

Depressed cardiac autonomic modulation in patients with chronic kidney disease

Depressão da modulação autonômica cardíaca em pacientes com doença renal crônica diagnosticada pela análise espectral da variabilidade da frequência

Autores

Carlos Alberto de Oliveira¹
Helio Lima de Brito Junior^{2,3}
Marcus Gomes Bastos³
Felipe Gomes de Oliveira⁴
Thais Gomes Casal⁵
Tiago Costa Bignoto⁴
Natalia Maria da Silva Fernandes³
Antonio Fernando de Castro Alves Beraldo³
Rogério Baumgratz de Paula^{3,6}

¹ School of Medical and Health Sciences of Juiz de Fora.

² Medical School of the University of São Paulo (USP).

³ Federal University of Juiz de Fora (UFJF).

⁴ Dante Pazzanese Institute of Cardiology.

⁵ Federal University of Minas Gerais (UFMG).

⁶ Paulista State University (UNESP).

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Correspondência para:

Rogério Baumgratz de Paula.
Universidade Federal de Juiz de Fora.
Rua Luiz Brant Horta, nº 125,
Bairro São Pedro. Juiz de Fora,
MG, Brazil. CEP: 36099-999.
E-mail: rogeriobaumgratz@gmail.com
Tel: (32) 3232-2091.
Fax: (32) 3217-1065.
CAPES, CNPq e IMEPEN.

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ABSTRACT

Introduction: A dysfunctional autonomic nervous system (ANS) has also been recognized as an important mechanism contributing to the poor outcome in CKD patients, with several studies reporting a reduction in heart rate variability (HRV). **Objective:** Evaluate the sympathovagal balance in patients with chronic kidney disease on conservative treatment. **Methods:** In a cross-sectional study, patients with CKD stages 3, 4 and 5 not yet on dialysis (CKD group) and age-matched healthy subjects (CON group) underwent continuous heart rate recording during two twenty-minute periods in the supine position (pre-inclined), followed by passive postural inclination at 70° (inclined period). Power spectral analysis of the heart rate variability was used to assess the normalized low frequency (LFnu), indicative of sympathetic activity, and the normalized high frequency (HFnu), indicative of parasympathetic activity. The LFnu/HFnu ratio represented sympathovagal balance. **Results:** After tilting, CKD patients had lower sympathetic activity, higher parasympathetic activity, and lower sympathovagal balance than patients in the CON group. Compared to patients in stage 3, patients in stage 5 had a lower LFnu/HFnu ratio, suggesting a more pronounced impairment of sympathovagal balance as the disease progresses. **Conclusion:** CKD patients not yet on dialysis have reduced HRV, indicating cardiac autonomic dysfunction early in the course of CKD.

Keywords: cardiovascular diseases; kidney diseases; nephrology; renal insufficiency, chronic.

RESUMO

Introdução: Um sistema nervoso autônomo disfuncionante tem sido relacionado a eventos cardiovasculares em pacientes com doença renal crônica (DRC), com vários estudos demonstrando redução da variabilidade da frequência cardíaca e o desenvolvimento de arritmias complexas nestes pacientes. **Objetivo:** Avaliar o balanço simpático-vagal em pacientes com DRC em tratamento conservador. **Métodos:** Em estudo transversal, foram avaliados pacientes com DRC estágios 3, 4 e 5 não dialítico pareados para indivíduos saudáveis. Todos os voluntários foram submetidos à monitorização contínua da frequência cardíaca durante, por 20 minutos na posição supina (período pré-inclinado), seguido de inclinação passiva a 70 graus por mais 20 minutos (período inclinado). A análise espectral da variabilidade da frequência cardíaca foi usada para se obter a baixa frequência normalizada (LF nu), indicativa da atividade simpática, e a alta frequência normalizada (HF nu), indicativa da atividade parassimpática. A razão entre essas duas variáveis (LF nu/HF nu) é representativa do balanço simpático-vagal. **Resultados:** Durante o período pré-inclinado, não houve diferença significativa da variabilidade da frequência cardíaca entre os pacientes com DRC e o grupo controle. No entanto, após a inclinação, os pacientes com DRC apresentaram menor atividade simpática, maior atividade parassimpática e menor balanço simpático-vagal quando comparados com o grupo controle. Comparados com pacientes em estágio 3, pacientes em estágio 5 apresentaram menor razão LFnu/HFnu, sugerindo piora do balanço simpático-vagal nos estágios mais avançados da DRC. **Conclusão:** Pacientes com DRC não dialíticos apresentam diminuição da variabilidade da frequência cardíaca, compatível com disfunção autonômica cardíaca precoce no curso da DRC.

