximetry, SBP, and DBP through a manual sphygmomanometer in the non-fistulated arm, and dyspnea and lower limbs fatigue perception were evaluated by Borg CR10 Scale [12, 14].

The patient observed the researcher performing the test and then was instructed to walk as far as possible for 6-min and maintain a normal walking pace. Patients were able to interrupt the test if necessary. At each minute of walking the researcher communicated clearly and calmly how many minutes remained until the end of the test. In the end, the walked distance was measured. Besides, HR, $\%HR_{max}$, SpO_2, SBP, and DBP delta values were registered.

The reference equation to predict the 6MWT distance was proposed by Enright and Sherrill [16]. The formula proposed by Cahalin et al. [13] was used to indirectly estimate $\dot{V}O_{2peak}$ by the 6MWT:

$$\dot{V}O_{2peak} = 0.02x \text{ distance}(m) - 0.191\, x \text{ age}(\text{years}) - 0.07x \text{ weight}(\text{kg}) + 0.09x\text{height}(\text{cm}) + 0.26x \text{ rate} - \text{pressure product} (x10-3) + 2.45$$

Both tests were performed on the same non-dialysis day, by the same physiotherapists' evaluator. The 6MWT was performed after a 20-min CPET considering when the patient's vital signs had returned to baseline levels, as previously proposed by Costa et al. [17]. It used the Karvonen method to predict the maximal HR and then calculated the $\%HR_{max}$ achieved after both tests [18].

Statistical analysis

All data were tested for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), and non-normally are presented as median (minimum; maximum values). Paired *t*-test was used to compare directly $\dot{V}O_{2peak}$ obtained by CPET and indirectly $\dot{V}O_{2peak}$ obtained by 6MWT. Pearson's correlation test was used to correlate directly and indirectly $\dot{V}O_{2peak}$. Spearman correlation test was used to correlate the difference between the vital sign and Borg CR10 Scale before and after both tests. The correlation size was classified as very low ($r < 0.300$, low ($r = 0.300$ to 0.500), moderate ($r = 0.500$ to 0.700), high ($r = 0.700$ to 0.900) and very high ($r = 0.900$ to 1.000) [19]. Chi-square was used to compare the dyspnea perception between both tests.

Bland–Altman analysis was used to evaluate the agreement limits between directly and indirectly $\dot{V}O_{2peak}$ values. The intraclass correlation coefficient (ICC) and Cronbach's Alpha were calculated to evaluate the reproducibility and reliability between both $\dot{V}O_{2peak}$ values. The ICC values were interpreted as low (< 0.40), moderate (0.40 to 0.75), and excellent (> 0.75), in accordance with Fleiss [20]. Statistical analysis was performed using the Statistical Package for the Social Sciences (version 26.0, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.0, GraphPad Software, Inc., CA, United States). Statistical significance was set as *p*-value < 0.05.

Results

Thirty-one patients were invited to participate. One patient was not eligible due to the lower-limb arteriovenous fistula and four patients were not included in the final analysis for not performing the 6MWT. Thus, the final sample consisted of 26 patients. The study flowchart may be seen in Fig. 1.

Characteristics of the included patients

Table 1 shows the general characteristics of the patients. The majority of the patients performed the CPET until the volitional exhaustion and only one patient had the test interrupted by the physician due to ischemic electrocardiographic abnormalities.

Association between CPET and 6MWT

There was no significant difference between directly and indirectly $\dot{V}O_{2peak}$ ($p = 0.160$) confirming that the

