
ORIGINAL ARTICLE**Assessment of heart rate variability in non-dialysis-dependent nondiabetic chronic kidney disease patients***Ashwini Patil¹, Neelam Prasad^{1*}, Krishnakant Patil²*

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Abstract

Background: Cardiovascular autonomic dysfunction is common in Chronic Kidney Disease (CKD) and linked to adverse outcomes. Heart rate variability serves as a practical, non-invasive tool to assess autonomic function, yet data in non-dialysis-dependent, nondiabetic CKD patients remain limited. **Aim and Objectives:** To assess heart rate variability in non-dialysis dependent, non-diabetic CKD patients. **Material and Methods:** In this study, short-term (5-min) heart rate variability was analysed using RMS-Polyrite D machine at sampling rate of 256 Hz, for frequency domain (LF, HF, LF/HF ratio, TP) and time domain (SDNN, rMSSD) parameters in 187 CKD patients (stages 2-5) and 200 age-and sex-matched healthy controls. These two groups were compared with unpaired t-tests ($p \leq 0.001$). Interstage comparisons used one-way ANOVA ($p \leq 0.05$) with Bonferroni correction ($\alpha = 0.0083$). **Results:** Frequency-domain HRV measures (LF, HF, TP) and time-domain indices (SDNN, rMSSD) were markedly lower in cases, while LF/HF ratio showed no significant difference when compared to controls. Stage-wise analysis revealed progressive decline in LF, HF, TP, and SDNN from stage 2 to stage 5. rMSSD showed reduction but without significant inter-stage differences. **Conclusion:** Autonomic dysfunction being present in CKD, the declining HRV indicates increasing cardiovascular autonomic dysfunction with the progression of stage in non-dialysis dependent, non-diabetic CKD patients.

Keywords: autonomic dysfunction, short-term HRV, renal disease, sympathovagal balance

Introduction

Chronic Kidney Disease (CKD) is a major global health concern, affecting one in every ten adults worldwide [1]. CKD is characterised by abnormalities of kidney structure or function lasting beyond three months, associated with health consequences. CKD is ordered into 5 stages according to cause, GFR [glomerular filtration rate] category (G1 to G5), and albuminuria category (A1 to A3); as per the Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update [2].

CKD patients exhibit over a fivefold increase in cardiovascular risk compared with the general

population, independent of age, sex, race, and diabetes; thus, Cardiovascular Disease (CVD) is the ruling contributor to death in CKD. CKD patients face increased susceptibility to CVD than End-Stage Renal Disease (ESRD). CVD commences early on over the course of CKD. Inventing novel clinical tools for characterising high-risk individuals carrying grim prognosis (particularly those at elevated risk of cardiac death), while averting the advancement of CVD is important [1].

Amidst the manifold aspects responsible for or emanating from CKD, cardiovascular autonomic dysfunction is a grave and meagrely comprehended

long-standing clinical issue in the CKD masses. Autonomic dysfunction largely pertains to modified tonic and reflex regulation of autonomic effluence, boosting sympathetic neural function while lowering parasympathetic activity [3]. Histologic inquest illustrate that renal sympathetic nerve endings are in proximity to vessels, tubules and juxtaglomerular cells. In animal prototypes, changes in these nerves' activity modify renal hemodynamics, tubular function, and renin release. Sympathetic denervation in animals causes natriuresis and diuresis and slows the furtherance towards renal failure [4,5].

Impaired vagal control, as evaluated by decreased Heart Rate Variability (HRV) alongside spontaneous Baroreflex Sensitivity (BRS), prevails in hypertensives with chronic renal failure raising the predisposition to sudden cardiac death. Sympathetic nervous system is overactive in CKD, as evinced by heightened plasma catecholamine concentrations and muscle sympathetic nerve activity. Sympathetic hyperexcitation is inclined to develop, maintain, and advance renal disease and explains the robust link between CKD and heightened cardiovascular morbidity and mortality. Blood Pressure (BP) regulation is usually poor in CKD, irrespective of the disease stage being initial or advanced, or of the patient undergoing dialysis; indicating obscure understanding of the underpinning etiology [3]. Several covariates affect HRV in CKD/ESRD, but diabetes is most impactful. Regardless of stage, diabetic CKD patients show lower HRV values [6].

