Positive correlation between six-minute walk test and heart rate variability in hemodialysis patients

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Research article

Keywords: hemodialysis patients, cardiovascular risk, walk test

Posted Date: July 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-46993/v1

Abstract

Background Autonomic dysfunction is a prevalent clinical condition in chronic renal patients on hemodialysis and adds patient's worse cardiovascular outcome, some studies in several populations relate worse cardiorespiratory performance with higher dysautonomia, but among chronic renal patients on hemodialysis these studies are still limited. The aim of this study was to verify whether there is an association between autonomic cardiac dysfunction and walking test performance in hemodialysis patients.

Methods A cross-sectional study was performed in 61 patients undergoing hemodialysis therapy performed clinical examination, blood sampling, electrocardiography of heart rate variability and 6-minute walk test.

Results There was a positive correlation between the 6 minute walking test and the heart rate variability variables RMSSD (r = 0.37 p = 0.005) and SD1 (r = 0.37 p = 0.0059) (Figures 1) (showing parasympathetic integrity), and there was a negative correlation with the pretest walking heart rate with these same variables (r = -0.33 p = 0.014) and (r = -0.34 p = 0.015) Regarding the walking test, it was negatively correlated with age (r = -0.39 p = 0.003) and positive with time on hemodialysis (r = 0.27 p = 0.04)

Conclusions Therefore, it is verified that the 6-minute walking test can be used to estimate autonomic dysfunction in hemodialysis patients and thus help in the screening of this dysfunction including the elaboration of treatment strategies.

Introduction

Chronic kidney disease adds very high cardiovascular risk to patients, especially in advanced stages, and morbidity and mortality from cardiovascular disease are very high compared to the general population, at increased risk of sudden death, coronary artery disease, and cardiomyopathy [1,2].

Concomitant with the traditional risk factors present in individuals with CKD (chronic kidney disease), such as age, arterial hypertension, diabetes, dyslipidaemia and obesity, it is possible to add non-traditional risk factors, including anaemia, alterations in bone mineral metabolism, vascular calcifications, intravascular volume expansion and uremic toxins, causing damage to vessels (atherosclerosis and arteriosclerosis) and cardiac muscle (cardiomyocytes and myocardial fibrosis) [3,4].

Autonomic dysfunction (AD) is a prevalent clinical condition in chronic renal patients on hemodialysis, with a prevalence greater than 50% in patients in some studies with varying clinical implications like non-cardiovascular symptoms such as pain, neurogenic bladder, intestinal dysmotility, sexual dysfunction to cardiovascular manifestations. postural hypotension, intradialytic hypotension, arrhythmias, and resistant hypertension[5]. Heart rate variability (HRV) is an important diagnostic method to verify sympathetic hyperactivity and has been increasingly used in clinical practice for the early detection of

this alteration in several clinical conditions where it is deleterious. In haemodialysis individuals should be increasingly used since it is possible to detect early changes in autonomic modulation and anticipate complications in this population [6,7].

The 6-minute walk test (6-MWT) is a widely used test in heart and lung disease patients, and in recent years has been used in chronic renal patients in physical training protocols and to assess physical performance and/or sarcopenia. Some studies correlate poorer 6-MWT performance with higher risk of mortality and hospitalizations [8]. Many studies have reported the impact of physical inactivity on increased mortality in hemodialysis patients [9–11].

Physical inactivity is well established as a strong independent risk factor for cardiovascular events. In a study by Greenwood and colleagues, it was found that in chronic renal patients undergoing a cardiopulmonary rehabilitation program, those who completed training had an increase in days free of cardiovascular events, with improvement in distance covered in a physical exercise test [11]. The aim of this study was to verify even if there is an association between autonomic cardiac dysfunction and walking test performance in hemodialysis patients.

Methods

Sample

A cross-sectional study was performed in 61 patients undergoing hemodialysis therapy at the Maranhão Nephrology Center, from October 2018 to June 2019. The study was authorized by the Ethics and Research Committee (CEP) of the University Hospital of the University. Federal of Maranhão according to resolution 196/96, under opinion number 2,926,492, CAAE: 99019318.0.0000.5086 on the date of 28/09/2018. Clinical and laboratory data were collected from individuals with chronic kidney disease on hemodialysis, and a 6-minute walk test and electrocardiogram were performed to analyze heart rate variability.