Palavras-chave: doenças cardiovasculares; insuficiência renal crônica; nefrologia; nefropatias.

INTRODUCTION

Cardiovascular events are the main cause of morbidity and mortality in patients with chronic kidney disease (CKD).¹ In this population, mortality from cardiovascular disease (CVD) stratified by age is 10 times higher than in the general population.² The pathophysiology of CVD in patients with CKD remains undetermined. Traditional risk factors such as hypertension, diabetes and hyperlipidemia are recognized as important mechanisms³ but do not fully explain the high prevalence of CVD in this population. Non-traditional risk factors that are seen throughout the spectrum of CKD such as oxidative stress, anemia, inflammation, left ventricular hypertrophy (LVH) and vascular calcification may be responsible for the early and accelerated atherosclerosis in CKD.⁴ A dysfunctional autonomic nervous system (ANS) has also been recognized as an important mechanism contributing to the poor outcome in CKD patients, with several studies reporting a reduction in heart rate variability (HRV) and the development of complex arrhythmias in CKD.⁵ In the last few years, non-invasive methods such as power spectral analysis of the HRV have been used to evaluate cardiac risk in a variety of conditions, including cardiac disorders, stroke, and diabetes.^{6,7} In the present study, we tested the hypothesis that power spectral analysis of the HRV coupled with postural stress would enable the detection of early changes in sympathovagal balance not diagnosed by traditional analysis of the HRV.

MATERIAL AND METHODS

PATIENTS

We evaluated 32 individuals (18 men and 14 women) with CKD at stages 3, 4 or 5 who were not yet on dialysis. The individuals were recruited at the Interdisciplinary Nucleus for Studies, Research and Treatment in Nephrology, Federal University of Juiz de Fora. All patients had been followed by a nephrologist for at least 6 months before inclusion in the study. Patients with severe cardiac disease, cancer, diabetes, collagen and demyelinating diseases, left ventricular systolic dysfunction, or a history of stroke were excluded. The control group consisted of 14 subjects with normal renal function who were non-diabetic, normotensive and free of heart disease. The study was approved by the Ethics Committee of the University Hospital of the Federal University of Juiz de Fora, document number 073/2007, and all subjects signed an informed consent before being included in the protocol.

STUDY DESIGN

This was a cross-sectional study in which we evaluated ANS function in patients with CKD under conservative treatment and compared the results to a control group. Power spectral analysis of the HRV at rest and during a passive orthostatic stress was performed in both groups.

CARDIOVASCULAR EVALUATION

The medical evaluation was performed by a cardiologist and consisted of an interview and clinical examination. Blood pressure was measured at each 2 minutes intervals using a conventional sphygmomanometer (model Tycos, USA). A conventional 12-lead electrocardiogram (ECG) was performed with an electrocardiograph (model Apex 1000, TEB, Brazil). To detect LVH, we used the Cornell criterion.⁸ Ventricular geometry and function were analyzed using a two-dimensional Doppler echocardiogram generated using a Philips EnVisor C Ultrasound System (Philips Medical Systems-Ultrasound, Andover, MA, USA). Measurements and indices of left ventricular function at rest were obtained through the two-dimensional and M modes, using a 3.5 MHz linear transducer placed over the third or fourth intercostal space. The diagnosis of LVH was based on the left ventricular mass index (LVMI), values for which were considered normal up to 115 g/m² for men and up to 95 g/m² for women.⁹ The data were interpreted according to criteria established by the American Society of Echocardiography.¹⁰

