Original Article

Evaluation of Cardiac Autonomic Control in Patients with Diabetic Nephropathy: Findings from a Cross-sectional Study

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Abstract

Introduction: Diabetic nephropathy (DN) is one of the most dreaded complications of diabetes mellitus (DM). Patients with DN have a high risk of early mortality and is associated with increased mortality when associated with cardiac autonomic neuropathy (CAN). The aim of this study was to assess cardiac autonomic control in patients with DN.

Methods: A cross-sectional study were conducted in 50 (17 females) outpatients with DN. Cardiac autonomic control was assessed by a monitoring of cardiac activity at supine and standing positions by a Holter EKG. RR interval data were exported in Kubios HRV Standard Software and 5 minute segments were read. HRV were classify according Sammito et al. and cardiac autonomic neuropathy were diagnosed by criteria of Bellavere et al.

Results: Parasympathetic nervous system parameters were in 22, 20 and 21 patients at supine position. Sympathovagal balance was also low in thirty-one patients. At the transition to orthostatic position only parasympathetic parameters such as pNN50 and HF.nu. were reduced significantly. CAN was diagnosed in thirty patients and majority of them were at the severe form ($p < 0.0001$) and arterial baroreflex was altered in seventeen patients.

Conclusion: Cardiac autonomic control was altered in majority of patient with diabetic nephropathy.

Key-words: Diabetic nephropathy – Heart rate variability – Cardiac autonomic neuropathy

Background

Diabetic nephropathy (DN) is one of the most dreaded complications of diabetes mellitus (DM) (1). Overall, its prevalence is growing rapidly, due to the high prevalence of obesity and sedentary lifestyles. In the United States of America (USA),

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DM is the leading cause of end-stage renal disease (54% of new cases). In Africa, meta-analysis studies concluded to an overall prevalence of 35.3% (2) with regional variations. Thusly, in Senegal, Diouf et al. reported a hospital prevalence of 48.72% (3).

Patients with DN have a high risk of early mortality and is associated with increased mortality when associated with cardiac autonomic neuropathy (CAN). In fact, patients with CAN more frequently experience proteinuria as a predictor of all-cause mortality in patients with DN than patients without CAN (4). In addition , a correlation between the progression of renal injury and autonomic dysfunction has been confirmed in literature (5). Hence, there is interest for patients with DM to diagnose CAN to regress the progression of diabetic nephropathy.

CAN is monitoring through the autonomic control of cardiac activity leading to the heart rate variability (HRV). The diagnosis is made using multiple autonomic function tests to assess both sympathetic and parasympathetic function. (6,7). The most frequently used Cardiac autonomic reflexes tests (CARTs) are based on heart rate variability (HRV) and Blood pressure (BP) with various maneuvers. Sympathetic function is assessed by BP variability to postural changes, the Valsalva maneuver while parasympathetic function is assessed by HR response to deep breathing, changes in posture (lying to standing) and the Valsalva maneuver (8).

These tests lead to diagnostic assessment of CAN although they don't provide a classification of its severity. It can be obtained by a Holter EKG recording that provides information based on changes in HR variability. The latter is based on a spectral analysis of the short-term variability of the R-R intervals. It can be used to study cardio-circulatory reflexes and interactions between parasympathetic (PNS) and sympathetic (SNS) nervous systems in heart rate control (9, 10).

These tests can be easier and more informative when the HRV is tested using time or frequency domain measurements with digital modalities and statistical analysis. The classification of subclinical CAN is based on changes in HRV and baroreflex sensitivity. The standard CARTs may be used to obtain an autonomic neuropathy score to assess the severity of CAN , then its classification (11, 12).

While there is no use to assess CAN in patients with DM in clinical practice in Senegal, we conduct this study to evaluate the autonomic control of heart in patients with diabetic nephropathy.

