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# HEART RATE VARIABILITY IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS: A CROSS-SECTIONAL STUDY

*Mohd Akmal[1], Sunita Tiwari[2], Vibha Gangwar[3], Ritu Karoli[4], Namrata Rao[5]*

[1]PG Resident, Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.
[2]Professor, Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.
[3]Professor JG, Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.
[4]Professor JG, Department of Internal Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.
[5]Professor JG, Department of Nephrology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.

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**Corresponding Author:**
**Dr. Mohd Akmal,**
PG Resident, Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.
Email: drsiddiquimbbs@gmail.com

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ABSTRACT

**Background:** The study aims to assess the heart rate variability in non-dialysis chronic kidney disease patients.

**Materials and Methods:** This was a cross-sectional study, carried out in the Department of Physiology, Dr RMLIMS, Lucknow. 102 patients in the age group of 30-60 years, having chronic kidney disease but not on dialysis were taken from the OPD of Nephrology. Samples were collected and serum was analyzed for lab parameters like creatinine, and blood urea. eGFR was calculated. HRV of the patient was done in the physiology department.

**Results:** A total of 102 patients fulfilling both criteria were enrolled in the study. The mean age was 45.44±11.13 years. Males constituted of 65.7% of the study population, while female were mere 34.3%. In terms of Blood pressure, SBP and DBP of the study population were 140.92±20.75 mmHg and 82.32±15.13 mmHg. Respiratory rate was 14.28±2.56 breaths per minute. At the first visit, kidney function was accessed using Urea, Creatinine, and eGFR and was recorded as 67.78±33.97 mg/dL, 2.82±1.73 mg/dL, and 36.35±24.58 respectively. Majority of the patients had reduced HRV (73.5%), while the remaining had HRV within the normal range (26.5%).

**Conclusion:** HRV, a non-invasive tool can be used for assessment of autonomic dysfunction in chronic kidney disease who are not on dialysis. Lower HRV has been associated with adverse outcomes in end-stage renal disease (ESRD). Hence the estimation of LF/HF can provide prognostic information on CKD progression and in its management.

**Keywords:** Creatinine, Urea, Heart Rate Variability, Estimated Glomerular Filtration Rate, Chronic Kidney Disease.

## INTRODUCTION

CKD is a leading public health problem worldwide.[1] and affects between 8% and 16% of the global population, however, evidence suggests that it is often under-recognized by patients and clinicians.[2,3] Ironically, CKD prevalence is more commonly reported in low- and middle-income populations than in high-income populations,[4] hence the association between CKD with poor healthcare infrastructure or on the contrary the association of CKD with poor quality of life. CKD is most commonly attributed to Type 2 diabetes mellitus and/or hypertension, but, other causes such as glomerulonephritis, infection, and environmental exposures to toxins are also common in Asia, sub-Saharan Africa, and other developing countries.[5]

CKD is seen as a major contributor to mortality and morbidity by the Global Burden of Disease collaboration.[6] The prevalence of CKD, increased by 30% globally, for all age groups since the last decade of the 20th century, up to the two decades of the 21st century. During the same period, mortality from CKD increased by almost 42%.

Much like in western countries, nearly half of the CKD cases in India are made up of Diabetes and

Hypertension.[7] Contemporary studies from India have reported the prevalence rate of CKD to be nearly 17.5%,[8,9] and attributed it to a constant rise in diabetics and hypertensives in the country. The prevalence of CKD in India is higher than the global average, necessitating further studies aimed at evaluating prognosis, markers, and associated comorbidities.

Chronic Kidney Disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause.[10] The progression of CKD leads to a loss in kidney function, ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). The poor prognosis of CKD makes early diagnosis and disease screening of utmost importance for managing the CKD epidemic.