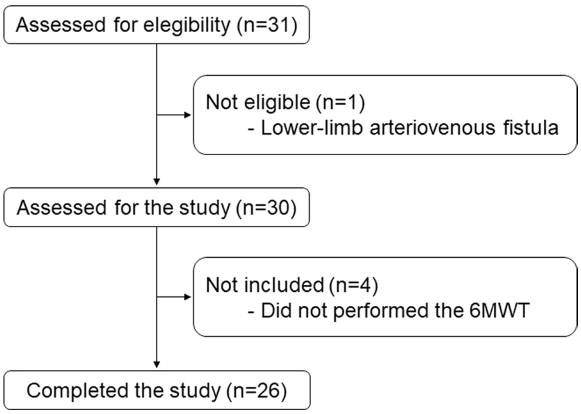

Fig. 1 Study flowchart

Table 1 Study sample characteristics

	n = 26
Male—*n* (%)	14 (53.84%)
Age (year) †	54.4 ± 14.4
BMI (kg/m^2) †	27.3 ± 4.2
Weight (kg) †	76.90 ± 15.28
Height (cm) †	167.57 ± 11.92
HD vintage (month) ‡	23.00 (4; 276)
CRP	8.44 (0.6; 68.0)
6MWT distance (meter) †	466.94 ± 83.57
%6MWT distance†	84.04 ± 15.19
CKD etiology—*n* (%)	
Glomerulopathy	9 (34.61%)
Systemic arterial hypertension	7 (26.92%)
Diabetes mellitus	5 (19.23%)
Autoimmune disease	4 (15.38%)
Alport syndrome	1 (3.84%)

BMI: body mass index. HD: hemodialysis. 6MWT: six-minute walk test. CRP: C-reactive protein

† Mean ± SD

‡ Median (Minimum; maximum)

measurements have similarities. Table 2 shows the correlation between directly and indirectly VO_{2peak}, HR, $\%HR_{max}$, SpO_2, SBP, and DBP variation, and Borg CR10 Scale. As seen, there was a significant strong positive correlation between directly and indirectly VO_{2peak} ($r = 0.734$; $p < 0.001$). Also, there was a low positive correlation in the dyspnea perception between both tests ($r = 0.443$; $p = 0.023$). This indicates that self-perception of shortness of breath is present in both the maximal test and the submaximal exercise test with the same behaviour.

Table 2 Correlations between $\dot{V}O_{2peak}$, vital signs, and self-perception of leg fatigue and dyspnea ($n = 26$)

	CPET	6MWT	*r*	*p*-value
$\dot{V}O_{2peak}$ †	15.91 ± 5.26	14.89 ± 4.21	0.734	< 0.001
Delta HR‡	18.00 (− 34; 68)	8.00 (− 9; 36)	− 0.223	0.274
$\%HR_{max}$ †	76.43 ± 16.12	56.81 ± 13.29	0.333	0.096
Delta SpO_2 ‡	− 0.50(− 8; 8)	0.00 (− 4; 3)	0.121	0.557
Delta SBP‡	− 30.00 (− 50; 0)	− 16.00 (− 60; 30)	0.003	0.988
Delta DBP‡	− 10.00 (− 30; 10)	− 2.50 (− 30; 20)	0.363	0.068
Borg Dyspnea‡	4.00 (0; 10)	1.50 (0; 9)	0.443	0.023
Borg Fatigue‡	7.50 (0.5; 10)	4.00 (0; 10)	0.002	0.994

CPET: cardiopulmonary exercise test. 6MWT: six-minute walk test. $\dot{V}O_{2peak}$: peak oxygen uptake. HR: heart rate. SpO2: peripheral oxygen saturation. SBP: systolic blood pressure. DBP: Diastolic blood pressure

† Mean ± SD

‡ Median (Minimum; maximum)

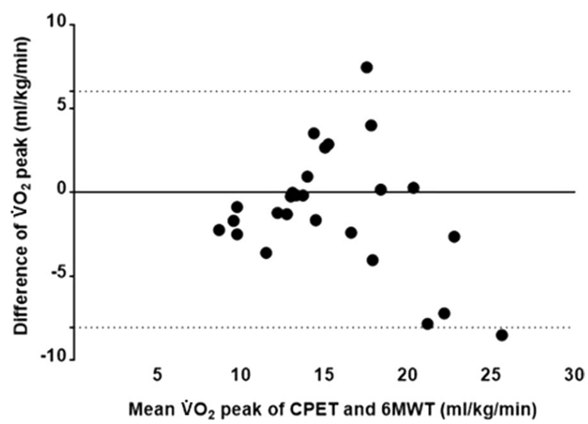

Fig. 2 The Bland–Altman analysis between directly and indirectly $\dot{V}O_{2peak}$ measurements