Methods

II.1. Study design

This was a cross-sectional study conducted in patients with DN living in Senegal, West Africa Country. They had a single study visit which they provide all relevant personal, clinical and biological information. Symptoms and sign-based clinical scores were determined, and CAN tests were performed.

II.2. Patients

The study sample comprised 50 participants with a good balance between sexes (17 females and 33 males), diabetic nephropathy patients were enrolled from Department of Nephrology of Dalal Jamm Hospital (Dakar, Senegal). Study was take between 01 July to 30 September 2021. All study participants provided written informed consent and information was anonymized before statistical analysis in accordance to Helsinki recommendations. Inclusion criteria were an established diagnosis of DM aged over, to be a regular patient with diabetic nephropathy at the Department of Nephrology of Dalal Jamm Hospital. Exclusion criteria were beta blocker intake, non-sinus heart rhythm on EKG or limb amputation making standing difficult or prior diagnosis of neuropathy from other etiology (toxic or auto immune).

The presence of nephropathy was determined by the estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2 (CKD-EPI).

Cardiovascular Function

Room experiment was quiet and its temperature constant. All measurements took place during the morning. Blood pressure were measured in both arms and twice in supine and orthostatic position. Classification of resting blood pressure was done according to the European Society of Cardiology guidelines (13). Tree leads electrocardiogram (ECG) were realized at rest 10 minutes at supine and 7 minutes on standing positions by an Holter EKG *AR4Plus Schiller®*.

Cardiac autonomic control

Cardiac autonomic nervous control was performed from the 5 min beat-to-beat time series constituted from inter-beat intervals from EKG R waves, i.e., the R-R interval. The HRV was assessed according to the consensual standards (11). *Kubios HRV Standard* software were used to analyze HRV.

Time-Domain Analysis of HRV

HRV parameters such as the mean RR, heart rate (HR), the standard deviation of the RR (SDNN) and of HR (SD HR), the square root of the mean squared differences between adjacent normal RRI (RMSSD), the count of successive normal beat lengths that differed more than 50 ms (NN50), the percentage of successive normal beat lengths that differed more than 50 ms (pNN50), the RR triangular index, and the triangular interpolation of the discrete distribution of the normal RR (TINN) were collected.

Frequency-Domain Analysis of HRV

Spectral analyses by fast Fourier transform Welch's periodogram technique were used. These parameters included the power frequency (pw expressed in ms^2) in 3 frequency bands of interest: high frequencies (HF, 0.15–0.4 Hz) and low frequencies (LF, 0.04–0.15 Hz). The total power (TP) and LH/HF ratio were also computed. The HF and LF powers were also expressed in normalized units (HFnu and LFnu, respectively).

Informational Domain Analysis of HRV

Most informational domain parameters are known to detect and highlight non-linear properties of the studied time series. The plot of the RR by the Poincaré plot method and the calculation of SD1, SD2 and SD1/SD2 defined as the standard deviation of the instantaneous beat-to-beat RR variability, the standard deviation of the continuous long-term RR variability and the axis ratio, respectively (14). Detrended fluctuation analysis $\alpha1$ and $\alpha2$ coefficients; Approximate Entropy (ApEn) and Sample Entropy (SampEn) were also collected.

Cardiac autonomic neuropathy

HRV parameters were compared with references values proposed by Sammito et al. (15). Patients aged over 60 years were classified according to the reference values for patients aged between 50 and 60 years proposed by Sammito et al.

Cardiac autonomic neuropathy (CAN) was retained using the values found by Bellavere et al. (12) by a total power (TP) measured in supine position at rest lower than the average – 2SD (TP < 1430 ms^2) of its diabetic population without CAN.

i. Cardiac autonomic neuropathy is rated moderate if HFpw and LFpw are below the mean – 2SD of their values in the moderate CAN population (LFpw < 54 ms^2 and HFpw < 32 ms^2).

ii. It was severe if HFpw and LFpw are lower than the mean – 2SD of the values in their population of diabetics with a severe form of CAN (LFpw < 4 ms^2 and HFpw < 10 ms^2).

iii. Patients who had low TP with LFpw and HFpw values are greater than the mean – 2SD of the HFpw and LFpw values found in the moderate form of CAN by Ballevere et al. considered to have a borderline form.