Considering the perplexity of the autonomic system, multiple tests related to diverse reflexes are ordered. Conventionally, batteries of autonomic tests have been known, most prevalent being the Ewing battery [7], comprising of response to deep

breathing, orthostatic testing, Valsalva manoeuvre and isometric exercise. Newer diagnostic approaches such as HRV analysis and microneurography have recently been inducted as diagnostic tools. HRV analysis is built upon the observance that even at rest the RR intervals' duration continuously vacillates around the mean value [8]. HRV carries the scope to be extensively used in CKD patients [9]. It's a practical tool owing to its non-invasiveness and convenient application even with short-term (5 minutes) recordings of electrocardiogram for analysing beat-to-beat R-R interval variability [10]. So far as we can ascertain, there are scarce studies on HRV in non-dialysis-dependent nondiabetic CKD patients giving rise to substantial knowledge gap. Research on autonomic dysfunction in CKD has largely been with crucial shortcomings such as a small sample, inclusion of CKD owing to various causes and of dialysis patients, etc. For strengthening treatment approaches, autonomic dysfunction in CKD should be first lucidly established by a potent and convenient method [9]. Validating the sensitivity and specificity of cardiovascular autonomic function test indices is vital for gauging the autonomic dysfunction severity in CKD. Early prediction and diagnosis of autonomic dysfunction will steer in timely intervention and resultant obviation of cardiovascular incidents in this community at high risk. Besides, in the Indian scenario, even fewer investigations exist assessing cardiovascular autonomic status in CKD patients (irrespective of their dialysis or diabetic condition).

Hence, we hypothesized primarily that cardiovascular autonomic dysfunction is present in non-dialysis dependent, non-diabetic CKD patients; and secondarily that cardiovascular autonomic dysfunction increases with the progression of stage in non-dialysis dependent, non-diabetic CKD patients.

Guided by these hypotheses, the study aimed to assess HRV in this population by evaluating and comparing HRV between CKD patients and healthy individuals, and by examining HRV across different CKD stages.

Material and Methods

This case control study was done in non-dialysis dependent, non-diabetic CKD patients, and age and sex matched healthy controls, randomly drawn using a simple random sampling technique from the outpatient and inpatient departments of a private medical college, hospital and research center, Pune. The study received ethical clearance, with informed consent obtained from all participants. With power of study as 80%, and level of significance of 5%, the total calculated sample size was 332. Considering a 20% loss to noncompliance, the ultimate sample size computed was 400 with 200 cases (50 cases of each CKD 2, 3, 4 and 5 stage); and 200 controls.

Inclusion criteria

Stage 2, 3, 4 and 5 CKD patients of both genders, aged 22-60 years were included along with healthy, gender and Body Mass Index (BMI) matched controls.

Exclusion criteria: Patients with history of diabetes mellitus, patients on dialysis, metabolic syndrome, cardiac rhythm abnormalities, congestive heart failure, myocardial infarction, uncontrolled hypertension or other severe cardiovascular disorders, any other non-cardiovascular disorders known to affect autonomic function, female subjects in their menstrual phase of the monthly cycle, or existing pregnancy, or on oral contraceptives, extreme obese and extreme underweight subjects, any other systemic, infectious disease, any psychiatric illness, any addiction to alcohol, tobacco, etc. were excluded. The actual sample consisted of 200 controls (male

[m]:female[f] = 123:77) and 187 CKD cases (m:f = 111:76) instead of 200 owing to incomplete records and non-compliance with test procedures; with 47 cases (m:f = 28:19) of Stage 2, 48 cases (m:f = 29:19) of Stage 3, 46 cases (m:f = 26:20) of Stage 4 and 46 cases (m:f = 28:18) of Stage 5. The cases and controls were matched for age, gender and BMI. Additionally, cases were age and gender matched across stages. Subjects received detailed methodological explanations, with demonstrations and trials as required. Data collection occurred between 9:00 and 11:00 a.m., without intake of any food or beverages. A socio-demographic proforma was documented for all before their participation. Resting BP was measured in the supine position by means of a mercury sphygmomanometer, identifying systolic and diastolic values as the first and fifth Korotkoff sounds, respectively. BMI in kg/m² was calculated.

