Heart Rate Variability Correlates to Functional Aerobic Impairment in Hemodialysis Patients

Maria Angela Magalhães de Queiroz Carreira[1], André Barros Nogueira[1], Felipe Montes Pena[1], Marcio Galindo Kiuchi[1], Ronaldo Campos Rodrigues[1], Rodrigo da Rocha Rodrigues[1], Jorge Paulo Strogoff de Matos[2], Jocemir Ronaldo Lugon[2]

Universidade Federal Fluminense, Department of Cardiology[1]; Universidade Federal Fluminense, Department of Nephrology[2], Rio de Janeiro, RJ - Brazil

Abstract

Background: Autonomic dysfunction (AD) is highly prevalent in hemodialysis (HD) patients and has been implicated in their increased risk of cardiovascular mortality.

Objective: To correlate heart rate variability (HRV) during exercise treadmill test (ETT) with the values obtained when measuring functional aerobic impairment (FAI) in HD patients and controls.

Methods: Cross-sectional study involving HD patients and a control group. Clinical examination, blood sampling, transthoracic echocardiogram, 24-hour Holter, and ETT were performed. A symptom-limited ramp treadmill protocol with active recovery was employed. Heart rate variability was evaluated in time domain at exercise and recovery periods.

Results: Forty-one HD patients and 41 controls concluded the study. HD patients had higher FAI and lower HRV than controls (p<0.001 for both). A correlation was found between exercise HRV (SDNN) and FAI in both groups. This association was independent of age, sex, smoking, body mass index, diabetes, and clonidine or beta-blocker use, but not of hemoglobin levels.

Conclusion: No association was found between FAI and HRV on 24-hour Holter or at the recovery period of ETT. Of note, exercise HRV was inversely correlated with FAI in HD patients and controls. (Arq Bras Cardiol. 2015; [online]. ahead print, PP.0-0)

Keywords: Sympathetic Nervous System / physiopathology; Exercise Test; Renal Dialysis; Mortality; Exercise.

Introduction

The treatment offered to end-stage renal disease (ESRD) patients on hemodialysis (HD) has improved over the past decades resulting in increased survival and better quality of life[1]. However, cardiovascular morbidity and mortality remain exceptionally high in this group of patients[2].

The prevalence of autonomic dysfunction (AD) is high in patients undergoing current standard HD treatment[1] and this has been associated with an increased risk of sudden death[2].

In the general population, cardiorespiratory fitness (CRF) is an independent predictor of all-cause and cardiovascular mortality[3]. In normal subjects, maximal functional aerobic capacity was inversely associated with the risk of all-cause and cardiovascular death. The risk was 2.50 times higher for all-cause death, and 2.04 times higher for cardiovascular death in men with a low exercise capacity than in men with a high exercise capacity, after adjustment for risk factors and ischemic ST changes during exercise[4]. Cardiorespiratory fitness is also a predictor of sudden cardiac death in normal subjects. As a continuous variable, one metabolic equivalent (MET) increment in CRF was associated with a 22% decrease in the risk of sudden cardiac death in normal men[4].

Exercise treadmill test (ETT) has been used in the assessment of autonomic function by analyzing changes in heart rate (HR) under physical stress.

The aim of this study was to assess the autonomic function of HD patients and controls by assessing HR variability (HRV) during an ETT and to correlate the results with functional aerobic impairment (FAI).

Methods

Study population

We conducted a cross-sectional study with ESRD patients on HD three times a week (4-hour duration sessions) for at least three months and a control group matched by sex and age without overt kidney disease. Hemodialysis patients were recruited from a single dialysis center and the control group consisted of individuals referred for exercise testing at the University Hospital. Informed consent was obtained, and the study protocol was approved by the Medical School ethical

Mailing Address: Maria Angela Magalhães de Queiroz Carreira •
Rua Arroio Fundo, 230, Anil. Postal Code 22765-260, Rio de Janeiro, RJ – Brazil
E-mail: macarreira@globo.com
Manuscript received September 12, 2014; revised manuscript January 14, 2015; accepted January 19, 2015.

DOI: 10.5935/abc.20150039

committee. Chronic medications, including those for blood pressure control, were not discontinued during the study.