Arterial baroreflex function was explored by assessing HRV in the orthostatic position and comparing it to that in the supine position. An increase in the LFpw/HFpw ratio in orthostatism was considered normal.

Statistical analysis

Statistics were performed using R statistical software version 4.3.1. Normality of variables distribution was checked by the Shapiro test. Data following the normal distribution were expressed as mean ± SD. While those not following the normal distribution were expressed in average (1st Quartile – 3rd Quartile).Variation of parameters between supine and orthostatic positions was studied by a paired t test. ANOVA was used to compare parameters between different groups of patients and if significant, a Tuckey post hoc test was being carried out. For parameters not following the normal distribution, the Wilcoxon test was used to compare parameters between groups of patients. The correlation between variables was sought using Pearson test. All tests were two tailed, and evaluated at a 0.05 significance level.

Results

The median age of our patients was 51 years and male predominated (sex ratio: 1.97) ($p < 0.0001$). Thirteen patients were overweight, including two obese. Majority of patients was with arterial hypertension (N = 31; $p < 0.001$), including 22 grade I and eight grade II. Patients with type 2 diabetes mellitus predominated with 92% of cases. Thirty patients were normoglycemic while the rest were hyperglycemic. eGFR was low (less than 60ml/min/1.73m^2 according to CKD-EPI) in 46 patients ($p < 0.0001$) and 44% ($p = 0.11$) of patients were at end stage chronic kidney disease (table 1).

Table 1: Characteristics of the study population

Parameters	Population N = 50[1]
Age (years)	51 (41, 61)
Gender	
F	17 (34%)
M	33 (66%)
Weight (kg)	70 (60, 81)
Height (cm)	175 (167, 177)
BMI (kg/m²)	23.1 (19.0, 25.1)
SABP (mmHg)	144 (131, 156)
DABP (mmHg)	90 (81, 100)
Uremia (mmol/L)	1.30 (0.67, 1.86)
Creatinine (mg/dl)	65 (26, 88)
CKD-EPI-eGFR (ml/min/1.73m2)	10 (7, 30)
Glycaemia (g/L)	1.22 (1.02, 1.43)
Calcemia (mmol/L)	83 (76, 90)
Phosphatemia (mmol/L)	47 (41, 56)
Proteinuria (g/24h)	1.00 (0.51, 2.74)
Diabetes type	
1	4 (8.0%)
2	46 (92%)
Diabetes duration (year)	8.5 (6.0, 12.8)
Stage of CKD	
2	4 (8.0%)
3	8 (16%)
4	16 (32%)
5	22 (44%)
[1]Median (IQR); n (%)	

HRV parameters

Time-Domain parameters

In supine position of rest, bradycardia was found in one patient while tachycardia was found in four patients. SDNN was low in 29 patients and high in 6 patients. While the RMSSD and pNN50 which explores the parasympathetic nervous system were lower of reference values respectively in 22 et 20 patients and high in 6 patients. During the transition from lying to standing position, PNS index and pNN50 tended strongly to decrease in patients while RR duration reduced significantly. However, the others time domain parameters had not significantly changed (table 2).

