Cardiac autonomic modulation in healthy subjects with a family history of chronic kidney disease

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ABSTRACT

Introduction: The positive family history of chronic kidney disease (FH+) is a risk factor for the appearance and development of this disease. Thus, it is important to assess traits that may be related to familial predisposition to chronic kidney disease. **Objective:** To evaluate the autonomic modulation by heart rate variability in individuals with FH+. **Methods:** We studied 9 health subjects with FH+ and 22 health subjects with negative family history for chronic kidney disease (FH-) matched for age (27 ± 6 *vs.* 26 ± 4 anos; $p = 0.39$, respectively). Heart rate was measured continuously by the Polar S810i® for 10 minutes of rest in the supine position. The heart rate variability was evaluated by the time domain, mean of NN intervals (MNN), standard deviation of the NN intervals (SDNN), root mean squared differences of successive NN intervals (RMSSD) and percentage of NN intervals with a difference of duration greater than 50 ms (pNN50) and the fields of low frequency (LF), high frequency (HF) and ratio low/high (LF/HF). Laboratory biochemical tests were performed after fasting for 12 hours. Results are expressed as mean ± standard deviation, adopting as significant $p < 0.05$. **Results:** The groups FH+ and FH-were similar in serum creatinine ($p = 0.98$), estimated glomerular filtration rate ($p = 0.49$) and heart rate ($p = 0.68$). The groups FH+ and FH- showed no significant differences in relation to indices of heart rate variability MNN; SDNN; RMSSD; pNN50; Total power; LF; HF and LF/HF ration, respectively. **Conclusion:** These findings suggest that the cardiac autonomic modulation is preserved in health subjects with HF+.

Keywords: heart rate, heredity, kidney failure, chronic.

INTRODUCTION

A family history of chronic renal disease (CRD) directly influences the onset and development of CRD in healthy individuals.[1-3] Healthy children of CRD patients show significantly higher values for albumin/creatinine ratios, systolic blood pressure, and blood glucose compared with the healthy children of individuals without CRD, although these values may still be within the normal limits.[4] Moreover, regardless of associated risk factors, the children of patients with CRD showed elevated blood pressure throughout the 1 year of follow-up, a finding that was not observed in children of healthy parents.[5] In addition, patients on renal replacement therapy for CRD who have a family history of CRD have a higher probability of developing renal failure than patients without a family history of CRD.[1,2] It is clear that genetics have a major influence on the development of this disease and on worsening its prognosis.

In established CRD, high mortality of cardiovascular origin seems to be related to autonomic dysfunction.[6-8] Penne *et al*. have shown that in individuals with CRD, sympathetic hyperactivity,[7,9] a trait of this disease,[10] was associated with the occurrence of cardiac events. In that study, high sympathetic nerve activity, directly measured through microneurography, was directly associated with the development of acute myocardial infarction.[7] Using the indirect method for assessment of autonomic modulation, Fukuta *et al*. have demonstrated that, in patients on dialysis, variability of heart rate was inversely

related to survival probability during a 4-year follow-up period.[6] Furthermore, these authors have shown that the high-frequency spectrum range, a variable that indicates vagal modulation, was significantly reduced in patients who died from cardiovascular causes when compared to patients who survived throughout that period.[6] However, until now, cardiac autonomic modulation in healthy children of CRD patients remains has not been elucidated.

Therefore, in this study, we aimed to assess cardiac autonomic modulation, through heart rate variability, in healthy individuals who are children of CRD patients.

Methods

Sample

For the study, 9 healthy individuals (7 female, 2 male), aged between 20 and 40 years and the children of CRD parents, were successively recruited (FH+ Group), along with 22 healthy individuals, matched by age and gender, without a family history of CRD (FH-).

All volunteers, in both the FH+ and FH- Groups, had systolic and diastolic blood pressure below 140 and 90 mmHg,[11] respectively; body mass index between 20 and 29.9 kg/m^2; serum creatinine below 1.4 mg/dL; no proteinuria or hematuria; and estimated glomerular filtration rate higher than 60 mL/min/1.73 m^2. Moreover, volunteers who practiced regular physical activity in the last 6 months and/or were taking any kind of medication were excluded.

For characterization of the groups, we used the following criteria:

FH+ Group

Each volunteer was the child of either a father or mother with CRD,[12] regardless of the stage and current treatment. Volunteers whose parents' CRD was caused by hypertensive nephrosclerosis, diabetic nephropathy, or polycystic kidney disease of the adult were excluded. In order to confirm this disease, the clinical records of those patients were accessed from the Center for Interdisciplinary Studies, Research, and Treatment in Nephrology (NIEPEN).

FH- Group

Each volunteer was the child of a father and mother without reported CRD and without use of any kind of medication.