Exclusion criteria were as follows: impaired gait that prevented walking on the treadmill, arrhythmias preventing proper HR assessment, and presence of symptomatic heart disease. Cardiac evaluation was always accomplished in a middle-of-week non-dialytic day and consisted of clinical examination, transthoracic echocardiogram, 24-h Holter, and ETT.

Echocardiography

A two-dimensional transthoracic echocardiography was performed with GE VIVID 7 System (General Electric, USA) to assess left ventricle wall motion and systolic and diastolic ventricular function.

24-h Holter

Patients underwent a 24-h Holter (Galix Biomedical Instrumentation, Florida, USA). A 3-channel recorder was used to record the electrocardiographic tracings. A time domain analysis of HRV was performed, and the following parameters were obtained: a) SDNN, standard deviation (SD) of all normal RR intervals (NN); b) SDANN, SD of the averages of 5-min NN intervals over 24h; c) rMSSD, the square root of the mean of the square of successive NN intervals; and d) triangular index (TI), integral of the density distribution (that is, the number of all NN intervals) divided by the maximal density distribution.

Exercise treadmill test

Patients underwent ETT with a treadmill ramp protocol using the Ergo13 program (Heart Ware Co., Minas Gerais, Brazil). The test was symptom limited, with 2-minute active recovery under 40% of the speed and incline of peak effort. Automatic ECG recordings were obtained on 13 simultaneous leads before exercise in the supine and standing positions, at peak exercise, and at every recovery minute. The following HRV parameters were analyzed: SDNN and rMSSD during exercise and recovery. For the ramp protocol, the predicted maximal VO_2 was reduced by 20% in HD patients. The maximal VO_2 peak exercise was obtained by the Foster formula backed with hands. The FAI was calculated using the formula: FAI= [(maximal predicted VO_2–VO_2 peak) /maximal predicted VO_2] x 100. In ETT, HRV was obtained with a software specially designed for the study, conveying electrocardiographic data findings from Ergo13 to Cardio Smart (Cardios, São Paulo, Brazil) during exercise and recovery separately.

Statistics

Results were expressed as mean and SD, for normal distribution, and median and range, otherwise. Categorical variables were expressed as frequencies and compared using the Chi-square test. Comparisons between two continuous variables were accomplished by the *t* test (for normal distribution) or its nonparametric equivalent (Mann-Whitney test). Correlation was assessed using the Pearson test. Logistic regression was used to analyze associations. Variables with p values <0.10 were included in the multivariate model, and $p<0.05$ was considered significant. Analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 125 patients from a single dialysis center were initially evaluated. Nine were promptly excluded due to gait impairment. Of the 116 remaining, 59 agreed to participate and signed the consent form. Eighteen patients were excluded: 10 did not show up for the exams, 4 had a past myocardial infarction, 2 had arrhythmia, 1 had artery-venous fistulas in both arms, and 1 had current pulmonary infection. At the end, 41 HD patients concluded the study. The most common renal disease etiologies were: hypertensive nephrosclerosis (56%), chronic glomerulonephritis (17%), adult polycystic kidney disease (10%), and diabetic nephropathy (7%). Table 1 shows the general features of patients and controls. Use of antihypertensive drugs and physical inactivity were more frequent among patients on HD. Use of beta-blockers tended to be higher in HD patients, but statistical significance was not found. Diuretic use was more common in the control group.

Left ventricular systolic function, analyzed by the ejection fraction on echocardiogram, was similar between groups (66.1±10.1% *vs.* 68.6±5.4% for HD patients and controls, respectively, P = 0.167), but diastolic dysfunction was more prevalent in HD patients (77% *vs.* 42%, P = 0.004).

Table 2 shows the cardiovascular parameters on ETT. There was no difference between groups in relation to pre-exercise test parameters. Functional aerobic impairment was found higher in HD patients (Figure 1). Reasons for stopping the exercise were as follows: general exhaustion, 80.5%; exhaustion of the muscles of lower limbs, 4.9%; left bundle branch block of high-grade, 2.4%; arrhythmia, 2.4%; and hypertension, 2.4%. No complications occurred during ETT in any group.