Laboratory evaluation: Patient charts provided the findings of the following tests: estimated glomerular filtration rate (eGFR), hemoglobin, blood urea, serum creatinine, sodium, potassium, calcium, phosphorus, uric acid, cholesterol, serum albumin, blood glucose [fasting (FBS) and post-prandial (PPBS)] and HbA1c. CKD was staged following KDIGO guidelines, with eGFR estimated utilising the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [2].

Evaluation of HRV [8,11,12]: All individuals were subjected to HRV testing for their cardiac autonomic (sympathetic and parasympathetic) status. Resting HRV was determined through the RMS Polyrite D multichannel digital polygraph (model version 2.4, Recorders and Medicare Systems Pvt. Ltd., Chandigarh, India) at a sampling rate of 256 Hz. Participants were allowed to rest supine for 10 minutes prior to baseline acquisition. Subsequently,

while the subject remained supine, continuous Electrocardiogram (ECG) recordings were obtained in Lead II mode for a duration of 5 minutes under quiet breathing and eyes closed. The system automatically filtered ectopic beats, artifacts, and noise, and stabilized signals were stored for analysis. Recordings were processed using the built-in software. HRV was evaluated under both time and frequency domain. Spectral density analysis in the frequency domain was accomplished through Fast Fourier Transformation (FFT). HRV recording and calculation were performed using validated proprietary RMS algorithms, in keeping with the standardized recommendations from the 1996 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [13].

Frequency domain parameters were assessed through: LF (low frequency): component of the low-frequency range, 0.04-0.15 Hz; in absolute values of power (ms^2); HF (high frequency): component of the high-frequency range, 0.15-0.4 Hz; in absolute values of power (ms^2); LF/HF ratio: ratio of low to high frequency power; TP (total power in ms^2).

Time domain parameters were assessed through: SDNN: the standard deviation of NN [normal-to-normal] intervals (ms); rMSSD: the square root of the mean squared differences of successive NN intervals (ms).

Statistical analysis

Data was entered in Microsoft Excel, and the Statistical Package for the Social Sciences software version 21 was used for statistical analysis. Owing to the skewness of the HRV data, its normality was attained by applying log transformation before conducting inferential statistical tests. The control and cases were compared with unpaired 't' test

considering $P \leq 0.001$ as significant. One-way ANOVA was adopted for intergroup comparisons, with statistical significance set at $P \leq 0.05$. Post-hoc analysis was executed with Bonferroni's correction for six pairwise comparisons, and the adjusted significance threshold of alpha was 0.0083.

Results

Independent samples t-test depicted that CKD patients possessed significantly higher systolic BP, while diastolic BP showed no significant difference. Resting heart rate was significantly elevated in CKD cases. eGFR was markedly reduced in CKD cases. (Table 1)

Across the CKD stages, age did not differ significantly. BMI showed a progressive increase from Stage 2 to Stage 5. The systolic and diastolic blood pressures, and resting heart rate rose continuously with advancing stage, reaching their highest values in Stage 5. eGFR declined progressively and significantly with stage progression (Table 2). CKD patients depicted significantly lower hemoglobin. FBS, PPBS, and HbA1c were all significantly higher in CKD cases. Sodium and calcium were significantly reduced, while phosphorus, serum creatinine, blood urea, and uric acid were markedly increased in CKD. Serum potassium and total cholesterol showed no significant difference between groups. Serum albumin was significantly lower in CKD cases. (Table 3)

Hemoglobin dropped progressively with advancing CKD stage. FBS and PPBS were markedly elevated, while HbA1c remained unchanged across stages. Serum sodium and calcium declined, whereas potassium and phosphorus rose significantly. Significant increase in creatinine and urea was noted. Uric acid and cholesterol were significantly higher, and serum albumin lower with advancing CKD. (Table 4)

Under HRV, except for LF/HF ratio, all indices went

significantly lower in cases, with LF (4.995E-12), HF (2.72E-15), LF/HF ratio (0.025), total power (1.828E-07), SDNN (4.913E-26), and rMSSD (3.111E-08)(Table 5).