All volunteers received information on the research and were only included as volunteers after they read, agreed to, and signed the Free and Informed Consent Form. This research was approved by the Ethics on Research Committee of the Federal University of Juiz de Fora (UFJF, approval nº 0119/2010), and conducted at the University Hospital of the Federal University of Juiz de Fora (HU/UFJF).

Measures and Procedures

Blood pressure, resting heart rate, and respiratory rate

For characterization of the sample, blood pressure and heart rate were measured after 10 min at rest in the supine position. Blood pressure was measured noninvasively in the right arm, using the auscultation method with a mercury column sphygmomanometer (Takaoka®). Korotkoff stages I and V were adopted for the identification of systolic and diastolic blood pressures, respectively.[11] The heart rate was noninvasively monitored using a Polar S810i® heart rate monitor (Polar Electro; Kempele, Finland). Spontaneous respiratory rate was monitored using a Dixtal 2023® apparatus (Amazon, Brazil).

Assessment of cardiac autonomic modulation

Cardiac autonomic modulation was assessed by the indirect method of heart rate variability, using the Polar S810i® heart rate monitor. Heartbeats were recorded at rest, in the supine position with spontaneous respiration, for a period of 10 min.

The individual values of the intervals between each heartbeat (iRR) were transferred to the microcomputer by transmission of the data from the pulse receptor to the *Polar Precision Performance software*. Next, the data were transferred to the MATLAB application, version 6.0, for automatic selection of the 5 min of least variance that would be used in the calculation of CFV through a previously implemented algorithm.[13] The selected 5-min time series were transferred to *Kubios HRV Analysis software*, version 2.0. In this application, artifact correction was performed using the mid-level filter of the *software*. CFV indices were calculated in the time domain (MNN = RR interval mean, SDNN = standard deviation of RR intervals, RMSSD = root mean square of the differences in successive RR intervals, and pNN50 = percent RR intervals with difference in duration higher than 50 ms). For estimation of the power spectral density function,

using the fast Fourier transform nonparametric method, the trend component of the time series was removed, by the smoothing method *a priori* and by decimation in the 4 Hz frequency through interpolation with the cubic spline.[13] For spectral analysis of the CFV, the low-frequency (LF) and high-frequency (HF) bands of the power spectrum were considered, expressed as absolute power and as normal units, in addition to the LF/HF ratio.[13]

Anthropometric assessment

Height was measured using a height measuring stand (Asimed®), and weight with a scale (Asimed®). Body mass index was calculated as weight divided by the square of height.

Assessment of physical activity levels

The level of physical activity of volunteers was assessed using Baecke's questionnaire, which was divided into 3 parts: physical activity at work (AFO), physical exercise during leisure time (EFL), and physical activities of leisure and walking (ALL). These were measured by their specific scores. The level of physical activity in the last 6 months was assessed according to the type, intensity, duration, and frequency.[14]

From that questionnaire, the practice of regular physical activity was considered to be the performance of scheduled physical activities more often than twice a week for a period greater than or equal to 6 of the last 12 months.

Laboratory assessment

After a 12h fast, 10 mL of blood was collected for analysis of blood glucose, cholesterol, cholesterol fractions, and creatinine.[15] The estimated glomerular filtration rate was calculated based on the serum creatinine levels, using the CKD-EPI formula.[16] A simple urine test (SUT) was performed to verify the absence of protein and hemoglobin in participants' urine.[17]

Experimental protocol

The whole experimental protocol, which is described below, was performed during an afternoon at the Physical Assessment Unit - HU/CAS. The volunteers were instructed to have a light breakfast up to 1 hour before data collection started, and not to drink any caffeine-containing beverages or alcoholic drinks or practice heavy physical activity in the 24 hours preceding the experiment. Moreover, the volunteers were questioned as to whether they had a relaxing sleep the previous night; if not, the experiment was rescheduled to a different day.

At the laboratory, the volunteers were informed about the research procedures and read and signed the Free Informed Consent Form. Next, the medical history was taken and the questionnaire on the usual level of physical activity was answered; subsequently, the anthropometric assessment was performed. Next, the volunteer remained in the supine position, and after a 10 min period of rest, HR was continuously monitored for 10 min at rest. At the end of this period, blood pressure was measured. When the procedures were completed, the volunteer underwent blood and urine tests.

Statistical analysis

In order to test normality of the data, the Kolmogorov-Smirnov test was used. The data are shown as mean ± standard deviation from the mean. CFV indices will be presented as median and interquartile deviation. The possible gender differences were tested using the Chi-square test. The possible statistical differences in the base characteristics between the groups under study were assessed by *Student's t*-test for variables with normal distribution and by the Mann-Whitney U test for variables with non-normal distribution. Significant difference was accepted for $p < 0.05$.