The study included individuals of both sexes, over 18 years old who had been on dialysis treatment for at least 03 (three) months. Patients with diseases or some type of musculoskeletal disability, with neurological, cognitive and behavioral alterations leading to misunderstanding or difficulty in the evaluation process were excluded, as well as patients with severe cardiovascular diseases such as untreated mitral regurgitation or severe aortic stenosis, clinically manifest coronary disease such as unstable angina, decompensated cardiac arrhythmia, decompensated heart failure, acute pericarditis or myocarditis, patients with severe pulmonary pathologies, conditions that interfered with physical evaluation (amputation, amaurosis and deep vein thrombosis) and patients without autonomy to decide on their participation in the study. The acceptance to participate in the research was given by consent of the Informed Consent (IC).

All subjects answered a questionnaire prepared by the researchers and applied as an interview containing personal data and information regarding hemodialysis treatment. Laboratory data on plasma hemoglobin, hematocrit, calcium, phosphorus, potassium, albumin, and creatinine values were verified in the Institution's database and recorded. Then, the physical evaluation was performed by recording the heart rate variability (HRV) and the 6-minute walk test (6-MWT).

Heart rate variability (HRV)

HRV was recorded with a 12-lead electrocardiograph (Micromed Biotecnologia Ltda) using WinCardio 6.1.1 software with a 600 Hz signal to obtain moment-by-moment R-R intervals. All participants were taken to a quiet room where a resting electrocardiogram was performed for 10 minutes in the supine position. At the end of the exam, the R-R interval series was extracted in txt format using Wincardio's analysis software to analyze the variability of the R-R interval in the time and frequency domain and nonlinear measurements.

The indices used in the time domain were SDNN (standard deviation of RR intervals) and RMSSD (square root mean square of differences between adjacent RR intervals). And the frequency domain indices were the low frequency (LF) bands that predominantly refer to sympathetic modulation, and the high frequency (HF) bands that represent parasympathetic modulation, in addition to the LF / HF ratio that establishes sympathovagal balance. For the HRV analysis by nonlinear methods, we used the indexes derived from the Poincare Plot: SD1 (the standard deviation of the instantaneous beat-to-beat interval variability) and SD2 (the long-term variability of the continuous R-R intervals). Normalized LF and HF components of R–R variability were considered, respectively, as markers of cardiac sympathetic and parasympathetic modulation, and the ratio between them (LF/HF) was considered as an index of the autonomic modulation of the heart [8]. The results were expressed in absolute values HF (ms^2) and LF (ms^2) and percentage (HFnu and LFnu). HRV indices were analyzed using Kubios HRV software, version 2.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland).

To assess functional physical capacity, the 6-minute walk test (6-MWT) was used according to the guidelines recommended by the American Thoracic Society. Before and after the test vital signs were monitored (heart rate, blood pressure, and peripheral oxygen saturation), at the end of the test the level of dyspnea was measured by the Borg scale. The subjects received standard verbal instructions and were instructed to walk for 6 minutes, along a flat corridor marked every three meters with cones to indicate to the participant the route to be followed, being advised to discontinue the test if he had any symptoms. Throughout the course, an examiner followed the subjects, positioning themselves posterolaterally for the participant's safety. At the end of 6 minutes, participants were given the “stop” command where they stopped immediately, regardless of where they were in the circuit, and the total distance traveled by each individual was verified and recorded[12].

Statistical analysis

Data were analyzed in GraphPad Prism 5 software. The Shapiro-Wilk test was used to assess data normality, presented as mean and standard deviation. For potential statistical differences in characteristics between the exercise regimens, Student's T-test it was used for normally distributed variables and Wilcoxon test for nonparametric variables. A significance level of $p < 0.05$ it was adopted. For variable correlation analysis Spearman was used for non-parametric variables and Pearson for parametric variables.