All frequency domain HRV measures of LF, HF and TP except LF/HF ratio and time domain measures of SDNN, rMSSD were significantly reduced in CKD across stages as compared to control. For LF, ANOVA revealed a clear statistical difference in means across the four CKD stages [$F(3,183) = 10.35$, $p = 2.518E-06$]. *Post-hoc* analysis depicted that mean in stage 2 was significantly higher than in stage 4 ($p < 0.001$) and stage 5 ($p = 4.543E-06$). Similarly, mean in stage 3 was significantly higher than in stage 4 ($p = 0.006$) and stage 5 ($p = 8.256E-05$). For HF, variance analysis indicated stage differences [$F(3,183) = 5.546$, $p = 0.001$]. *Post-hoc* analysis indicated that mean in stage 2 was significantly higher than in stage 4 ($p = 0.004$) and stage 5

($p < 0.001$). In addition, mean in stage 3 was significantly higher than in stage 5 ($p < 0.001$). For mean of LF/HF ratio, ANOVA testing revealed no substantial stage variation ($p > 0.05$). For mean of TP, ANOVA reflected a significant variation across the four CKD stages [$F(3,183) = 6.774$, $p < 0.001$]. *Post-hoc* analysis illustrated mean in stage 5 as significantly lower than in stage 2 ($p = 8.085E-05$) and stage 3 ($p = 0.001$). For SDNN mean, variance analysis showed values differing significantly across CKD stages [$F(3,183) = 7.018$, $p < 0.001$]. *Post-hoc* analysis delineated that mean in stage 5 was significantly lower than in stage 2 ($p = 4.833E-05$) and stage 3 ($p = 0.003$). Additionally, mean in stage 4 was significantly lower than in stage 2 ($p = 0.006$) For rMSSD, ANOVA portrayed means varying significantly across stages [$F(3,183) = 2.88$, $p = 0.037$], but further inter-group analysis confirmed no significant variation (Table 6).

Table 1: Baseline demographic and clinical profile of control and cases

Parameter (Mean $\pm$ SD)	Control (n = 200)	Cases (n = 187)	t-test
Age (years)	42.23 $\pm$ 10.06	44.53 $\pm$ 13.59	$p > 0.001$
BMI (kg/m ²)	21.71 $\pm$ 2.33	21.29 $\pm$ 2.16	$p > 0.001$
SBP (mm Hg)	129.26 $\pm$ 10.38	133.65 $\pm$ 12.49	$p = 0.001$
DBP (mm Hg)	82.7 $\pm$ 5.45	84.02 $\pm$ 7.49	$p > 0.001$
Resting heart rate (beats/ min, derived from RR intervals)	84.49 $\pm$ 12.04	88.74 $\pm$ 9.95	$p < 0.001$
eGFR (ml/min/1.73m ²)	102.15 $\pm$ 8.03	37.21 $\pm$ 23.01	$p < 0.001$

BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; eGFR – Estimated glomerular filtration rate

Table 2: Baseline demographic and clinical profile across various CKD stages

Parameter (mean $\pm$ SD)	CKD				One-way ANOVA test
	Stage 2 (n = 47)	Stage 3 (n = 48)	Stage 4 (n = 46)	Stage 5 (n = 46)	p
Age (years)	42.74 $\pm$ 14.27	48.13 $\pm$ 11.58	42.24 $\pm$ 14.37	44.37 $\pm$ 13.12	$p > 0.05$
BMI (kg/m ²)	20.12 $\pm$ 2.04	21.50 $\pm$ 2.01	21.52 $\pm$ 2.01	22.04 $\pm$ 2.16	$p < 0.05$
SBP (mm Hg)	129.39 $\pm$ 12.79	131.19 $\pm$ 11.45	135.65 $\pm$ 12.51	138.54 $\pm$ 10.88	$p < 0.05$
DBP (mm Hg)	82.27 $\pm$ 8.72	82.23 $\pm$ 7.58	84.8 $\pm$ 7.06	87.13 $\pm$ 7.26	$p < 0.05$
Resting heart rate (beats/ min, derived from RR intervals)	83.78 $\pm$ 11.11	88.52 $\pm$ 9.02	90.10 $\pm$ 9.18	92.67 $\pm$ 8.38	$p < 0.05$
eGFR (ml/min/1.73m ²)	69.96 $\pm$ 9.26	42.64 $\pm$ 8.48	23.02 $\pm$ 5.12	12.25 $\pm$ 2.28	$p < 0.05$

BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; eGFR – Estimated glomerular filtration rate

Table 3: Comparison of haematological parameters between control and cases

Haematological parameters (Mean $\pm$ SD)	Control (n = 200)	Cases (n = 187)	t-test
Hb (g %)	12.39 $\pm$ 2.92	9.47 $\pm$ 1.68	$p < 0.001$
FBS (mg/dl)	85.49 $\pm$ 10.37	101.48 $\pm$ 13.23	$p < 0.001$
PPBS (mg/dl)	126.40 $\pm$ 17.40	144.83 $\pm$ 27.14	$p < 0.001$
HbA1c (%)	5.53 $\pm$ 0.61	5.78 $\pm$ 0.61	$p < 0.001$
Sodium (meq/dl)	140.06 $\pm$ 2.72	138.95 $\pm$ 2.92	$p < 0.001$
Potassium (meq/dl)	4.20 $\pm$ 0.48	4.27 $\pm$ 0.56	$p = 0.207$
Calcium (mg/dl)	9.09 $\pm$ 0.56	8.83 $\pm$ 0.54	$p < 0.001$
Phosphorus (mg/dl)	2.82 $\pm$ 1.07	4.58 $\pm$ 1.05	$p < 0.001$
Creatinine (mg/dl)	0.71 $\pm$ 0.37	3.05 $\pm$ 1.69	$p < 0.001$

Blood Urea (mg/dl)	27.53 ± 8	62.24 ± 27.53	$p < 0.001$
Uric acid (mg/dl)	3.64 ± 1.59	6.43 ± 1.64	$p < 0.001$
Cholesterol (mg/dl)	149.49 ± 27.24	158.89 ± 36.6	$p = 0.004$
Albumin (g/dl)	4.20 ± 0.51	3.47 ± 0.36	$p < 0.001$

Hb – Hemoglobin; *FBS* – Fasting blood sugar; *PPBS* – Post prandial blood sugar; *HbA1c* – Glycosylated hemoglobin

Table 4: Comparison of haematological parameters across different CKD stages

Haematological parameters	CKD				One-way ANOVA test
(Mean ± SD)	Stage 2 (n = 47)	Stage 3 (n = 48)	Stage 4 (n = 46)	Stage 5 (n = 46)	<i>p</i>
Hb (g %)	11.04 ± 1.32	10.12 ± 1.28	8.36 ± 1.07	8.32 ± 1.18	$p < 0.05$
FBS (mg/dl)	98.77 ± 14.59	97.97 ± 14.01	105.05 ± 11.34	104.36 ± 11.39	$p < 0.05$
PPBS (mg/dl)	138.91 ± 24.08	140.49 ± 24.70	146.75 ± 27.79	153.48 ± 30.10	$p < 0.05$
HbA1c (%)	5.70 ± 0.62	5.74 ± 0.62	5.76 ± 0.61	5.92 ± 0.60	$p > 0.05$
Sodium (meq/dl)	139.58 ± 3.10	139.31 ± 2.29	138.89 ± 3.22	137.99 ± 2.82	$p < 0.05$
Potassium (meq/dl)	3.95 ± 0.45	4.15 ± 0.52	4.28 ± 0.57	4.70 ± 0.41	$p < 0.05$
Calcium (mg/dl)	9.11 ± 0.57	8.86 ± 0.47	8.76 ± 0.53	8.59 ± 0.45	$p < 0.05$
Phosphorus (mg/dl)	3.94 ± 0.61	4.12 ± 0.82	5.02 ± 1.03	5.27 ± 1.04	$p < 0.05$
Creatinine (mg/dl)	1.57 ± 0.19	2.02 ± 0.43	3.16 ± 0.60	5.53 ± 1.22	$p < 0.05$
Blood Urea (mg/dl)	27.98 ± 7.45	49.24 ± 8.18	77.48 ± 10.31	95.57 ± 10.98	$p < 0.05$
Uric acid (mg/dl)	5.36 ± 1.13	5.80 ± 1.17	6.85 ± 1.42	7.75 ± 1.69	$p < 0.05$
Cholesterol (mg/dl)	142.41 ± 27.88	146.75 ± 29.47	152.90 ± 31.82	194.40 ± 32.50	$p < 0.05$
Albumin (g/dl)	3.56 ± 0.36	3.51 ± 0.39	3.43 ± 0.31	3.37 ± 0.35	$p < 0.05$