Table 2: Time-Domain HRV parameters in lying- to- standing position

Parameters	Lying N = 50[1]	Standing N = 50[1]	p
PNS Index	-1.17 (-1.73, -0.09)	-1.40 (-2.01, -0.39)	0.06
SNS Index	2.1 (0.3, 4.4)	1.93 (0.64, 4.38)	0.89
Stress Index	15 (10, 27)	14 (10, 26)	0.48
RR (ms)	765 (657, 844)	699 (648, 830)	$2.009.10^{-5}$
SDNN (ms)	20 (11, 34)	24 (10, 41)	0.76
HR (bpm)	78 (71, 91)	86 (72, 93)	0.99
SD HR (bpm)	2.24 (1.28, 3.27)	2.6 (1.5, 4.9)	0.92
RMSSD (ms)	23 (10, 41)	23 (9, 39)	0.51
pNN50 (%)	2 (0, 11)	2 (0, 8)	0.06
RR Triangular index	4.5 (2.4, 8.7)	4.3 (2.6, 8.7)	0.3
TINN (ms)	144 (63, 246)	158 (57, 252)	0.74
[1]Median (IQR)			

Frequency-Domain parameters

In lying position, sympathetic activity (LFpw) and parasympathetic activity (HFpw) were lower than standard values respectively in 36 and 21 patients. While LFnu and HFnu were lower than standard values respectively 33 and 3 patients. The same parameters were higher than standard values respectively in 3 and 33 patients. The sympathovagal balance given by the LF/HF ratio was significantly lower than normal values in 31 patients ($p < 0.0001$). During the transition to orthostatic position, autonomic nervous system response characterized by an increase of LFpw and a decrease of HFpw were not observed. On the other hand, HFnu decreased significantly in orthostatic position compared to lying position (table 3).

Table 3: Frequency domain HRV parameters in lying- to -standing

Parameters	Lying N = 50[1]	Standing N = 50[1]	p
LFpw (ms²)	108 (15, 384)	140 (21, 779)	0.95
HFpw (ms²)	117 (28, 385)	108 (17, 347)	0.68
LFnu	43 (27, 60)	57 (32, 78)	0.99
HFnu	57 (39, 73)	43 (22, 68)	0.002
LF/HF	0.75 (0.38, 1.53)	1.31 (0.48, 3.54)	0.96
Total power (ms²)	238 (55, 808)	326 (47, 1,609)	0.82
[1]Median (IQR)			

Non-Linear HRV parameters

In the lying position, SD1 which explores short-term variability or parasympathetic activity was lower than reference values in 22 patients. While 22 patients had normal values and the rest had higher values. Long-term heart rate variability or sympathetic modulation given by SD2 was considered low in 49 patients ($p < 0.0001$). While patients moved to standing, alone ApEn who explore the short term variability and SampEn who explore the global variability were significantly decreased. SD1/SD2 ratio who explore arterial baroreflex and α2 who explore respiratory modulation of the heart rate tend strongly to increase in lying position (table 4).

Table 4: Non-linear HRV parameters during lying and standing positions

Parameters	Lying N = 50[1]	Standing N = 50[1]	p
SD1 (ms)	16 (7, 29)	16 (6, 28)	0.96
SD2 (ms)	23 (11, 39)	27 (12, 51)	0.34
SD2/SD1	1.66 (1.00, 1.93)	1.67 (1.29, 2.43)	0.05
ApEn	1.17 (1.06, 1.22)	1.11 (0.97, 1.18)	0.02
SampEn	1.58 (1.38, 1.82)	1.43 (1.06, 1.71)	0.004
α1	0.82 (0.61, 1.10)	0.98 (0.62, 1.21)	0.08
α2	0.44 (0.33, 0.57)	0.54 (0.39, 0.65)	0.05
[1]Median (IQR)			

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy (CAN) was found in 30 patients (Twenty-three with severe form). Sixteen within severe form of CAN had resting HTN and were mainly made up of patients with grade 1 (N = 11; $p < 0.0001$) whereas Seventeen of patients with severe forms of CAN were in stage V of chronic kidney disease ($p < 0.0001$). Two patients had borderline cardiac autonomic control (a decrease total power associated with LFpw and HFpw values within normal limits). However, 18 patients had autonomic control within normal limits. Parasympathetic tone was low only in patients with autonomic dysfunction (p = 0.0001) and was found in 15 patients with severe form.