At the epicenter of barriers to diagnosing CKD is the lack of knowledge of the patient developing symptoms for CKD, rather usually the diagnosis is delayed due to the presence of speculative symptoms like loss of appetite, itchiness, and nausea. A confirmed diagnosis of CKD can only be made after screening tests (urinary dipstick or blood tests), or the appearance of severe symptoms. Moreover, in recent studies aimed at establishing the causal mechanism, suggest the dysfunctioning of the autonomic nervous system, specifically, a decrease in parasympathetic function relative to sympathetic function.[11]

One of the hypotheses for the involvement of autonomic dysfunction resulting in renal damage is through changes in renal hemodynamics, eventually progressing to kidney damage and failure.[12,13]

Usually, kidney function estimation can be made using Serum Creatinine concentration, blood urea nitrogen (BUN) level, and urine analysis. However, accumulating evidence has demonstrated that these biomarkers are not optimal to detect kidney disease in early stages.

The KDIGO (Kidney Disease Improving Global Outcomes) recommends that CKD be diagnosed, classified, and staged by GFR. GFR is the volume of fluid filtered from the glomerular capillaries into the Bowman's capsule per unit of time.[15]

**Kidney Disease Improving Global Outcomes (KDIGO) stages of chronic kidney disease (CKD)**

| |
|---|
| Stage 1 GFR greater than 90 ml/min/1.73 m² |
| Stage 2 GFR-between 60 to 89 ml/min/1.73 m² |
| Stage 3a GFR 45 to 59 ml/min/1.73 m² |
| Stage 3b GFR 30 to 44 ml/min/1.73 m² |
| Stage 4 GFR of 15 to 29 ml/min/1.73 m² |
| Stage 5-GFR less than 15 ml/min/1.73 m² (end-stage renal disease) |

**Creatinine**

Creatinine is the most commonly used endogenous marker for assessing glomerular function.[16]

The principle of creatinine estimation is based on Jaffe's method,[17] in which creatinine reacts with picric acid at alkaline PH to form a yellow-orange complex. the rate of change of absorbance at 520 nm is proportional to the creatinine concentration in the sample.[18]

Serum creatinine is utilized in GFR estimating equations such as the Modified Diet in Renal Disease (MDRD) and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. These eGFR equations are superior to serum creatinine alone since they include race, age, and gender variables.

**Urea**

Urea is a product of protein catabolism, the biosynthesis of urea from ammonia is exclusively carried out by hepatic enzymes. More than 90% of Urea is excreted through the kidneys, with the remainder excreted through the gastrointestinal tract or skin. Urea is used, as a proxy for CKD severity and dialysis adequacy in clinical settings. Urea is considered a direct and indirect uremic toxin,[19] The principle of Urea estimation is enzymatic-uv-kinetic (Urease UV).[20]

The autonomic nervous system (ANS), a sub-part of the peripheral nervous system (PNS), regulates involuntary physiologic processes, including BP, HR, RR, digestion, and sexual arousal. It comprises sympathetic, parasympathetic, and enteric nervous systems, which are three anatomically distinct divisions.

The autonomic nervous system (ANS) includes all regions implicated in controlling "autonomic," unconscious, and involuntary functions in total body homeostasis. In general, the full range of physiologic functions is ultimately necessary for human survival and allows us to interact with the external environment in a wide range of conditions. Autonomic dysfunction can arise from a myriad of factors, often with multiple causes affecting the same patient. Given the extensive reach of the autonomic nervous system, a wide range of conditions can impact it.

Heart rate is the number of heartbeats per minute. Heart rate variability (HRV) is the fluctuation in the time intervals between adjacent heartbeats.[21] HRV indexes neuro-cardiac function and is generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes.

HRV is an emergent property of interdependent regulatory systems that operate on different time scales to help us adapt to environmental and psychological challenges. HRV reflects the regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles.[22] The oscillations of a healthy heart are complex and non-linear. The variability of non-linear systems provides the flexibility to rapidly cope with an uncertain and changing environment.

Higher HRV is not always better since pathological conditions can produce HRV. When cardiac conduction abnormalities elevate HRV measurements, this is strongly linked to an increased risk of mortality (particularly among the elderly).

An optimal level of HRV is associated with health self-regulatory capacity, and adaptability or resilience.