When analyzing the 24-h Holter, HD patients showed less HRV than controls. Differences were observed regarding the mean HRV values during exercise and recovery (Table 3). SDNN was significantly lower in HD patients than in controls on 24-h Holter, and during exercise and recovery (Figure 2). Exercise SDNN correlated with FAI in HD patients and controls (Figure 3). On 24-h Holter, there was no correlation between HRV and FAI (Table 4). An exercise SDNN < 40 ms (median) was used as the dependent variable to test associations with FAI. In every multivariate logistic regression model tested, exercise SDNN < 40 ms was independently associated with FAI, regardless of age, sex, body mass index, smoking, diabetes, and beta-blocker or clonidine use. However, the association was found to be dependent on serum levels of hemoglobin (Table 5).

Table 1 – General features of HD patients and controls

	HD patients	Controls	p value
Age, years	50 ± 14[a]	50 ± 13	0.975
Male, %	21 (51.2)[b]	21 (51.2)	1.000
Race, non-white %	27 (65.9)	21 (51.2)	0.391
Body mass index, kg/m^2	25.1 ± 5.1	27.3 ± 4.1	0.030
HD vintage, months	67.2 ± 47.3	n.a.	
Diabetes, %	4 (9.8)	5 (12.2)	0.724
Smoking, %	3 (9.1)	8 (20.5)	0.180
Familial CAD,%	15 (36.6)	17 (41.5)	0.520
Familial hypertension, %	26 (63.4)	21 (51.2)	0.525
Sedentary lifestyle, %	33 (80.5)	24 (58.5)	0.031
Anti-hypertensive drugs, %	33 (80.5)	20 (48.8)	0.003
Beta-blocker	14 (34.1)	7 (17.1)	0.077
Diuretic	2 (4.9)	8 (19.5)	0.043
Calcium channel blocker	5 (12.2)	2 (4.9)	0.236
ACE inhibitor/ARB	12 (29.3)	16 (39.0)	0.352
Clonidine	8 (19.5)	-	0.003
Alfa-blocker	6 (14.6)	-	0.011
Hemoglobin, g/dL	11.5±1.4	13.8±1.2	< 0.001
eGFR (MDRD study), ml/min/1.73m^2	n.a.	87.5 ± 23.1	

HD: hemodialysis; CAD: coronary artery disease; ACE: angiotensin-converting-enzyme; ARB: AT1-receptor blocker; n.a.: not applicable; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease. [a] Mean ± SD; [b] n (%).

Table 2 – Baseline and peak values of heart rate, blood pressure and functional capacity on ETT in HD patients and controls

	HD patients	Controls	p value
pre-exercise HR, bpm	77 ± 12[a]	76 ± 13	0.705
pre-exercise SBP, mmHg	131 ± 39	130 ± 31	0.860
pre-exercise DBP, mmHg	82 ± 11	83 ± 9	0.135
peak HR, bpm	130 ± 25	160 ± 19	< 0.001
peak SBP, mmHg	193 ± 26	199 ± 21	0.273
peak DBP, mmHg	99 ± 11	93 ± 11	0.040
Exercise time, min	8.5 ± 1.9	10.1 ± 2.4	0.002
FAI, %	29.5 ± 12.0	2.8 ± 20.1	< 0.001

HD: hemodialysis; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure. FAI: functional aerobic impairment. [a] Mean ± SD

Discussion

In ESRD patients, AD is a frequent abnormality and a marker of cardiovascular events and death[5-8]. Exercise treadmill test, a valuable tool to assess AD, is hardly used in HD patients.

We studied autonomic parameters related to HRV during ETT in HD patients as compared to a control group, and the ETT results were correlated with FAI.

In our sample, the body mass index was in the upper limit of normality (borderline overweight) in HD patients, and clearly above that limit in the control group. This is not unexpected considering that malnutrition was common in HD patients in the past[9], but not in the present, and that obesity is a recognized risk factor for cardiovascular disease[10,11]. The proportion of diabetes mellitus in our sample was lower than that reported in international series[12,13], and even lower than that reported for the Brazilian