LABORATORY EVALUATION

The results of the following tests were obtained from the patients' charts: glomerular filtration rate (eGFR; estimated from creatinine using the Modification of Diet in Renal Disease equation),¹¹ urea, potassium, calcium, phosphorus, hemoglobin, uric acid, parathyroid hormone (PTH), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose and urinalysis. The diagnosis of CKD was based on the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (KDOQI/NKF);¹² eGFR < 60 ml/min/1.73 m² and/or at least one marker of renal parenchymal damage (e.g., proteinuria), present for a period of ≥ 3 months.

ANALYSIS OF HEART RATE VARIABILITY

The HRV was measured at rest in the supine position and during orthostatic stress. All subjects were instructed to fast for six hours and not to smoke

or drink caffeine for 12 hours prior to the test. All medications that could potentially interfere with the cardiovascular response such as non-dihydropyridine calcium channel blockers, beta-blockers, central sympatholytic, tricyclic antidepressants as well as anti-arrhythmic drugs were withdrawn for at least five drug half-lives before the study. The evaluation was conducted in the morning in a calm environment with low light on a tilting table with seat belts and a platform for a footrest. The subjects underwent continuous HR recording using a Holter system (Cardio Light Cardiosistemas, Brazil) during two 20 minute periods in the supine position (pre-inclined), followed by passive postural inclination at 70° (inclined period).¹³ To evaluate the spectral analysis of HRV, a fast Fourier transform was used,¹⁴ obtained by means of Holter-specific software (Analizador Cardio Smart 550, Cardiosistemas, Brazil), that allows periodic signals, an average of 500 sequential R-R intervals, to be divided into various bands of frequency response: ultra-low frequency (ULF: < 0.0033 Hz), very low frequency (VLF: 0.0033 to 0.04 Hz), low frequency (LF: 0.04 to 0.15 Hz), and high frequency (HF: 0.15 to 0.4 Hz). The LF and HF components were used as markers of sympathetic and parasympathetic activities, respectively, and the LF/HF ratio was used as a measure of the sympathovagal balance. To minimize the effects of changes in ULF and VLF bands, the data were normalized and the results expressed as normalized units (nu). The normalization was done by dividing the power of a given component (LF or HF) by the total power spectrum; from this result, the VLF component was subtracted, and this number was then multiplied by 100. Thus, the variables used for the HRV analysis were LFnu, HFnu and the LFnu/HFnu ratio. The data were interpreted following previously published guidelines.¹⁵ The HRV was analyzed using the highest total power expressed in msec², which was obtained after 10 minutes in the supine position and during the first 5 minutes after tilting the table.

STATISTICAL ANALYSIS

The variables are described as mean, standard deviation, percentage or median. The descriptive statistics and normality of the data were tested by the Kolmogorov Smirnov test. The laboratory data of the control and CKD groups at baseline were compared using an independent sample *t* test,

Chi-square test or Mann Whitney test depending on the characteristics of the variable. Spectral analysis of heart rate variability was assessed within groups in the pre-inclined and inclined periods by Kruskal Wallis or ANOVA (with post Hoc Bonferroni test) for both the control group and for the CKD group divided into disease stages three, four and five. The LFnu/HFnu ratio for the control and CKD groups was compared by the Mann Whitney Test. To assess the correlation between CKD stages and biochemical variables with the LFnu/HFnu ratio, Spearman's linear correlation coefficient was used. A *p* value less than or equal to 0.05 was considered statistically significant. All analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, USA).