Results

Patients characteristics

We analyzed data from 61 chronic renal patients on hemodialysis. Anthropometric characteristics are described in Table 1. Patients have chronic kidney disease stage 5 and are oligoanurics with estimated glomerular filtration rate lower than 10 ml / min.

Table 1
Clinical, laboratory variables of 6-minute walk test and heart rate variability of hemodialysis patients

Clinical and laboratories variables	
Variables	mean ± SD
Hemoglobin (mg/dl)	11,38 ± 1,78
Hematocrit	34,4 ± 5,17
Calcium (mg/dl)	8,94 ± 0,64
Phosphor (mg/dl)	4,76 ± 1,26
Potassium(mg/dl)	5,27 ± 0,86
Time in hemodialysis (months)	58,9 ± 50,7
Age (years)	48,4 ± 13,7
Male/female	32/29
Creatinine (mg/dl)	10,2+/-2,9
Albumin (mg/dl)	4,04+/-0,41
6 minutes walk test	
6mWT (meters)	423,4 ± 115,3
Borg scale	9,76 ± 2,44
HR before 6mWT	80,1 ± 11,59
HR after 6mWT	89,09 ± 14,81
SBP before 6mWT	140,3 ± 20,96
DBP before 6mWT	83,37 ± 14,66
SBP after 6mWT	149,7 ± 26,85
DBP after 6mWT	88,84 ± 17,38
SpO2 before 6mWT	96,31 ± 2,23
SpO2 after 6mWT	97,41 ± 1,76
Variables rate heart variability	

6mWT-6 minutes walking test, HR-heart rate, SBP-systolic blood pressure, DBP- diastolic blood pressure, SpO2-saturation arterial oxygen, SDNN-standard deviation of RR intervals, RMSSD- square root mean square of differences between adjacent RR intervals, SD1-standard deviation of the instantaneous beat-to-beat interval variability, SD2- long-term variability of the continuous R-R intervals, LFnu- low frequency bands, HFnu-high frequency bands, LF/HF-ratio sympathovagal balance

Clinical and laboratories variables	
SDNN (ms)	15,17 ± 8,18
RMSSD (ms)	10,44 ± 6,44
SD1 (ms)	7.47 ± 4,57
SD2 (ms)	19,83 ± 11,25
LF (nu)	55,65 ± 25,25
HF (nu)	44,15 ± 25,19
LF/HF	2,58 ± 2,64
6mWT-6 minutes walking test, HR-heart rate, SBP-systolic blood pressure, DBP- diastolic blood pressure, SpO2-saturation arterial oxygen, SDNN-standard deviation of RR intervals, RMSSD- square root mean square of differences between adjacent RR intervals, SD1-standard deviation of the instantaneous beat-to-beat interval variability, SD2- long-term variability of the continuous R-R intervals, LFnu- low frequency bands, HFnu-high frequency bands, LF/HF-ratio sympathovagal balance	

Regarding the walking test (Table 1), the average distance traveled by the patients was 423 ± 115 meters, with Borg's effort scale 9.76 ± 2.44 points, heart rate, blood pressure, and oxygen saturation did not differ before and after the walking test.

The variables of the heart rate variability test are described in Table 1 and it is verified that the mean values of LF and SD2 (show increased sympathetic activity) are increased without relation to the average values of HF and SD1 (parasympathetic integrity).

There was a positive correlation between the 6 minute walking test and the heart rate variability variables RMSSD ($r = 0.37$ $p = 0.005$) and SD1 ($r = 0.37$ $p = 0.0059$) (Figs. 1) (showing parasympathetic integrity), and there was a negative correlation with the pretest walking heart rate with these same variables ($r = -0.33$ $p = 0.014$) and ($r = -0.34$ $p = 0.015$) Regarding the walking test, it was negatively correlated with age ($r = -0.39$ $p = 0.003$) (Fig. 2) and positive with time on hemodialysis ($r = 0.27$ $p = 0.04$) (Fig. 2) (Table 2).

Table 2
Correlation between 6MWT distance RMSSD, SD1, time in HD, and age (years).