The arterial baroreflex was altered in 17 patients characterized by an absence of increasing in LFpw in orthostatic position. Comparison of standard deviation of the instantaneous beat-to-beat RR variability (SD1) among patient's groups of cardiac autonomic control were expressed in figure 1.

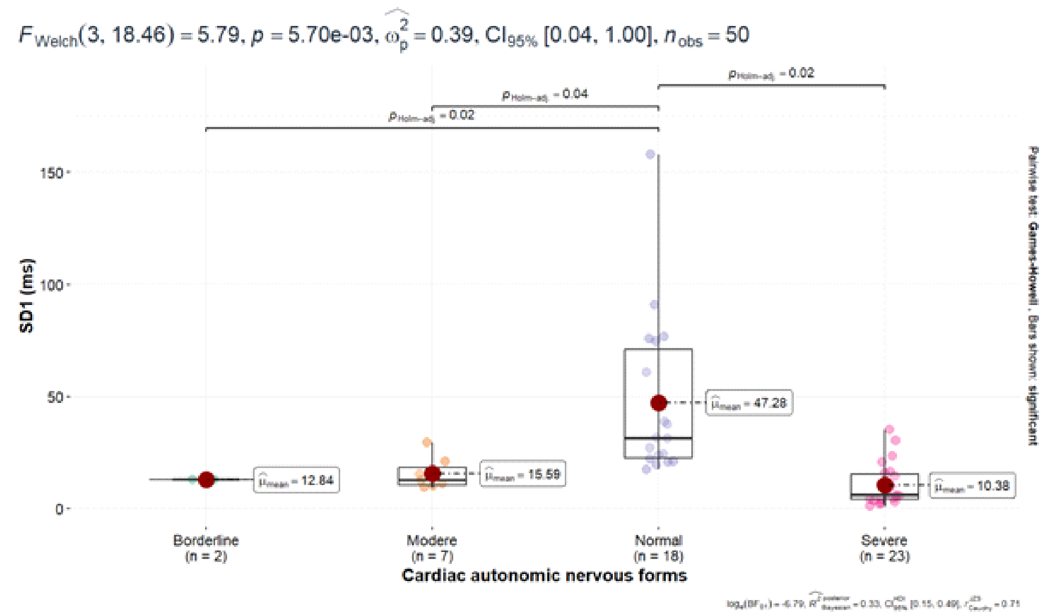

Figure 1: Comparison of SD1 among cardiac autonomic nervous control

The analyze of this figure showed that SD1 was statistically and significantly higher in patients with normal autonomic cardiac control compared to patients with other form of cardiac autonomic control. While comparing the standard deviation of the continuous long-term RRI variability (SD1), we noted results who are represented in the figure below.