In humans, a non-invasive way of assessing autonomic function is by calculating heart rate variability (HRV), a measure of autonomic control over heart rate. It is the variation in duration between normal-to-normal (NN) RR intervals.[23] Moderate-to-high HRV indicates healthy autonomic function, whereas low HRV reflects poor autonomic function and has been associated with cardiovascular risk factors and adverse cardiovascular outcomes. The relation between HRV and CKD has been explored in several small-scale studies. Participants with CKD were found to have lower HRV compared with those without CKD. In addition, low HRV was associated with adverse outcomes during follow-up (i.e., progression to end-stage renal disease and mortality) in CKD patients, although results are inconsistent between studies.[24,25] The mechanisms underlying this association are still under investigation, but it is commonly believed that autonomic imbalance is a complication of renal damage.[26]

## MATERIAL AND METHODS

The present study was a Cross-sectional Study conducted in The Department of Physiology, Nephrology and Medicine, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, after obtaining Institutional Ethical Committee approval (IEC No.74/22).

After receiving informed written consent,102 patients in the age group of 30-60 years, having chronic kidney disease but not on dialysis were taken from the OPD of Nephrology. The duration of the study was 18 months.

Inclusion criteria include Subjects in the age group of 30-60 years of both sexes who were willing to participate in the study, all chronic kidney disease patients who were not on dialysis, and patients with hypertension & chronic kidney disease on medical treatment. While exclusion criteria included Subjects 60 years or above not willing to participate in the study, patients with diabetes, a history of angina, arrhythmia, myocardial ischemia, heart failure, intrinsic and infiltrative cardio-myopathies or any other cardiovascular disease, peripheral ischemic disease with documented claudication, history of debilitating Neurological diseases and non-ambulatory/bedridden patients.

**Investigations and Tests:** Diagnosed clinical details of the patient, including age, sex, and patient of hypertension with Lab parameters including serum Creatinine level and urinary albumin excretion level, collected from the Nephrology OPD for the evaluation of heart rate variability in the physiology department. Serum Creatinine was estimated By Jaffe's method,[17] (Jaffe's reaction),[18] with a Beckman Coulter analyzer (Kit).Blood UREA was estimated By Enzymatic-UV-Kinetic (Urease UV)[20] UAE-(Urinary albumin excretion) was measured by urinary ACR (Albumin to Creatinine ratio) in a spot urine sample. e-GFR was estimated by e-GFR Calculator with serum Creatinine in micro-mol/lit. Weight (Wt.) in kilograms (kg) and Height (Ht.) in centimeters (cm.) was noted and BMI was calculated using (Quetlet index) as per World Health Organization which is defined as a person's weight in kilograms divided by the square of the person's height in meter (kg/m2). Systolic and Diastolic blood pressure was measured in millimeters of mercury (mm Hg). HRV (Heart rate variability)- was analysed for assessment of sympathovagal balance by LF-HF ratio in short term (5 minutes) ECG- recording by Labchart-8/AD Instrument (4 channel physiograph). Several methods are employed to assess HRV in clinical settings, including time domain analysis, frequency domain analysis, and nonlinear dynamics:

Frequency Domain Analysis: Frequency domain analysis decomposes HRV into different frequency bands using spectral analysis, including low frequency (LF, 0.04-0.15 Hz), high frequency (HF, 0.15-0.40 Hz), and very low frequency (VLF, <0.04 Hz) components. LF power reflects sympathetic and parasympathetic modulation, while HF power primarily represents parasympathetic activity.

Prerequisites-Subjects were asked to take a sufficient amount of rest prior, to the HRV test. They were informed prior to the test not to consume tea/coffee or any cardio-modulator substance at least 6 hours before the test and were asked to remove any wrist or ankle jewelry before the test itself.

Methods to measure HRV The HRV was done in a quiet environment in the autonomic function laboratory of the Physiology department, Dr RMLIMS, Lucknow. The subject was explained about the procedure. The participants were asked to lie comfortably, with their eyes closed, and relax for about 5-10 min prior to the HRV test. Disposable hydrogel ECG electrodes were placed on the right (two electrodes) and left (one electrode) wrist, right ankle (one electrode), and left ankle (one electrode) just above the medial malleoli. The computer was switched on and the software LABCHART PROV 8.1.8 with HRV module V.2.0.3 was turned on. HRV was recorded by ECG lead II for 5 minutes at a frequency of 500 samples per second by a 4-channel Physiograph (AD Instruments South Asia (India) Pvt. Ltd., New Delhi, India.). HRV was analyzed by spectral analysis using software LABCHART PROV 8.1.8 with HRV module V.2.0.3. The frequency domain analysis was performed using fast Fourier transformation.