RESULTS

DEMOGRAPHIC AND LABORATORY DATA

The age distribution was similar in both CKD and control (CON) groups. The average ages was 54.9 ± 1.2 at stage 3, 55.7 ± 13.4 at stage 4 and 57.7 ± 12.1 at stage 5, respectively. Regarding race, 25/32 patients in the CKD group were white (78%), 4/32 were black (12%), and 3/32 were mixed (10%). In the CON group, 12/14 patients were white (85%) and 2/14 were black (15%). In the CKD group, 11/32 patients were in stage 3 (34%; mean eGFR equal to 40.3 ± 7.4 ml/min/1.73 m²), 11/32 patients were in stage 4 (34%; mean eGFR equal to 23.5 ± 4.4 ml/min/1.73 m²), and 10/32 patients were in stage 5 (32%; mean eGFR equal to 12.7 ± 2.0 ml/min/1.73 m²). In the CON group, the mean eGFR was 97.3 ± 28.9 ml/min/1.73 m². Etiologies of CKD were chronic glomerulonephritis (16%), hypertensive nephropathy (25%), autosomal dominant polycystic kidney disease (16%), urolithiasis (13%), and chronic pyelonephritis (5%); and in 25% of the patients the cause was not determined.

Table 1 presents the laboratory data for the participants. As expected, the CKD patients had higher phosphorus, higher calcium x phosphorus product, and higher PTH levels compared to the CON group. The uric acid and triglycerides levels were higher, and HDL cholesterol was lower in the CKD group compared to the CON group. Blood glucose and plasma potassium levels were within normal ranges in both groups. The urinalysis was normal in the CON group.

TABLE 1 BASELINE LABORATORY DATA OF THE CKD AND HEALTHY CON GROUPS

Parameters	CKD group (n = 32)	CON group (n = 14)	p value
Creatinine (mg/dL)	3.1 ± 1.3	0.9 ± 0.3	< 0.001
eGFR (ml/min/1.73 m ²)	26.0 ± 12.5	97.3 ± 28.9	< 0.001
Urea (mg/dL)	75.9 ± 34.0	30.3 ± 7.8	< 0.001
Potassium (mEq/L)	4.5 ± 0.5	4.1 ± 0.4	NS
Calcium (mg/dL)	9.8 ± 1.0	8.8 ± 0.6	< 0.001
Phosphorus (mg/dL)	4.3 ± 1.1	3.5 ± 0.7	< 0.005
Ca x P (mg ² /dL ²)	41.6 ± 11.3	30.6 ± 6.9	< 0.001
Hemoglobin (g/dL)	13.1 ± 1.4	14.5 ± 1.2	< 0.006
Uric acid (mg/dL)	7.0 ± 1.7	5.2 ± 1.5	< 0.001
PTH (pg/ml)	214.5 ± 205.9	52.2 ± 18.7	< 0.001
Cholesterol (mg/dL)	190.6 ± 42.8	195.8 ± 35.9	NS
HDL (mg/dL)	43.3 ± 12.7	51.0 ± 11.6	< 0.010
LDL (mg/dL)	113.7 ± 35.8	125.7 ± 26.3	NS
Triglycerides (mg/dL)	170.5 ± 74.2	101.8 ± 26.7	< 0.003
Blood glucose (mg/dL)	89.7 ± 10.8	87.1 ± 10.0	NS
Urinalysis	Altered	Normal	

CKD: Chronic kidney disease; CON: Control group; Ca x P, calcium x phosphorus product; HDL: High density lipoprotein; LDL: Low-density lipoprotein; PTH: Parathyroid hormone; eGFR: Estimated glomerular filtration; altered, presence of hematuria and/or proteinuria; NS: Not significant.

CARDIOVASCULAR PARAMETERS

The prevalence of hypertension in the CKD group was 100%, with mean systolic blood pressure (SBP) of 150.3 ± 23.4 mmHg and mean diastolic blood pressure (DBP) of 93.6 ± 17.0 mmHg. In the CON group, all subjects were normotensive, with a mean SBP of 121.2 ± 8.8 mmHg and a mean DBP of 81.8 ± 9.2 mmHg.

Left ventricular hypertrophy in the ECG was diagnosed in nine CKD patients (28%) but was not present in the CON group. There were no arrhythmias in ECG at rest in any of the participants.