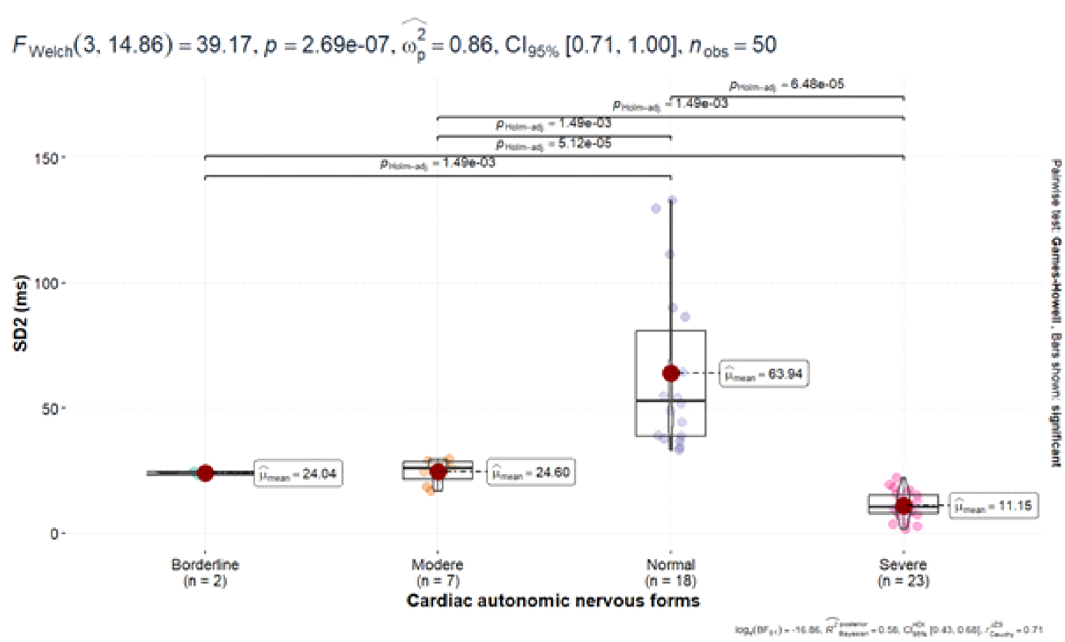

Figure 2: Comparison of SD2 of patients classify among cardiac autonomic nervous forms

Analysis of this figure also showed that SD2 was significantly lower in patients with abnormal cardiac autonomic control compared to those with normal control. On the other hand, the other HRV parameters of the nonlinear domain such as SD1/SD2, ApEn, SampEn, α1 and α2 were not significantly different between groups of patients. Some of them were significantly correlated with some clinical parameters such as SABP, creatinine and GFR (figure 3).

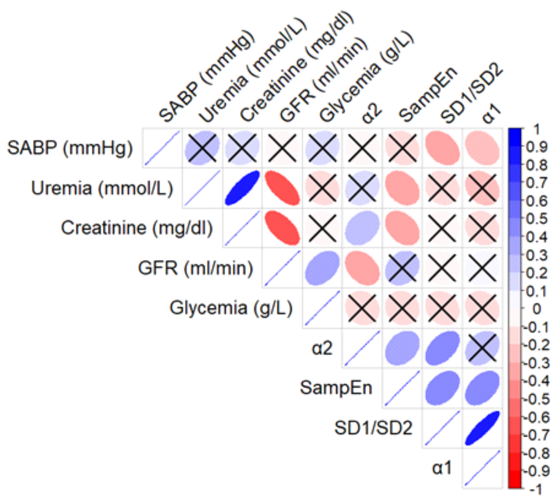

Figure 3: Link between non-linear HRV with clinical parameters

SABP was negatively correlate with arterial baroreflex given by SD1/SD2 ratio (r = -0.35; p = 0.01) and α1 (r = -0.29; p = 0.03). While global variability given by SampEn was negatively correlate with uremia (r = -0.30; p = 0.02) and creatinine (r = -0.36; p = 0.01). However, creatinine was positively correlate with respiratory modulation given by α2 (r = 0.29; p = 0.03).

Discussion

Measuring heart rate variability is a tool for assessing cardiac autonomic neuropathy. Thus, we aimed to evaluate the cardiac autonomic control of the heart in patients with diabetic nephropathy. Our results showed a decrease in parasympathetic tone in approximately 22 patients. While switching to orthostatic position, patients did not show significant variability comparatively to the supine position. However, the sympathetic tone has not significantly increased in our patients. Global variability explored by SampEn has decreased in orthostatic position. The arterial baroreflex function was impaired in 17 patients. Thirty patients had cardiac autonomic neuropathy and decreased parasympathetic tone was found in 20 of them. SD1 and SD2 were significantly lower in patients with severe cardiac autonomic neuropathy and α1 was negatively correlated with systolic blood pressure.