The following frequency domain indices were considered:

I. Low frequency (LF) power(ms2/%/nu)
II. High frequency (HF) power (ms2/%/nu)
III. Total power (ms2)
IV. Very Low Frequency (VLF)) power (ms2/%)
V. LF/HF ratio.

**Data Analysis**

SPSS version 21 was used for Statistical computation and analysis. Categorical data was represented in numbers (frequency) and percentages. Continuous data was represented as mean and standard deviation. Parametric tests and non-parametric tests were done as applicable. For parametric tests, the normality test i.e., Shapiro-Wilk test was applied.

## RESULTS

Table 1 shows Renal Function Test parameters at recruitment (n=102). Serum Urea ranged from 8.23 to 165.0 mg/dL, the mean S. Urea was 67.78±33.97 mg/dL. mean Creatinine was 2.82±1.73 mg/dL & ranged from 0.75 mg/dL to 9.20 mg/dL. In the same test, eGFR ranged from 10 to 123. The mean eGFR was 36.35±24.58. [Table 1]

Table 2 shows the distribution of the study population according to HRV outcome(n=102). Heart rate variability in majority of the cases was Reduced (73.5%), while it was Normal in the remaining cases (26.5%). [Table 2]

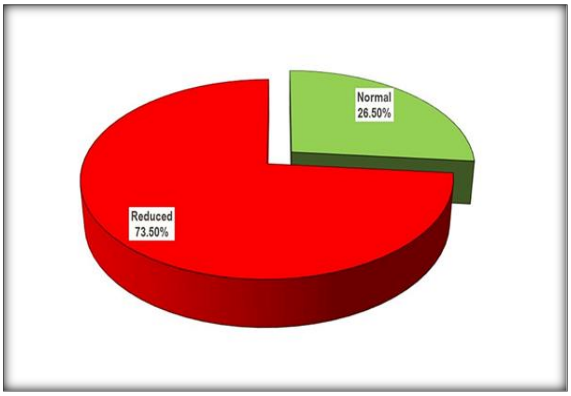


**Figure 1: Pie diagram of the distribution of the study population according to HRV outcome**

Table 3 implies that Total power and HF (m/s2) were significantly higher in patients with Stage-V CKD as compared to all other patients, while none of the other HRV parameters were significantly different among patients with different severity of CKD. This is because of increase in vagal activity or nodal tissue dysfunction due to increased parasympathetic overactivity. [Table 3]

**Table 1: Renal Function Test parameters**

| SN | Parameter | Min. | Max. | Mean±SD |
|---|---|---|---|---|
| 1 | Urea (mg/dL) | 8.23 | 165.0 | 67.78±33.97 |
| 2 | Creatinine (mg/dL) | 0.75 | 9.20 | 2.82±1.73 |
| 3 | eGFR | 10 | 123.0 | 36.35±24.58 |

**Table 2: Distribution of study population according to HRV outcome**

| SN | Outcome | No. | % |
|---|---|---|---|
| 1 | Normal | 27 | 26.475 |
| 2 | Reduced | 75 | 73.525 |