Also, there was no significant correlation in vital signs' behaviour (HR, SpO_2, SBP, and DBP), $\%HR_{max}$, and lower limbs fatigue self-perception between both tests. Similar behaviour on dyspnea perception after both tests according to the Chi-square test was seen (CPET 30.8% vs 6MWT 11.5%, $p = 0.090$).

The Bland–Altman analysis to evaluate the agreement between directly and indirectly VO_{2peak} measurements is shown in Fig. 2. The difference between VO_{2peak} mean in both tests was not significantly different from zero ($p = 0.103$). The majority of the values remained within the 95% CI. Besides, there was no significant proportion bias which means that the distribution of the values is homogeneous both above and below average ($p = 0.119$). Thus, both VO_{2peak} measurements (directly and indirectly) agreed with each other.

Also, the reproducibility and the reliability between directly and indirectly $\dot{V}O_{2peak}$ evaluated by ICC (0.829 [0.623–0.923]) and Cronbach's Alfa (0.846), respectively, presented high values and were classified as excellent.

Discussion

The present study aimed to evaluate the agreement and reliability between directly and indirectly $\dot{V}O_{2peak}$ measurements in patients undergoing HD. Our results indicated a strong positive correlation and a high agreement between directly and indirectly $\dot{V}O_{2peak}$, measured by CPET and 6MWT, respectively. Thus, 6MWT seems to be a reliable predictor of $\dot{V}O_{2peak}$ and could be routinely used to evaluate cardiorespiratory fitness in patients undergoing HD.

The $\dot{V}O_{2peak}$ is the most reliable and accurate index of the cardiorespiratory fitness in many clinical populations. CPET provides reliable cardiorespiratory fitness values as it is a maximum physiological exertion test, leading the patient to a high limit of physical, cardiac, respiratory, and cardiovascular tolerance [8]. However, CPET is an unaffordable test in many health settings, as it requires a spacious room and a specialized medical team, turning it into a high-cost exam [8]. On the other hand, the 6MWT is a submaximal test with a predetermined time and standardized procedures which barely expose the patient to physical exhaustion, although it evaluates the global and integrated responses of all the systems involved during exercise (pulmonary, cardiovascular, neuromuscular and musculoskeletal) [12].

In this sense, several submaximal functional tests reflecting daily life activities and incorporating elements of lower-limb functionality and gait speed have been proposed to be alternatives to evaluate improvements in rehabilitation programs or functional impairments due to chronic diseases, such as CKD [11–13, 21–23]. Furthermore, as CPET, the 6MWT also presents a strong correlate of mortality in CKD patients [6, 24].

People with chronic diseases show higher physical impairment than healthy individuals and many studies have been carried out to demonstrate the importance of cardiorespiratory fitness evaluation [3, 25]. Although CPET is often used in several studies because it accurately measures cardiorespiratory fitness, this is not widely seen in clinical routine, where the 6MWT is more commonly adopted [11]. Besides, the 6MWT seems to show an advantage to evaluate the functional capacity in clinical populations because usually the maximal exercise tests are more difficult to be performed and understood by the patients [26, 27].

Carvalho et al. (2011) [28] also evaluated the agreement from directly and indirectly $\dot{V}O_{2peak}$ in heart failure patients evaluated by CPET and 6MWT, respectively, and found similar results to ours. They concluded that the 6MWT is a reliable tool to systematically identify cardiorespiratory fitness adaptations following clinical exercise programs through indirect $\dot{V}O_{2peak}$ [29].