Hb – Hemoglobin; *FBS* – Fasting blood sugar; *PPBS* – Post prandial blood sugar; *HbA1c* – Glycosylated hemoglobin

Table 5: Comparison of heart rate variability parameters (log transformed) between control and cases

HRV parameters (Mean $\pm$ SD) [log transformed]	Control (n = 200)	Cases (n = 187)	t-test
LF, ms ²	5.255 $\pm$ 1.099	4.225 $\pm$ 1.697	$p < 0.001$
HF, ms ²	4.75 $\pm$ 1.225	3.545 $\pm$ 1.636	$p < 0.001$
LF/HF	0.504 $\pm$ 0.432	0.68 $\pm$ 1.012	$p < 0.001$
TP, ms ²	6.502 $\pm$ 0.984	5.898 $\pm$ 1.246	$p < 0.001$
SDNN, ms	3.708 $\pm$ 0.44	3.021 $\pm$ 0.723	$p < 0.001$
rMSSD, ms	3.56 $\pm$ 0.571	3.183 $\pm$ 0.735	$p < 0.001$

HRV – Heart rate variability; LF – Low frequency; HF – High frequency; TP – Total power; SDNN - standard deviation of NN [normal-to-normal] intervals; rMSSD – Square root of the mean squared differences of successive NN intervals

Table 6: Comparison of heart rate variability parameters (log transformed) across different CKD stages

HRV parameters (mean $\pm$ SD) [log transformed]	CKD				One-way ANOVA test
	Stage 2 (n = 47)	Stage 3 (n = 48)	Stage 4 (n = 46)	Stage 5 (n = 46)	p
LF, ms ²	4.919 $\pm$ 1.433	4.757 $\pm$ 1.64	3.82 $\pm$ 1.613	3.366 $\pm$ 1.632	$p < 0.05$
HF, ms ²	4.146 $\pm$ 1.559	3.83 $\pm$ 1.468	3.214 $\pm$ 1.525	2.963 $\pm$ 1.755	$p < 0.05$
LF/HF	0.773 $\pm$ 0.983	0.927 $\pm$ 0.899	0.606 $\pm$ 0.997	0.402 $\pm$ 1.115	$p > 0.05$
TP, ms ²	6.374 $\pm$ 1.21	6.121 $\pm$ 1.102	5.743 $\pm$ 1.231	5.332 $\pm$ 1.224	$p < 0.05$
SDNN, ms	3.313 $\pm$ 0.658	3.147 $\pm$ 0.667	2.911 $\pm$ 0.712	2.701 $\pm$ 0.724	$p < 0.05$
rMSSD, ms	3.418 $\pm$ 0.667	3.124 $\pm$ 0.712	3.201 $\pm$ 0.628	2.988 $\pm$ 0.867	$p < 0.05$

CKD – Chronic kidney disease; SD – Standard deviation; HRV – Heart rate variability; LF – Low frequency; HF – High frequency; TP – Total power; SDNN - standard deviation of NN [normal-to-normal] intervals; rMSSD – Square root of the mean squared differences of successive NN intervals

Discussion

In frequency-domain analysis of HRV, the HF factor reflects short-term heart rate fluctuations mediated predominantly by parasympathetic activity; the LF factor represents contributions from sympathetic as

well as parasympathetic modulation; and the LF/HF ratio serves as an index of sympatho-vagal balance, and TP denotes overall HRV.

In the time domain parameters, SDNN is an estimate of overall HRV and rMSSD indicates high frequency fluctuations and parasympathetic influence [11]. Each of these measures has shown strong reproducibility [14]. In the present study, HRV analysis revealed marked autonomic dysfunction in CKD patients, with all frequency -domain (except LF/HF ratio) and time-domain parameters significantly reduced compared with controls.