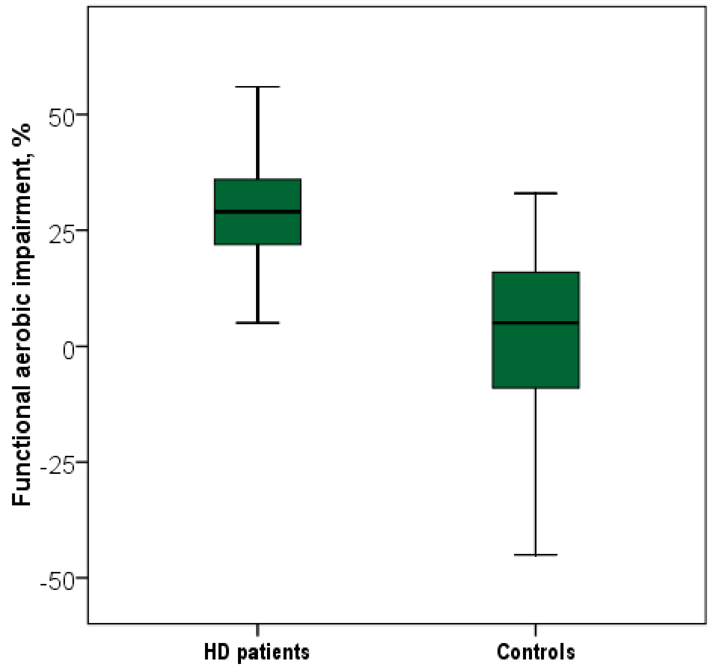

Figure 1 – *Functional aerobic impairment in hemodialysis (HD) patients and controls.*

Table 3 – Heart rate variability parameters during 24-h Holter and exercise treadmill test in HD patients and controls

	HD patients	Controls	p value
24-h Holter			
SDNN, msec	82.6 ± 27.6	119.1 ± 47.6	< 0.001
SDANN, msec	74.3 ± 26.8	113.1 ± 43.2	< 0.001
rMSSD, msec	17.4 ± 7.7	27.6 ± 11.1	< 0.001
Triangular index, msec	23.3 ± 8.4	34.4 ± 9.3	< 0.001
Exercise treadmill test			
exercise SDNN, msec	33.7 ± 14.2	50.0 ± 21.8	< 0.001
exercise rMSSD, msec	11.0 ± 5.5	15.3 ± 14.7	0.092
recovery SDNN, msec	20.1 ± 9.8	27.3 ± 17.4	0.024
recovery rMSSD, msec	11.5 ± 7.8	15.4 ± 17.3	0.196

HD: hemodialysis; SDNN: standard deviation (SD) of all normal RR intervals (NN); SDANN: SD of the averages of 5-min NN intervals over 24h; rMSSD: the square root of the mean of the square of successive NN intervals. Values shown as mean ± SD.

dialysis population[14], probably as a result of the inclusion and exclusion criteria adopted in the study. In support to the majority of reported series[1,12-14], a substantial number of HD patients used anti-hypertensive drugs. Consistent with the concept that sympathetic hyperactivity may play an important role in the hypertension of CKD patients, drugs mainly affecting this pathway were more frequently prescribed for HD patients[15]. In agreement with previous reports[16,17], left diastolic dysfunction on echocardiogram was more frequent in HD patients. In contrast, left ventricular systolic function was similar in both groups, perhaps due to our enrollment criteria, which excluded patients with overt heart failure.

When analyzing cardiovascular parameters in ETT, no difference was found between groups regarding systolic (SBP) or diastolic blood pressure (DBP) either at rest or exercise peak. Similarly, the HR at rest did not differ between groups, but the HR at peak exercise was lower in