Left ventricular hypertrophy by echocardiography was diagnosed in 64% of the CKD patients and in none of the control group. The mean left ventricular

mass index in the CKD group was 136.3 ± 39.9 g/m² in men and 117.7 ± 37.1 g/m² in women. In the CON group, these values were significantly lower: 98.1 ± 5.4 g/m² in men and 86.5 ± 5.1 g/m² in women.

BLOOD PRESSURE AND HEART RATE DURING THE AUTONOMIC TESTS

During the pre-inclined period, the mean SBP in the CON group was 121.0 ± 81.8 mmHg, which decreased slightly but significantly to 114.0 ± 79.0 mmHg ($p < 0.05$) after the tilt. There was no significant difference between the mean DBP before and after tilting. A significant increase in HR from 72 ± 15 bpm before the tilt to 83 ± 14 bpm post-tilt was observed in the CON group, ($p < 0.05$). In the CKD there were no significant changes in SBP, DBP and HR following tilting.

Blood pressure did not change significantly between the subgroups of CKD patients. Thus, in CKD stage 3, the mean SBP and DBP were 150.7 ± 94.0 mmHg in pre-inclined period and 142.2 ± 96.5 mmHg after tilting.

In stage 4 were 148.1 ± 96.1 mmHg in pre-inclined period and 139.0 ± 93.8 mmHg after tilting. In stage 5 were 152 ± 90.2 mmHg in pre-inclined period and decreasing slightly to 148.0 ± 90.8 mmHg after the tilt. The HR showed a non-significant elevation from 72 ± 13 bpm to 74 ± 14 bpm after the tilt.

ASSESSMENT OF HEART RATE VARIABILITY

The variables LFnu and HFnu and the LFnu/HFnu ratio were analyzed in the pre-inclined and inclined periods in the CON and CKD groups. As can be seen, there were no significant differences in LFnu, HFnu and LFnu/HFnu between the CON and CKD groups during the pre-inclined period. However, when these variables were compared during the inclined period, LFnu was higher in the CON group than in the CKD group (84.5 ± 8.1 *versus* 73.5 ± 13.0, respectively, $p < 0.05$), HFnu was lower in the CON group than in the CKD group (15.4 ± 8.1 *versus* 26.5 ± 13.0 respectively, $p < 0.05$), and LFnu/HFnu was higher in the CON group than in CKD (7.9 ± 5.6 *versus* 3.3 ± 1.3, respectively, $p < 0.05$) (Table 2 and Figure 1).

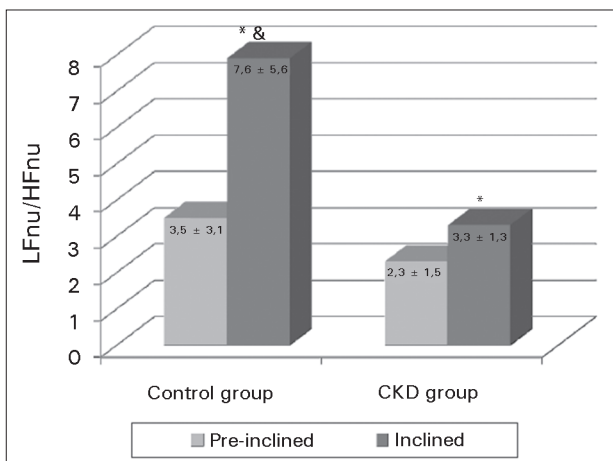
The comparisons between individuals with different stages of CKD (3, 4 and 5) with individuals from the CON group did not show significant differences in the pre-inclined LFnu, HFnu and LFnu/HFnu variables. However, during the inclined