	6MWT	
RMSSD	r = 0,37	p = 0,005
SD1	r = 0,37	p = 0,0059
Age (years)	r= -0,39	p = 0,003
Time in HD	r = 0,27	p = 0,04
6mWT-6 minutes walking test, RMSSD- square root mean square of differences between adjacent RR intervals, SD1-standard deviation of the instantaneous beat-to-beat interval variability, HD-hemodialisis		

Discussion

The aim of this study was to verify even if there is an association between autonomic cardiac dysfunction and walking test performance in hemodialysis patients. Autonomic dysfunction (AD) in chronic renal patients is characterized by increased sympathetic activity and impairment of parasympathetic activity and may contribute to several cardiovascular clinical manifestations in such patients as resistant hypertension, orthostatic and/or intradialytic hypotension decreased heart rate variability and impaired activity baroreflex with increased risk of sudden death[13].

In the present study, a cardiorespiratory performance test was used in this population and the correlation between worse cardio-respiratory performance and worse heart rate variability was verified, showing that the autonomic dysfunction of the chronic renal patient is worse in those with worse walking test performance.

The 6-minute walk test is a useful test with prognostic value for morbidity and mortality. A 2012 study of chronic renal patients showed the prognostic value of 6-MWT in a group of 55 patients followed for 144 months, with a 5% increase in survival for every 100 meters walked, including a correlation with peak VO^2 improvement, being one of the first studies that associated survival with the 6-MWT in this population[14].

In 2014, a study of 296 patients from various hemodialysis centers in Italy found a positive correlation between poorer physical performance in the walk-at-risk-of-death walk test and found that a 20-meter increase in the 6-MWT was associated with a decrease in the 6-MWT 6% risk mortality and hospitalization, denoting the importance of the test[15].

In the present study, laboratory variables were not correlated with the distance covered in the walking test, even hemoglobin (related to anemia), potassium (related to muscle weakness), phosphorus or albumin. This finding may be partially explained by the fact that the mean values of these variables were within

the expected range for chronic dialytic renal patients, and perhaps due to a sample bias (patients in a better general condition felt after to perform the walking test). Similar data were found in other studies[16,17].

A study conducted in a Japanese dialysis population found a positive correlation between walking test performance and transferrin saturation only, even in a sample of older individuals with lower mean hemoglobin and higher serum phosphorus[17]. In a Slovenian study, it was found that the worst performance in the walking test was associated with higher serum levels of ultrasensitive CRP (variable inflammation cellular), a variable not measured in the present study and perhaps explaining the difference in performance between hemodialysis patients - degree of subclinical inflammation presented and not measured in clinical practice [18].

The physical performance of these patients is also much lower than normal for age and gender, and it has been verified by previous studies showing that the average 6-MWT for these patients is 400 meters. In the present study, the average 6-MWT was 423.5 ± 115 meters and obtained a positive correlation with the patients' age, similar data observed [16]. In study, an improvement in physical performance was verified by the walk test and the sit-to-test stand and also by tests that assess quality of life ratifying the importance of these tests as evaluators of cardiorespiratory performance [19].

In a study of chronic renal patients with peritoneal dialysis, it was found that patients with shorter 6-minute walk distance were older, had a lower left ventricular ejection fraction, and had a higher failure rate with hemodialysis transfer, reflecting lower cardiac performance. even within normal ranges [20], which may be a useful tool in predicting patients who would need more intervention and possibly more effort in indicating the physical training program.

In other patient populations such as heart disease, the walking test has been widely used and has been proposed as a tool to follow up these patients, being a strong predictor of frailty and morbidity and mortality, correlating better aerobic capacity (better 6-MWT) with better cardiac output and lower blood pressure. Pulmonary artery average [21]. Being readily applicable even to a group of octogenarians undergoing hemodialysis, which after a low-intensity physical training program during the intradialytic, improved physical performance was verified by the walking test [22].

Regarding the variables of the autonomic nervous system, this study shows that higher SD1 and RMSSD values that show better parasympathetic nervous system integrity and, therefore, lower autonomics, were more prevalent in those patients who had the greatest distance covered in the test walk. In a Brazilian study with hemodialysis patients, it was found in the exercise treadmill test that those patients with worse cardiorespiratory performance had lower RMSSD (higher degree of dysautonomia) than controls [23]. It is noteworthy that this test is performed in cardiac clinics, in a separate environment from the hemodialysis clinic, on a treadmill, and that many patients have difficulty accessing the exam, with tc6min and heart rate variability electrocardiogram being a more alternative applicable to hemodialysis clinics.