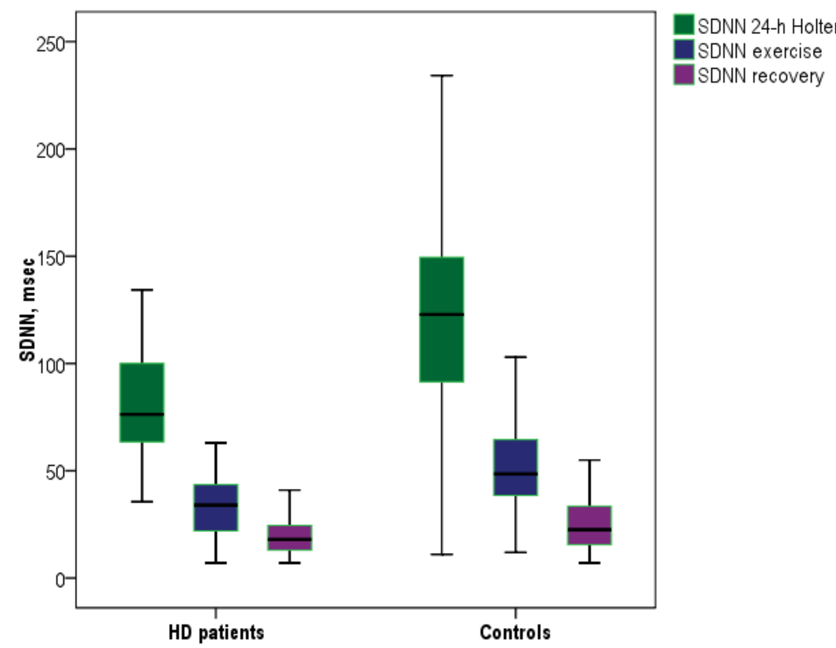

Figure 2 – *Heart rate variability (SDNN) during 24-h Holter, exercise, and recovery in hemodialysis (HD) patients and controls.*

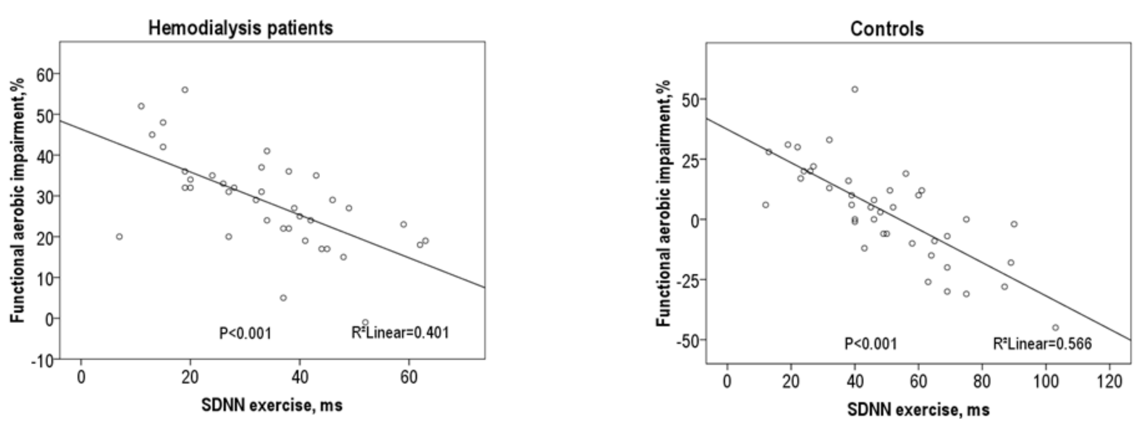

Figure 3 – *Correlation between functional aerobic impairment and heart rate variability (SDNN) during exercise in hemodialysis patients (left) and controls (right).*

HD patients. An attenuated HR response to exercise has been shown to predict adverse cardiac events in subjects without overt cardiovascular disease. Reduced HR response to exercise also predicts major adverse cardiac events among individuals with overt or suspected cardiovascular disease even after adjusting for left ventricular function and the severity of exercise-induced myocardial ischemia[18].

Our population comprised individuals of different ages. For this reason, to analyze functional aerobic capacity we resort to the use of FAI, which compares the obtained VO_2 with that expected for age and sex. In our results, FAI was higher in HD patients, a well-documented finding in HD patients[3,19]. In the general population, the functional aerobic capacity is a factor independently associated with cardiovascular and overall mortality. Our results found a mean FAI of 30% in the HD group and of 3% in the control group. In this population, the FAI may reach 65% of that predicted for sex and age as compared to controls[20]. Many factors may be involved with this reduction, some relating to the pathophysiology of the disease and others

Table 4 – Correlation coefficients between functional aerobic impairment and heart rate variability during 24-h Holter and exercise treadmill test in hemodialysis (HD) patients and controls

	HD patients		Controls	
	r	p	r	p
24-h Holter				
SDNN	-0.046	0.780	-0.183	0.260
SDANN	-0.044	0.792	-0.274	0.087
rMSSD	-0.090	0.585	0.248	0.123
Triangular index	-0.072	0.661	-0.123	0.451
Exercise treadmill test				
exercise SDNN	-0.633	< 0.001	-0.752	< 0.001
exercise rMSSD	0.300	0.858	0.023	0.887
recovery SDNN	-0.017	0.917	0.038	0.813
recovery SDNN	0.080	0.622	-0.028	0.864

r: Correlation coefficient; SDNN: standard deviation (SD) of all normal RR intervals (NN); SDANN: SD of the averages of 5-min NN intervals over 24h; rMSSD: the square root of the mean of the square of successive NN intervals.