TABLE 2 SPECTRAL ANALYSIS OF HRV OF THE CKD AND CON GROUPS

Variable	LFnu	HFnu	LFnu/HFnu ratio
Pre-inclined			
CON (n = 14)	70.6 ± 13.7	29.6 ± 13.6	3.5 ± 3.1
CKD (n = 32)	63.2 ± 17.6	36.8 ± 17.6	2.3 ± 1.5
CKD stage 3 (n = 11)	67.5 ± 10.1	32.5 ± 10.1	2.4 ± 1.3
CKD stage 4 (n = 11)	61.4 ± 15.6	38.6 ± 15.6	1.9 ± 1.1
CKD stage 5 (n = 10)	57.9 ± 15.0	39.1 ± 14.6	1.9 ± 1.1
Inclined			
CON (n = 14)	84.5 ± 8.1* ^ε	15.4 ± 8.1* ^ε	7.9 ± 5.6* ^ε
CKD (n = 32)	73.5 ± 13.0	26.5 ± 13.0	3.3 ± 1.3
CKD stage 3 (n = 11)	78.5 ± 5.2	21.5 ± 5.2	3.9 ± 1.2
CKD stage 4 (n = 11)	73.7 ± 11.6	26.5 ± 11.6	3.3 ± 1.3
CKD stage 5 (n = 10)	66.9 ± 12.9 ^{&}	33.1 ± 13.0 ^{&}	2.4 ± 1.2 ^{&}

CKD: Chronic kidney disease; CON: Control group; HF: High frequency; LF: Low frequency; NU: Normalized unit; HRV: Heart rate variability. ^ε $p < 0.05$ vs. CKD. * $p < 0.05$ vs. CKD Stage 3 (GFR = 40.3 ± 7.4 ml/min/1.73 m²), Stage 4 (GFR = 23.5 ± 4.4 ml/min/1.73 m²), and Stage 5 (GFR = 12.7 ± 2.0 ml/min/1.73 m²); [&] $p < 0.05$ vs. Stage 3.

Figure 1. LFnu/HFnu ratio in the control and chronic Kidney disease (CKD) groups LF: Low frequency, HF: High frequency, nu: Normalized unit; * $p < 0.05$ vs. pre-inclined, & $p < 0.05$ vs. CKD group.



period, LFnu was significantly lower, HFnu was higher, and the HFnu/LFnu ratio was lower in CKD patients than in the CON group indicating reduced sympathovagal balance in patients with CKD.

An interesting finding in our study was the inverse correlation between LFnu/HFnu ratio and the stage of the CKD ($r = -0.436$, $p < 0.05$), during the inclined period. This finding, together with the lower LFnu/HFnu ratio

in stage 5 compared to stage 3 patients, suggests that cardiac autonomic modulation is depressed in CKD deteriorates as the disease progresses.

DISCUSSION

In the present study, power spectral analysis of HRV was used to evaluate the autonomic nervous system in patients with varying levels of kidney dysfunction. We showed that sympathovagal imbalance in CKD patients without clinical manifestations of disautonomy were only elicited upon postural stress.

Impaired cardiac baroreflex sensitivity has been widely reported in CKD patients on renal replacement therapy.¹⁶ However, only a few studies have addressed autonomic nervous system function in patients under conservative treatment.^{17,18} Traditional approaches to study ANS activity utilize pharmacological blockades and/or invasive physiological tests, which are difficult to perform in daily practice.¹⁹ The advent of power spectral analysis of the HR in recent years has permitted the non-invasive estimation of ANS activity.²⁰⁻²² This technique provides information about autonomic modulation of the heart by quantifying waves of low and high frequencies in electrocardiogram R-R intervals, which are representative of sympathetic and parasympathetic activity, respectively. In addition, the LF/HF ratio is a measure of the sympathovagal balance.²⁰ The power spectral analysis of the HRV has been used for the evaluation of the ANS in patients with a variety of diseases, including neurocardiogenic syncope, atrial fibrillation and diabetes.²³⁻²⁵ However, to the best of our knowledge, there are no reports on HRV in CKD patients not yet on dialysis using spectral analysis coupled with postural stress. Using this simple approach, we showed that patients with CKD stages 3 to 5 under conservative treatment and without clinical evidence of autonomic dysfunction have an ANS imbalance characterized by a lower LF/HF ratio than in patients in the control group. This ANS imbalance was only detected following postural stress, suggesting the presence of subtle ANS dysfunction in CKD patient not yet on dialysis.