Ross et al. [11] also examined the relationship between directly and indirectly $\dot{V}O_{2peak}$ in different clinical populations and all prediction equations were able to estimate $\dot{V}O_{2peak}$ from 6MWT with minimal loss of accuracy. Their study did not include studies estimating $\dot{V}O_{2peak}$ from 6MWT in patients with CKD and we believe that it may occur due to the absence of studies evaluating this outcome in patients with CKD. Additionally, in terms of clinical routine application, a recent scoping review showed that several studies have been using the 6MWT to evaluate rehabilitation programs' effectiveness, as well as cardiorespiratory fitness in patients with CKD [10]. To the authors, is necessary further investigation into the validity, reliability, and practicality of outcome measures. Besides, defining consistent, relevant, and patient-important outcome measures allow for more meaningful conclusions to guide clinical decisions [10].

The correlation and Chi-square analysis have found similar behaviour on dyspnea self-perception after both tests, even with 30.8% of patients reporting very severe respiratory effort after CPET while 11.5% after 6MWT. We hypothesized that vital signs and self-perception of lower limbs fatigue and dyspnea would not agree due to the physiological differences between both tests (maximum versus submaximal exertion). However, we were surprised with our results that demonstrated similar behaviour in dyspnea perception.

According to the ATS, the Borg CR10 Scale is the main tool to quantify symptoms during both exercise tests (CPET and 6MWT) and it incorporates a nonlinear spacing of severity verbal descriptors which corresponds to specific numbers. Its reproducibility for dyspnea measurement during exercise has shown good results [8, 12]. However, as a symptom, dyspnea is a multidimensional perceptual experience of breathing discomfort that consists of qualitatively distinct sensations [30]. It is often associated with fluid overload and coexisting morbidities and HD seems to cause a definite regression of these symptoms turning its quantification difficult with ambiguous results [30, 31].

This study has some strengths and limitations. The strengths are: (a) our findings, showing that the 6MWT may predict $\dot{V}O_{2peak}$, strengthen the clinical importance of our results and indicate the 6MWT as a reliable tool to evaluate the cardiorespiratory fitness in patients with CKD; (b) to the best of our knowledge, this is the first study showing the agreement between a direct and indirect VO_{2peak}, evaluated by CPET and 6MWT in patients undergoing HD.

The main limitations are: (a) the small sample size; (b) despite VO_{2peak} being 5–10% higher in cycle ergometer test than in treadmill test, and safer to clinical individuals, a treadmill test could have provided a better relevant comparison to 6MWT [32]; (c) the performance of both tests on the same day may have underestimated 6MWT results, which has been corrected by a 20-min resting whereas the patient's vital signs had returned to baseline levels; and d) we recognized that the formula proposed by Cahalin et al. (1996) [13] was described to be used in heart failure patients, however, due to heart failure being one of the main comorbidities associated with the fluid overload caused by CKD and the excellent reproducibility and reliability when compared to the CPET, we decided to present it to the scientific community as an alternative to evaluating the cardiorespiratory fitness through a field test in patients undergoing HD.

Conclusion

Thus, we conclude that the 6MWT may be used to estimate VO_{2peak} in patients undergoing HD, as it shows excellent reproducibility and reliability when compared to the CPET (i.e., gold standard method). Also, the 6MWT seems to be an important, practical, and low-cost test for evaluating and monitoring cardiorespiratory fitness (i.e., $VO_{2peak)}$ in dialysis centres. We believe that more studies may be performed with the major sample size, aiming to propose new formulas to indirectly evaluate VO_{2peak} through functional capacity submaximal tests in patients undergoing HD.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by FPA, HB, SGO, HSR. The first draft of the manuscript was written by FPA and HB and all authors commented on previous versions of the manuscript. All authors have read and approved the final version.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (40167014.3.0000.5327). Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors agreed with the content and gave explicit consent to submit and obtained consent from the responsible authorities at the organization where the work has been done before the work is submitted.

Competing interests

The authors report no conflict of interest.

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