Table 5 – Crude and adjusted OR and 95% CI in different models of multivariate logistic regression to test for associations of exercise SDNN <40 msec with functional aerobic impairment in hemodialysis patients

	OR	95% CI	p value
Crude	1.145	1.033-1.270	0.010
Model 1	1.213	1.059-1.390	0.005
Model 2	1.160	1.022-1.318	0.022
Model 3	1.141	1.010-1.288	0.034
Model 4	1.149	1.007-1.312	0.039
Model 5	1.153	0.979-1.357	0.088

The models consisted of the progressive inclusion of the following confounding factors: age and sex (model 1); smoking and body mass index (model 2); diabetes (model 3); clonidine and beta-blocker use (model 4); and hemoglobin (model 5).

to age and environment.[3] During exercise, there is an increased oxygen demand to supply muscle activity. The provision of this increase depends on many factors: peripherally, increased blood flow and increment of the arteriovenous oxygen extraction; and centrally, increased cardiac output. The raise in cardiac output during exercise depends mainly on HR increase. However, in HD patients, the chronotropic reserve is often reduced and this has been attributed to AD, admittedly present in uremia.[3]

Autonomic tests are frequently abnormal in HD patients. Heart rate variability during a 24-h Holter has been considered a good marker of dysautonomia in those patients[7,8]. Reduced HRV in the time or frequency domain has been associated with reduced survival in individuals on HD[6,7,21]. In consonance with previous studies, the HRV during 24-h Holter was lower in our HD patients demonstrating an altered autonomic function[5-7,21,22].

During ETT, HRV in the time domain decreases in the supine position and during exercise, and increases very slowly in the recovery period after exercise. Sympathetic hyperactivity persists for at least 45 minutes after exercise, being accompanied by a reduction in HRV[20]. In our results, SDNN during ETT was significantly lower in HD patients during exercise and recovery. These findings again may reflect the hyperadrenergic state characteristic of HD patients, because SDNN represents a general evaluation of the autonomic nervous system balance, which depends on modulation by sympathetic and parasympathetic branches[6]. In contrast, the variable predominantly affected by the parasympathetic branch, rMSSD, was not different between groups.

Our results showed a significant correlation between FAI and SDNN during exercise in both HD patients and controls. This finding reinforces the hypothesis that the reduction in functional aerobic capacity is strongly associated with the presence and severity of dysautonomia.[23] The stress resulting from exercise requires substantial changes of the autonomic nervous system, facilitating recognition of disturbances that otherwise could remain undetectable.

Our HD patients had reduced serum levels of hemoglobin, a finding not uncommon in ESRD. To control for anemia and other confounding factors regarding the association of HRV during exercise with FAI, we resort to a variety of logistic regression models in which smoking and diabetes (associated with lower HRV), and anemia and use of beta-blocker or clonidine (associated with increased FAI) were included as explanatory variables. Exercise SDNN was independently associated with FAI in all models tested, except for the one in which serum levels of hemoglobin were included. Several authors[23-27] have reported that the reduction of serum levels of hemoglobin causes a significant reduction in CRF and that the higher the reduction, the greater the FAI.[23] Furthermore, red cell transfusion[23,24] or administration of erythropoietin[25-27] was associated with a significant improvement in functional aerobic capacity, with a 6%-18% increase in VO_2 peak in different series and protocols.

The clinical relevance of our findings is prominent. Both AD and FAI are important predictors of mortality, justifying that efforts be made to find ways to reduce the risk of affected patients. From the pharmacological point of view, in addition to the treatment of anemia with erythropoietin, which effectively increases the functional capacity of those patients, alternatives are sparse.[3,26,,27] In this regard, the use of inhibitors of hepcidin, a peptide involved in the pathogenesis of anemia of chronic/inflammatory diseases[28,29], looks promising. On the other hand, it is well established that training improves functional capacity and reduces the rate of overall and cardiovascular mortality of those patients[30,31]. The mechanisms by which this occurs are multiple and certainly involve improvement in autonomic function and inflammation[31,32].