ANS dysfunction has been documented in a few studies in patients under conservative treatment, mainly in advanced stages of CKD.^{17,18,26} For example, Hathway *et al.*¹⁸ identified severely compromised autonomic function in 278 patients awaiting renal transplant, including 43 patients who were not dependent on dialysis. In a prospective study

Banavandan *et al.*¹⁷ found that impaired baroreflex sensitivity was associated with decreased GFR and a trend towards poor prognosis after a mean follow up period of 42 months. Our results add to these studies by showing that depressed autonomic cardiac modulation in CKD patients can be better diagnosed upon orthostatic stress.

Low HRV has been associated with CKD-related hospitalizations²⁷ and is also considered to be an independent prognostic factor for sudden cardiac death.²⁸ An interesting finding in our study was the correlation between the extent of ANS imbalance and stage of CKD. Although being cross-sectional in nature, our study showed that patients with stage 5 CKD had a lower LFnu/HFnu ratio than those with stage 3, suggesting that ANS response to stress worsens as the disease progresses. This data is in accordance with the study of Banavandan *et al.*¹⁷ in patients with a median GFR of 23 ml/min/1.73 m², which identified a positive correlation between ANS dysfunction and low GFR.

We did not aim to further explore the pathophysiology of ANS dysfunction in patients with CKD, although a number of factors have been implicated in this disturbance.^{16,29} For instance, ANS dysfunction may be the result of vascular calcification secondary to changes in the levels of circulating calcium, phosphorus and PTH that occur early in CKD.³⁰ Elevated PTH increases intracellular calcium in cardiomyocytes and smooth muscle cells, thereby contributing to myocardial fibrosis and vascular calcification.^{31,32} These changes interfere with ANS function, as suggested by the decrease of HRV in patients with secondary hyperparathyroidism.³³ However, the lack of correlation between high plasma PTH levels and decreased LFnu/HFnu ratio in our patients (data not shown) does not support this concept. Another condition associated with reduced HRV and autonomic cardiac function is anemia, based on a study by Furuland *et al.*²⁶ in which erythropoietin treatment led to an improvement in HRV. This mechanism, however, was not applicable to our study since our patients were not anemic. Left ventricular hypertrophy has also been associated with ANS dysfunction in patients with CKD.³⁴ In hypertensive patients with left ventricular hypertrophy, the baroreflex effectiveness index predicts all-cause mortality and sudden cardiac death.³⁵ In our study, 64% of the CKD patients had LVH, which could have contributed to the low HRV. Finally, ANS dysfunction has been

associated with hypertension, which is very common in CKD patients even prior to diagnosis. Hypertensive patients with CKD have lower sensitivity of the baroreflex arc secondary to changes in the modulation of the heart rate or even due to reduced distensibility and vascular calcification of the blood vessels.³⁶ As a consequence, the adaptation of baroreflex sensitivity to changes in blood pressure is compromised, predisposing these patients to intradialytic hypotension and to cardiac arrhythmias.³⁷ Low baroreflex sensitivity has been showed in hypertensive patients with CKD by Johanson *et al.* in a large study group that included patients on conservative treatment as well as those on renal replacement therapy.³⁸ Although we did not observe changes in baroreflex sensitivity at baseline in CKD group, after a postural stress we observed a low LFnu/HFnu ratio, indicating impaired baroreflex. Thus, we could speculate that hypertension might have contributed to this change.

This study was limited by the low number of subjects included, which was due to the difficult to recruit large numbers of patients without pre-existing conditions known to interfere in ANS function.

In conclusion, using a simple, low cost and non-invasive autonomic test, we have demonstrated depressed cardiac autonomic modulation in subjects with CKD under conservative treatment. This finding suggests subtle changes in autonomic function and needs to be confirmed in larger samples.

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CONFLICTING INTERESTS

The authors declare that they have no conflict of interests.

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