By the sample calculation of normally distributed variables, using an alpha error of 95% and a beta error of 80%, it was concluded that a minimum of 9 individuals should be recruited in each group.

Results

The disease etiologies for parents with a CRD diagnosis were glomerulonephritis (n = 3), reflux nephropathy (n = 2), and undetermined (n = 4), with 3 on renal replacement therapy and 6 receiving conservative therapy between stages 2 to 4.

The FH+ and FH- groups were similar with regard to gender, age, weight, height, body mass index, and level of usual physical activity (Table 1). Moreover, no significant differences were observed between groups with regard to fasting blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, systolic and diastolic blood

pressure, and heart rate (Table 2). Serum creatinine levels and estimated glomerular filtration rates were similar between individuals with and without a family history of CRD (Table 2).

Table 1 Physical characteristics of the FH+ and FH- groups

Variables	FH+ (n = 9)	FH- (n = 22)	*p*
Gender (F/M)	7/2	7/15	0.72
Age (years)	27 ± 6	26 ± 4	0.45
Weight (kg)	69 ± 11	69 ± 12	0.98
Height (m)	1.65 ± 0.06	1.68 ± 0.09	0.28
BMI (kg/m^2)	25 ± 4	24 ± 2	0.28
Level of Physical Activity (Total Score)	7 ± 1.5	7 ± 1	0.47

FH+: Individuals with family history of chronic renal disease; FH-: Individuals with no family history of chronic renal disease; F: Female; M: Male; BMI: Body mass index.

Table 2 Biochemical and hemodynamic characteristics of the FH+ and FH- groups

Variáveis	HF+ (n = 9)	HF- (n = 22)	*p*
Total cholesterol (mg/dL)	174 ± 32	184 ± 41	0.56
HDL-c (mg/dL)	57 ± 8	51 ± 11	0.14
LDL-c (mg/dL)	102 ± 30	111 ± 40	0.59
Triglycerides (mg/dL)	74 ± 52	114 ± 65	0.16
Blood glucose (mg/dL)	80 ± 4	80 ± 9	0.93
Creatinine (mg/dL)	0,88 ± 0,14	0,92 ± 0,22	0.62
eGFR (ml/min/1.73 m^2)	95 ± 16	96 ± 21	0.87
Proteinuria	Absent	Absent	-
Hematuria	Absent	Absent	-
SBP (mmHg)	116 ± 8	114 ± 7	0.40
DBP (mmHg)	70 ± 6	68 ± 5	0.21
HR (bpm)	70 ± 9	71 ± 10	0.85

FH+: Individuals with family history of chronic renal disease; FH-: Individuals with no family history of chronic renal disease; eGFR: Estimated glomerular filtration rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

Cardiac autonomic modulation, both for indices within the time domain and for indices in the frequency domain, were similar between the FH+ and FH- groups (Table 3). Mean spontaneous respiratory rate was similar between the FH+ and FH- groups (20 ± 3 *vs.* 17 ± 4; $p = 0.07$, respectively).

Discussion

The main finding of this study is that individuals with a family history of CRD showed cardiac autonomic modulation similar to that of individuals without a family history of this disease.

Although there have been few studies describing the influence of family history of CRD on histological, biochemical, and cardiovascular parameters, it has been shown that the hereditary factor for CRD may promote alterations in those parameters, even though the values often remain within the normal range.[4,5] Dimitrov *et al.* have observed that individuals without CRD but with a family history of the disease, when compared with those without a family history, already showed reduced kidney mass, which could promote future compromise of renal function.[5] Moreover, in that same study, the reduction in kidney mass was directly associated with an increase in systolic blood pressure during the 1 year of follow-up, regardless of associated risk factors.[5] Therefore, early histological alterations are directly related to the progressive hemodynamic compromise that is observed in individuals who are children of CRD patients.[5]

As with Dimitrov *et al.* work, in this study, no significant differences were observed in blood pressure values between the positive and negative CRD family history groups. That finding may be explained by the similar characteristics between the individuals belonging to the 2 groups under study; they all were young, healthy and, most importantly, showed similar values for creatinine and estimated glomerular filtration.