Stage-wise comparisons showed that LF was significantly higher in stage 2 and 3 as compared with stages 4 and 5. HF was significantly higher in stage 2 as compared with stages 4 and 5; and that in stage 3, too, was elevated significantly relative to stage 5. TP and SDNN were significantly lower in Stage 5 compared with Stage 2 and Stage 3; also, SDNN was significantly lower in stage 4 than stage 2. However, LF/HF ratio and rMSSD did not show interstage differences. Hence, overall HRV declined progressively across CKD stages, concurrent with reductions in both sympathetic and parasympathetic activity.

Chandra *et al.* in 2000-2006 conducted a multicentric study employing 24-hour HRV (median follow-up for 2.7 years) on 305 non-dialysis CKD patients of stages 3-5. Crude comparisons between the Renal Research Institute (RRI)-CKD cohort and healthy populations reported in the literature indicated that HRV frequency-domain (VLF, LF, HF, LF/HF) and time-domain (SDNN) measures were significantly attenuated in the CKD group compared with controls [11]. Studies show spectral HRV indices (TP, HF, LF) are similar in stage 4/5 non-dialysis CKD and dialysis, though time-domain (SDNN, SDANN) measures may rise in dialysis. This implies that the suppressive effect of renal disease on HRV may have already plateaued before the initiation of renal replacement therapy [15].

This underscores the need to gauge how early autonomic imbalance arises in the trajectory of CKD. Our findings are in consonance with Chou *et al.* (2019) who observed that values of SDNN, lnTP, lnHF, lnLF, lnVLF were maximal in stage 2 CKD and declined with worsening renal function. Additionally, they found lnLF/HF served as an independent determinant of rapid CKD progression at all stages, irrespective of diabetic status. Both parasympathetic and sympathetic tone and overall HRV diminished with stage progression [16]. Although certain HRV indices varied significantly across CKD stages, the greatest variations were evident in stage 5 compared with Stages 3 and 4. SDNN, SDANN (SD of the averages of 5-min NN intervals over 24 h), LF/HF and VLF (very low frequency) were markedly diminished in patients with eGFR < 15 mL/min/1.73m² in contrast to those with higher eGFR values. LF/HF ratio was identified as a predictor for ESRD, but with its significance disappearing when LVMI was excluded from the multivariate analysis. Reduced HRV, particularly in the frequency domain, was significantly linked to greater CVD risk and the compound end point of CVD or death [11].

Oliveira *et al.* in 2014 compared 32 non-diabetic, non-dialysis CKD patients at stages 3, 4 or 5 with 14 healthy controls; by means of HRV at rest and on orthostatic stress (postural inclination at 70 degrees). On tilting, CKD patients exhibited reduced sympathetic drive, increased parasympathetic activity, and reduced sympathovagal balance compared to controls. Relative to stage 3, stage 5 patients showed lower LFnu/HFnu ratios, indicating more pronounced imbalance with disease progression. They deduced that CKD patients not yet on dialysis possess decreased HRV, suggesting early cardiac autonomic dysfunction [17]. Lal *et al.*

in 2017 studied short-term HRV, BRS, blood pressure variability (BPV) and arterial stiffness through Pulse Wave Velocity (PWV) in 30 non-diabetic predialytic CKD patients of stage 4 and 5 and 30 healthy controls. Patients demonstrated an adverse hemodynamic profile, with lower HRV and BRS, and higher PWV compared to controls. Reduced HRV demonstrated independent predictive significance for impaired BRS [18].

As a part of their study, Clyne *et al.* in 2016 analysed 24-hour HRV in 124 CKD patients not on renal replacement therapy. They found a curvilinear link between the deterioration in renal function (reflected by GFR), and a rising sympathovagal dysfunction (reflected by SDNN). Decreased SDNN modulates the autonomic activity towards sympathetic hyperexcitation and/or vagal withdrawal. Their comprehensive inference was that cardiac sympathetic overdrive alongside diminished vagal control occurs in CKD 4 and 5 [19]. Findings of the atherosclerosis risk in communities study underscored the association between diminished LF and HF power and ensuing renal impairment, persisting even after controlling for conventional risk factors like diabetes, hypertension, and reduced baseline renal function [4]. While reductions in individual HRV parameters are inconsistently reported in CKD/ESRD, overall HRV estimation via SDNN remains a reliable prognostic marker for sudden cardiac death [6].