Limitations

Some limitations of this study are the fact that it is a cross-sectional study with a small sample and no inflammatory markers were dosed, requiring further studies to verify the clinical applicability of these tools.

Conclusion

Therefore, it is verified that the walking test can be used to estimate autonomic dysfunction in hemodialysis patients and thus help in the screening of this dysfunction including the elaboration of treatment strategies.

Declarations

Acknowledgements:

We are thankful to Emanuel Catarino for excellent technical assistance.

Compliance with Ethical Standards:

This study protocol was approved by the ethical committee at University Federal do Maranhão. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration, revised in 2008 and its later amendments or comparable ethical standards. Weitten informed consent obtained from all participants.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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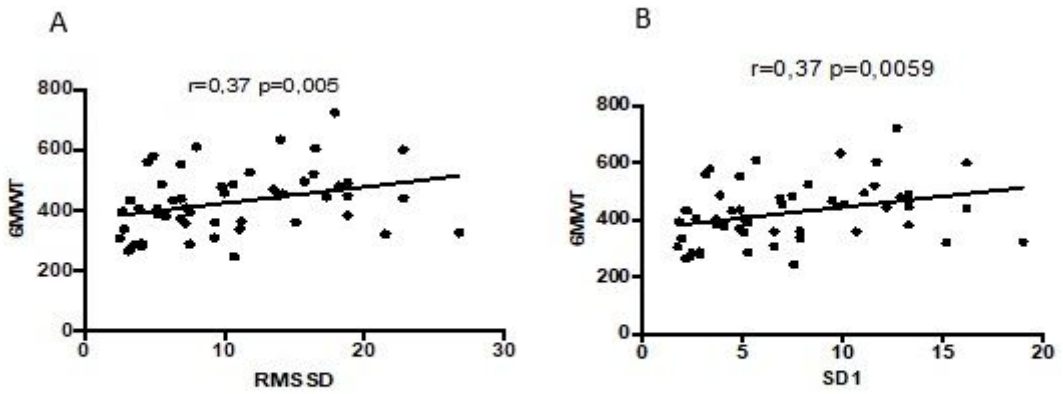
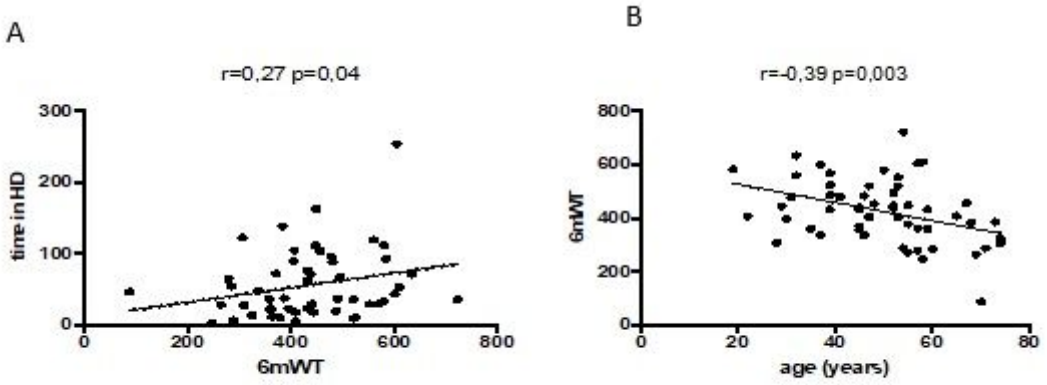
Figures



6mWT-6 minutes walking test, RMSSD- square root mean square of differences between adjacent RR intervals, SD1-standard deviation of the instantaneous beat-to-beat interval variability

Figure 1

Correlation between 6MWT distance RMSSD (A) and SD1(B).



6mWT-6 minutes walking test,HD-hemodialysis

Figure 2

Correlation between 6MWT distance and time in HD (A)and age (years)(B).