**Table 3: Association of the HRV with disease severity**

| HRV parameters | Stage I | Stage II | Stage III | Stage IV | Stage V | ANOVA | |
|---|---|---|---|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | F | 'p' |
| LF ($m/s^2$) | 324.92±619.58 | 250.48±218.64 | 120.76±163.67 | 149.82±174.74 | 223.59±461.40 | 1.171 | 0.328 |
| LF (%) | 25.19±12.22 | 20.51±9.10 | 24.51±11.30 | 23.84±11.82 | 23.84±19.45 | 0.178 | 0.949 |
| LF (nu) | 50.24±21.56 | 47.97±18.91 | 50.34±23.04 | 55.15±22.64 | 38.28±25.16 | 1.355 | 0.255 |
| HF ($m/s^2$) | 41.59±28.62 | 235.66±229.50 | 148.31±237.94 | 208.98±402.45 | 828.20±1815.24 | 2.569 | 0.043 |
| HF (%) | 30.34±19.54 | 27.59±16.95 | 27.87±20.88 | 34.03±61.33 | 42.02±23.71 | 0.395 | 0.812 |
| HF (nu) | 49.25±20.91 | 50.74±17.60 | 45.90±19.71 | 44.82±21.55 | 57.93±21.36 | 1.171 | 0.329 |
| VLF ($m/s^2$) | 282.21±341.25 | 290.70±261.19 | 212.32±205.10 | 217.15±172.33 | 322.28±465.64 | 0.653 | 0.626 |
| VLF (%) | 64.16±66.13 | 50.51±21.75 | 45.82±23.38 | 64.27±80.52 | 37.69±20.98 | 0.964 | 0.431 |
| LF/HF | 1.41±1.26 | 1.31±1.33 | 1.92±2.10 | 1.91±1.85 | 1.03±1.15 | 0.849 | 0.498 |
| T. Power | 853.10±1387.64 | 1080.06±1241.35 | 488.78±540.00 | 517.33±656.23 | 2383.06±3271.06 | 5.606 | <0.001 |

## DISCUSSION

Serum urea levels, which measure the concentration of urea nitrogen in the blood, were found to be 67.78±33.97 mg/dL on average among the participants in our study. [Table 1] Elevated serum urea levels typically indicate decreased kidney function, as the kidneys play a crucial role in filtering urea from the bloodstream and excreting it in the urine. Therefore, higher levels of serum urea suggest impaired kidney function and reduced clearance of waste products from the body.

Similarly, serum creatinine levels were observed to be 2.82±1.73 mg/dL on average in our study population. [Table 1] Creatinine is a waste product generated from the breakdown of muscle tissue, and its levels in the blood are typically regulated by kidney function. Elevated serum creatinine levels are indicative of decreased kidney filtration and clearance capacity, as the kidneys normally filter creatinine from the blood and excrete it in the urine. Therefore, higher serum creatinine levels are often associated with impaired kidney function and reduced glomerular filtration rate.

Additionally, the estimated glomerular filtration rate (eGFR), a calculated measure based on serum creatinine levels, was determined to be 36.35±24.58 on average among the participants. [Table 1] eGFR provides an estimate of the kidney's ability to filter waste products from the blood, with lower eGFR values indicating decreased kidney function. A reduced eGFR is a hallmark of CKD and is used to classify the severity of the disease into different stages, ranging from mild to severe impairment of kidney function.

In the present study, majority of the patients had reduced HRV (73.5%), while the remaining had Normal HRV (26.5%).

on stratifying the patients according to the stages of CKD, while all HRV parameters like Total Power, VLF, LF, HF, LF/HF ratio were not well associated among patients with Stage V CKD as compared to all others, but only HF (m/s2) and Total Power were significantly elevated in patients with CKD stage V as compared to all others (Table3). In their study, Chou et al,[27] had reported very similar findings, however the study was conducted on CKD patients on dialysis, and it was found that HRV parameters were worse stage V CKD patients. Similarly, Chang et al,[28] measured24 hour HRV in patients with GHF and reported a significant association of HRV with GHF(Glomerular hyperfiltration).

Autonomic dysfunction measured by HRV appears to be closely related to CKD, playing a significant role in its pathogenesis and progression. Further research in this area is warranted to elucidate the underlying mechanisms and therapeutic implications of this relationship, with the potential to improve risk stratification and management strategies for CKD patients, delving into the intricate mechanisms that underpin the progression of both conditions.

**Limitations**

24-hour HRV analysis would be a better approach to analyze the heart rate variability. Since it was a cross-sectional study hence, the patients included were not followed up for the progression of disease/outcomes.

## CONCLUSION

The present study concluded that reduced HRV is more common in patients with more severe CKD, however statistically, the association of severity of CKD and HRV was not significant. On the other hand, among the various component of HRV test, Total Power and HF were significantly associated with severity of CKD that while some of the HRV parameters (Total Power and HF) were significantly higher in patients with more severe CKD.Hence HRV can be used as an intervention to predict severity of CKD. Future studies with larger sample size should be undertaken to further elaborate on the findings of the present study.

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