Decreased parasympathetic activity was noted in approximately 22 affected patients. These results are in line with other studies. Indeed, Pfeifer et al. (16), during a comparative study of parasympathetic activity between normal subjects and diabetic patients, found similar results. They 've shown that during the administration of propranolol which is a β adrenergic antagonist a decrease in the variation of the RR interval in diabetic patients. The latter was secondary to altered vagal tone in diabetic patients and not to increased sympathetic activity. Singh et al. (17) found that SDNN, LF, HF and the LF/HF ratio were lower in diabetic patients. Thus, chronic hyperglycemia leading to noxious glycation of the plasma and vessel wall proteins and increased generation of reactive oxygen species (ROS) as well as derangement of various metabolic pathways, aggreviating serum lipid profile, markers of inflammation and hemostasis. All these changes contribute to development of degenerative nerve lesions (18) which can affect the vagus nerve, reducing its influence on the heart. These latter modifications also accelerated development of atherosclerotic vascular changes (19, 20). In this respect, DM leads to the dysfunction of macro- and micro-vessels, with this being related to metabolic, endothelial and autonomic nervous system dysfunction, which are in turn linked to altered vascular reactivity (21-24).

The response to orthostatic position was not satisfactory. Indeed, LF did not significantly increase between the two states and also 17 patients had an altered arterial baroreflex, all associated with a decrease of global variability by a decrease in SampEn. Our results were in line with those of Pfeifer et al. (16) who found that diabetics showed less variation in the duration of the RR interval. Now it is the parameter which is the basis on which the HRV software is based. Thus, a lesser variation in the variability of the heart rate in orthostatic position can be linked to the other branch of the autonomic nervous system, in this case the sympathetic system. These results would explain the alteration of the arterial baroreflex found in certain patients by the absence of increase in sympathetic activity in orthostatic position.

More than the majority of patients presented cardiac autonomic neuropathy, mainly consisting of the severe form. Majority of these patients were more frequently had low resting parasympathetic tone, high blood pressure and chronic kidney disease. SD1 and SD2 were also lower in patients with severe CAN. Then, SD1/SD2 ratio and α1 were negatively correlated with systolic arterial blood pressure. Huikuri et al. (25) found that the decrease in α1 was the most powerful RR variability measure predictive of all-cause mortality in survivors of myocardial infarction EF < 35%. Given that abnormalities of cardiac autonomic control are strongly linked to the occurrence of cardiac events (26-28) and mortality (26, 29). A good management of diabetes and arterial hypertension could slow the onset of cardiac autonomic neuropathy and reduce the occurrence of these events.

Our study also enabled the use of HRV measurement for the diagnosis of cardiac autonomic neuropathy. Although clinical methods exist, the use of continuous measurement of cardiac activity during maneuvers exploring the parasympathetic system, as is the case in our study with monitoring of the supine position or in deep breathing (30). Other maneuvers such as standing or exploring HRV using cold water allow sympathetic tone to be explored (31). But the exploration of cardiac autonomic control with continuous recording of RR duration offers an evaluation with many parameters in the different informational domains of HRV. It thus allows for earlier diagnosis of NAC in developing countries.

Our study has some limitations related to the fact that it was carried out in a single center compared to multicenter studies which could involve a larger number of patients with diabetic nephropathy. This would allow for more robust results with stronger links between clinical parameters and HRV. The cross-sectional aspect of our work also does not allow us to follow the evolution of cardiac autonomic nervous control according to the stages of chronic kidney disease.

Conclusion

Diabetic nephropathy is a major complication of diabetes. Its association with autonomic dysfunction such as cardiac autonomic neuropathy could worsen the prognosis of patients with this disease. Therefore, it would be necessary for these patients to provide adequate and multidisciplinary care in order to slow down the occurrence of cardiovascular events. But also, good monitoring of diabetes is necessary in order to prevent the occurrence of nephropathy but also neuropathy by balancing blood glucose. Which could reduce the impairment of renal function and cardiac autonomic control. Finally, to be more effective, it is necessary to prevent the onset of diabetes through programs aimed at encouraging people to do more physical activity and adopt a healthy and balanced diet.

Conflict of Interest Disclosure: The authors declare no conflicts of interest related to this study.

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