Conversely, in the population-based Prevention of RENal and Vascular ENdstage Disease (PREVEND) study, where HRV was tested at baseline and renal outcomes were followed longitudinally, low SDNN initially appeared associated with incident CKD; with this relationship attenuating post adjustment for demographic and cardiovascular risk factors. No reliable link emerged between SDNN and eGFR decline in the overall sample. In participants with

CKD at baseline, low SDNN was related to lower eGFR, though not to accelerated deterioration [20]. A multi-centric study by Drawz *et al.* in 2003-2009 utilising short-term HRV on 3245 patients with an eGFR in the range of 20 to 70 ml/min/1.73m² (follow-up for 4.2 years), delineated that lower HRV was not linked to elevated risk of renal or cardiovascular outcomes. However, low as well as high rMSSD were shown to be linked with elevated all-cause mortality risk [21].

Renal disease being usually asymptomatic in the initial phases, its detection is prone to happen by chance during routine health check-ups or follow-ups of patients carrying risk of cardiovascular events (hypertensives or diabetics) [22]. Neurotoxin build-up may disrupt autonomic regulation [16,23]. Interleukin-6 (IL-6) showed association with HRV (LF, VLF, TP, SDNN, SDANN,) in stages 3-4 CKD patients; but, no association was observed between the inflammatory markers (C-reactive protein [CRP], IL-6) and HRV in hemodialysis patients; signifying towards the possibility of IL-6 modulating the autonomic operation in non-dialysis group [24].

The autonomic alterations in CKD include an early onset of adrenergic dysfunction in direct proportionality to the gravity of kidney malfunction, decreased vagal inhibitory effect on sinus node, distorted vagal as well as sympathetic cardiovascular outcomes through the arterial baroreceptors, dysfunctional cardiopulmonary receptor influence on sympathetic vasoconstrictor tone and discharge of renin from the juxtaglomerular cells, chemoreflex activation and attenuated reactivity of the alpha adrenergic vascular receptors. The parasympathetic as well as sympathetic variations hold clinical significance for ascertaining patients' prognosis, even on adjustment for confounders during data analysis [25].

This study supports validation of HRV as a potential autonomic function test for gauging dysfunction severity in CKD. The findings may aid for earlier recognition of autonomic impairment, enabling timely intervention and reducing cardiovascular risk. Future work integrating wearable sensors and AI analytics may expand HRV's diagnostic scope [26]. The role of time-domain, frequency-domain, and non-linear HRV measures in tracking CKD progression and evaluating therapeutic strategies should be steered through peer-reviewed studies across diverse populations. Evidence from hypertensive rat models showed that therapeutic interventions can modulate HRV and restore autonomic balance, while beyond conventional time- and frequency-domain indices, non-linear HRV analyses in Parkinson's disease revealed reduced complexity and unstable autonomic regulation; together these findings highlight HRV's dual role as a modifiable target and a sensitive biomarker, supporting its translational potential for tracking autonomic dysfunction and guiding interventions in chronic conditions such as CKD [27,28]. Crucially, whether reduced HRV is a causal mechanism in CKD or a secondary complication remains unresolved.

Limitations: This being a cross-sectional survey just providing a snapshot at a single point in time; a long term, follow up study shall prove helpful in

establishing the causality. This study was not multi-centric. Also, the medications commonly prescribed in CKD, such as ACE inhibitors, beta-blockers and erythropoietin, are recognised modulators of autonomic function. Given the clinical necessity of these therapies, treatment was not discontinued in patients, and our findings therefore represent HRV alterations in CKD under standard medical care. Such a limitation was also recognised in earlier autonomic function studies in CKD [16,29,30], which emphasize that inclusion of treated patients enhances external validity and reflects real-world scenario.

Conclusion

Cardiovascular autonomic dysfunction is seen in CKD, with progressive stage-wise reductions in HRV underscoring its advancing nature in non-dialysis, nondiabetic patients. HRV assessment demonstrates potential as a screening approach for the early recognition of autonomic dysfunction in CKD.

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