The reduced number of patients recruited from a single dialysis center is a limitation of our study. It should also be pointed that the maximal VO_2 during peak exercise was obtained by using the Foster formula, backed with hands, and not by using direct measurement of gas exchange during exercise. This should be especially considered, because we could not find validation studies of the cited formula for HD patients. In view of that, additional studies are needed to confirm our findings.

Conclusion

Functional aerobic impairment showed a strong correlation with HRV during exercise. This association was independent of age, sex, body mass index, smoking, diabetes, use of beta-blockers or clonidine, but not of serum levels of hemoglobin.

Author contributions

Conception and design of the research:Carreira MAMQ, Nogueira AB, Pena FM, Kiuchi MG, Rodrigues RC, Rodrigues RR, Matos JPS, Lugon JR. Acquisition of data:Carreira MAMQ, Nogueira AB, Pena FM, Kiuchi MG, Rodrigues RC, Rodrigues RR, Matos JPS, Lugon JR. Analysis and interpretation of the data: Carreira MAMQ, Nogueira AB, Pena FM, Kiuchi MG, Rodrigues RC, Rodrigues RR, Matos JPS, Lugon JR. Statistical analysis: Carreira MAMQ, Nogueira AB, Pena FM, Kiuchi MG, Rodrigues RC, Rodrigues RR, Matos JPS, Lugon JR. Obtaining financing: Carreira MAMQ, Matos JPS, Lugon JR. Writing of the manuscript:Carreira MAMQ, Pena FM, Rodrigues RC, Matos JPS, Lugon JR. Critical revision of the manuscript for intellectual content: Carreira MAMQ, Nogueira AB, Pena FM, Kiuchi MG, Rodrigues RC, Rodrigues RR, Matos JPS, Lugon JR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was partially funded by FAPERJ.

Study Association

This article is part of the thesis of Doctoral submitted byMaria Angela M. Q. Carreira, from Universidade Federal Fluminense.

References

1. Lugon JR, Warrak EA, Lugon AS, Salvador BA, Nobrega AC. Revisiting autonomic dysfunction in end-stage renal disease patients. Hemodial Int. 2003;7(3):198-203.
2. Herzog CA, Mangrum JM, and Passman R. Sudden cardiac death and dialysis patients. Semin Dial. 2008;21(4):300-7.
3. Painter P. Determinants of exercise capacity in CKD patients treated with hemodialysis. Adv Chronic Kidney Dis. 2009;16(6):437-48.
4. Laukkanen JA, Mäkikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death. J Am Coll Cardiol. 2010:56(18):1476-83.
5. Chan CT, Levin NW, Chertow GM, Larive B, Schulman G, Kotanko P; Frequent Hemodialysis Network Daily Trial Group. Determinants of Cardiac Autonomic dysfunction in ESRD. Clin J Am Soc Nephrol. 2010;5(10):1821-7.
6. Fukuta H, Hayamo J, Ishihara S, Sakata S, Mukai S, Ohte N, et al. Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis. Nephrol Dial Transplant. 2003;18(2):318-25.
7. Oikawa K, Ishihara R, Maeda T, Yamaguchi K, Koike A, Kawaguchi H, et al. Prognostic value of heart rate variability in patients with renal failure on hemodialysis. Int J Cardiol. 2009;131(3):370-7.
8. Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, et al. Heart rate variability predicts ESRD and CKD-related hospitalization. J Am Soc Nephrol. 2010;21(9):1560-70.
9. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15(7):953-60.

10. Bonanni A, Mannucci I, Verzola D, Sofia A, Saffioti S, Gianetta E, et al. Protein-energy wasting and mortality in chronic kidney disease. Int J Environ Res Public Health. 2011;8(5):1631-54.

11. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K et al; International Society of Renal Nutrition and Metabolism. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84(6):1096-107.

12. United States Renal Data System. Cardiovascular disease. [Accessed in 2014 Feb 10]. Available from: http://www.ursds.org/2012/pdf/v2_ch4_12.pdf

13. Foster MC, Rawlings AM, Marrett E, Neff D, Willis K, Inker LA, et al. Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States. Am Heart J. 2013;166(1):150-6.

14. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Watanabe Y, Santos DR. [Chronic dialysis in Brazil: report of the Brazilian dialysis census, 2011]. J Bras Nefrol. 2012; 34(3):272-7.

15. Joles JA, Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. Hypertension. 2004;43(4):699-706.

16. Ie EH, Zietse R. Evaluation of cardiac function in the dialysis patient - a primer for the non-expert. Nephrol Dial Transplant. 2006;21(6):1474-81.

17. Jakubovic BD, Wald R, Goldstein MB, Leong-Poi H, Yuen DA, Perl J, et al. Comparative assessment of 2-dimensional echocardiography vs cardiac magnetic resonance imaging in measuring left ventricular mass in patients with and without end-stage renal disease. Can J Cardiol. 2013;29(3):384-90.

18. Elhendy A, Mahoney DW, Khandheria BK, Burger K, Pellikka PA. Prognostic significance of impairment of heart rate response to exercise impact of left ventricular function and myocardial ischemia. J Am Coll Cardiol. 2003;42(5):823-30.

19. Fotbolcu H, Duman D, Ecder SA, Oduncu V, Cevik C, Tigen K, et al. Attenuated cardiovascular response to sympathetic system activation during exercise in patients with dialysis-induced hypotension. Am J Nephrol. 2011;33(6):491-8.

20. Lahiri MK, Chicos A, Bergner D, Ng J, Banthia S, Wang NC, et al. Recovery of heart rate variability and ventricular repolarization indices following exercise. Ann Noninvasive Electrocardiol. 2012;17(4):349-60.

21. Ranpuria R, Hall M, Chan CT, Unruh M. Renal-heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. Nephrol Dial Transplant. 2008;23(2):444-9.

22. Rubinger R, Revis N, Pollak A, Luria MH, Sapoznikov D. Predictors of haemodynamic instability and heart rate variability during haemodialysis. Nephrol Dial Transplant. 2004;19(8):2053-60.

23. Rocha Messias L, de Queiroz Carreira MÂ, Ribeiro de Miranda SM, Cunha de Azevedo J, Ambrósio Gava I, Campos Rodrigues R, et al. Relação entre imagem adrenérgica cardíaca e teste ergométrico. Arq Bras Cardiol. 2011;96(5):370-5.

24. Ekblom B, Goldbarg AN, Gullbrin B. Response to exercise after blood loss and reinfusion. J Appl Physiol. 1972;33(2):175-80.

25. Ekblom B, Wilson G, Astrand PO. Central circulation during exercise after venesection and reinfusion of red blood cells. J Appl Physiol. 1976;40(3):379-83.

26. Thomsen JJ, Rentsch RL, Robach P, Calbet JA, Boushel R, Rasmussen P, et al. Prolonged administration of recombinant human erythropoietin increases submaximal performance more than maximal aerobic capacity. Eur J Appl Physiol. 2007;101(4):481-6.

27. Barany P, Freyschuss U, Pettersson E, Bergstrom J. Treatment of anaemia in haemodialysis patients with erythropoietin: long-term effects on exercise capacity. Clin Sci (Lond). 1993;84(4):441-7.

28. Robertson HT, Haley NR, Guthrie M, Cardenas D, Eschbach JW, Adamson JW. Recombinant erythropoietin improves exercise capacity in anemic hemodialysis patients. Am J Kidney Dis. 1990;15(4):325-32.

29. Poli M, Asperti M, Ruzzenenti P, Regoni M, Arosio P. Hepcidin antagonists for potential treatments of disorders with hepcidin excess. Front Pharmacol. 2014;5:86.

30. Stamatakis E, Weiler R. Prevention of cardiovascular disease: why do we neglect the most potent intervention? Heart. 2010;96(4):261-2.

31. Voller H, Gitt A, Jannowitz C, Karoff M, Karmann B, Pittrow D, et al. Treatment patterns, risk factor control and functional capacity in patients with cardiovascular and chronic kidney disease in the cardiac rehabilitation setting. Eur J Prev Cardiol. 2014;21(9):1125-33.

32. Jae SY, Heffernan KS, Yoon ES, Lee MK, Fernhall B, Park WH. The inverse association between cardiorespiratory fitness and C-reactive protein is mediated by autonomic function: a possible role of the cholinergic antiinflammatory pathway. Mol Med. 2009;15(9-10):291-6.