Moreover, the one-time clinical measurement of blood pressure may not be sufficient to identify hemodynamic compromise in that population. This is because it has been shown that blood pressure level compromise is accompanied by progressive renal alterations, which are identified only in longitudinal studies.[5] Thompson *et al.* have observed that healthy individuals with a family history of CRD showed albumin/creatinine ratio, and systolic blood pressure, blood glucose, and total cholesterol levels that are significantly higher than those in individuals without a family history of CRD.[4] On the other hand, in the study by Thompson *et al.*, the individuals under study were smokers, which may misguide interpretation of the results, since smoking directly influences some of those variables. In our study, healthy nonsmokers were investigated who were not using any medication,

Table 3 Resting heart rate variability between the FH+ and FH- groups

Variable	FH+ (n = 9)		FH- (n = 22)		*p*
	Median (1st-3rd Quartiles)		Median (1st-3rd Quartiles)		
Time Domain					
MNN	840.5	(761.7-983.5)	828.2	(794.4-875.8)	0.74
SDNN	42.7	(33.2-59.4)	41.45	(33.0-45.6)	0.98
RMSSD	44.1	(41.4-69.6)	45.25	(37.6-53.5)	0.99
pNN50	27.2	(13.0-43.1)	17.35	(8.2-24.8)	0.17
Frequency Domain					
Total power	2011	(1171.0-4360.0)	1465	(968-2141)	0.96
LF (ms²)	1327.1	(435.8-2205.2)	581.9	(358.5-900.2)	0.71
HF (ms²)	767.1	(240.5-2439.1)	752.45	(519.7-1076.9)	0.85
LF u.n.	54.5	(39.5-78.7)	40.7	(30.7-59.4)	0.55
LF u.n.	45.5	(28.3-77.6)	59.3	(40.6-69.3)	0.51
LF/HF ratio	1.2	(0.7-3.7)	0.7	(0.4-1.5)	0.43

FH+: Individuals with family history of chronic renal disease; FH-: Individuals with no family history of chronic renal disease; MNN: Mean of RR intervals; SDNN: Standard deviation of RR intervals; RMSSD: Root mean square of the differences between successive RR intervals; pNN50: Percent RR intervals with difference in duration longer than 50 ms; LF: Low-frequency; HF: High-frequency; LF/HF: Low/high frequency ratio.

and therefore, no differences were found in the levels of total cholesterol, HDL-c, LDL-c, fasting blood glucose, and blood pressure values. Therefore, the similarity in cardiac autonomic modulation between the FH+ and FH- groups may be justified with the similarity in physical, metabolic, and hemodynamic parameters.

With arterial hypertension, on the other hand, autonomic dysfunction is observed early in healthy individuals with a family history of this disease. Pitzalis *et al*. found a decrease in cardiac autonomic control in the children of hypertensive individuals, observed as a low SDNN index, which reflects both sympathetic as well as parasympathetic modulation of heart rate.[18] Piccirillo *et al*. observed that children of 1 or 2 hypertensive parents showed a significant decrease in the high-power spectral band (HF), as well as an elevation in the low-power (LF) spectral band and of the LF/HF ratio when compared with children of normotensive parents.[19] Thus, we can infer that those healthy individuals, albeit with a family history of hypertension, already exhibit damage in cardiac autonomic control that is characterized by an elevation in sympathetic modulation detrimental to vagal modulation. In all those studies, the children of hypertensive parents, even when normotensive, already showed blood pressure values higher than those of children of normotensive parents.[18,19] Therefore, the preserved autonomic modulation in the children of CRD subjects may also be related to the similar blood pressure values between the groups under study.

In patients with CRD, those with a family history of CRD have a greater probability of developing renal failure than patients with a negative family history.[1,2] That information shows that the hereditary factor has a great impact on worsening the disease prognosis. Therefore, screening for possible CRD-related alterations in individuals with a positive family history is extremely important.

It is known that CRD presents a number of complications; among these is a high prevalence of cardiovascular events, which consequently increases mortality.[6-8] There is clear evidence that the increase in cardiovascular mortality is directly associated with damage in cardiac autonomic control observed in those patients.[6] Although our study is the first to demonstrate that autonomic modulation is preserved in healthy persons who are the children of CRD parents, it has been demonstrated that individuals without CRD but with a family history of that disease show a reduction in kidney mass and elevation of blood pressure levels throughout the 1 year of follow-up,[5] which are factors that might accompany cardiac autonomic dysfunction. As such, follow-up of healthy individuals who are the children of CRD patients is highly relevant for building strategies for preventing the development and controlling the progression of CRD and its complications.

There is clear evidence that physical capacity or the regular practice of physical exercise markedly improves cardiac autonomic modulation.[20] Although we did not assess physical capacity directly through the ergospirometric stress test, all our volunteers, both those with FH+ as well as FH-, were sedentary in the 6 months prior to our assessments. Moreover, when indirectly assessed, the FH+ and FH- groups were similar relative to the level of physical activity, a fact which minimizes the evaluative effect.

Conclusion

Healthy individuals with a family history of CRD show no difference in cardiac autonomic modulation when compared with healthy individuals without a family history of CRD.

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