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CORRELATION OF HEART RATE VARIABILITY PARAMETERS WITH CHRONIC KIDNEY DISEASE DURATION

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ABSTRACT

Introduction- Autonomic dysfunction commonly presents with Chronic Renal Failure. Its pathophysiology is obscure. Autonomic dysfunction contributes to cardiovascular morbidity and mortality and can be evaluated with heart rate variability (HRV).

AIM- To evaluate the correlation of chronic kidney disease duration with Heart Rate Variability parameters to better understand autonomic dysfunction in chronic renal failure

Materials and Method

The present cross sectional observational study was carried out in Department of Physiology at King George's Medical University, Lucknow UP from April 2019 to march 2020, on 92 patients of chronic kidney disease. Heart rate variability of the subjects was assessed from five-minute digitalized Electrocardiography. The Coefficient of correlation (r value) of heart rate variability parameters (both time and frequency domain) with respect to duration of CKD were calculated. The data was analyzed for changes in HRV parameters in relation to CKD duration.

Results

The analysis showed Time domain HRV parameters had negative Coefficient of correlation (-r value) with respect to CKD duration indicating deteriorating autonomic balance with CKD

duration. Frequency domain parameters showed differential change. The relative low frequency (LF) component showed + r value. The high frequency (HF) showed -r values. The

LF mainly corresponds to sympathetic and HF Parasympathetic arm of Autonomic Nervous System. The result emphasize that CKD duration causes relative increased sympathetic and decreased parasympathetic effect (sympathovagal imbalance).

Conclusion:

This study showed that CKD duration have negative impact on HRV parameters implying deterioration of autonomic system.

Keywords: Heart Rate Variability, Chronic kidney disease, Chronic renal failure, sympathetic arm, parasympathetic arm.

INTRODUCTION

Chronic Kidney Disease (CKD) is a scourge of modern times. Its incidence and prevalence is increasing. About 860 million people are now suffering from CKD. The exact etiopathology of CKD and its complications is still obscure1.

CKD has been divided into five stages based on Glomerular Filtration Rate (GFR).

Stage 5 CKD is End-stage renal disease (ESRD) needing dialysis or Renal transplant. Moderate to severe CKD (stage 3–5) is associated with a significantly higher risk of cardiovascular morbidity and mortality. Majority of CRF patients succumb before reaching the last stage (ESRD). Cardiovascular system (CVS) complications are one of the main reasons of morbidity and mortality in these CRF patients. The etiopathology of CVS complications in CKD is unclear. 2,3,15,16

“Why and how CKD patients develop CVS consequences?” is a clinically significant question. Autonomic dysfunction in the form of relatively increased sympathetic and decreased parasympathetic arm of Autonomic Nervous System (ANS) is a frequent accompaniment of CRF which may contribute to comorbid cardiovascular morbidity and mortality 4,5,10,11

The underlying mechanism of autonomic changes in CKD patients remains elusive. Correlation of Autonomic Nervous system (ANS) changes with CKD duration may be an important clinical parameter. Heart Rate Variability (HRV) derived from digitalized ECG signals is an easy way to study ANS. It is non-invasive and easily applied technique. It does not need patient’s effort which may be cumbersome to get. Advanced CRF patients often fail

or unwilling to perform Cardiac autonomic reflex test (CART), such as Valsalva which needs patient's effort. HRV in such patients is an easy way to study cardiac ANS. The short-term gathering (5 minutes) of Heart Rate signals is a well-known and practical approach to study HRV at any setting (clinic or lab)7,13.

HRV is the difference in duration (in ms) of RR interval between adjacent heart beats. HRV shows two types of parameters. "Time domain parameters" and "frequency domain parameters". Time domain indices of HRV measure the inter beat interval variability. Frequency domain indices mainly considers the power which is the signal energy found within a frequency band. This makes the power spectral analysis a quantitative marker of autonomic function of the heart. In frequency domain parameters, the effect on sympathetic and parasympathetic arms of ANS can be studied separately through Low frequency (LF) and high frequency (HF) variables and is more elaborative. The changes in HRV parameters with CKD duration was assessed in the present study. The present study was part of the larger study. The objective of present study was to compare the coefficient of correlation (r-value) of various HRV parameters with CKD duration as HRV is a marker of autonomic activity. The hypothesis of the present study was "HRV decrease with CKD duration." 6,9

Materials and Methods:

This cross-sectional study was conducted in the Autonomic Nervous System (ANS) lab of Department of physiology in collaboration with the Medicine department at King George's Medical University, Lucknow, Uttar Pradesh (KGMU). The study was carried on 92 CKD outpatients enrolled at the Outpatient Department (OPD) of General Medicine of King George's Medical University at Lucknow, over a period of one year from April 2019 to March 2020. The study protocol was approved by the Institutional ethical committee of KGMU. The IEC no. is 96th ECM II B-thesis/P23. Informed written consent was obtained from all participants8,12

I**NCLUSION CRITERIA:** CKD patients both male and female aged between 18 to 70 years old enrolled at KGMU Medicine OPD.

Exclusion Criteria: Subject with previous cardiac events and diabetic patients, as these conditions may affect HRV parameters.

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Sample size Calculation: Sample size calculated by formula (As the population in question is infinite population)

P = 6% = .06

Q = 1-p = 1-0.06 = 0.94

n =

1.96 X 1.96 X 0.06 X 0.94

0.0025

= 87

z= Z score 1.96 for 95% confidence level

p= prevalence of CRF (. According to SEEK (Screening and Early Evaluation of Kidney Disease) study, the prevalence of CRF ~ 6% having CKD stage 3 or worse (eGFR less than 60ml per minute) per 1.73 mt/sq (CKD stages using NKF-KDOQI guidelines)) in Indian population.

Q=1- P

d= .05 (Margin of error or confidence interval.)

type1 error =5% corresponds to 95% confidence interval

Random sampling was done to choose the study population.

The calculated sample size was 87 subjects.

Pro Lab Chart data analysis software (Power Lab 8 Pro) of AD instrument was used for HRV processing and analysis.

Data Collection: Once the subjects were selected, informed written consent was obtained from all the participants. They were instructed to report to the Autonomic Nervous System (ANS) research lab of the department of physiology KGMU, at around 10 AM, with instructions to have breakfast before 8 AM and to avoid coffee or tea for at least two hours prior to the test. A detailed history, general, and systemic examination of the subjects were conducted to follow the inclusion/exclusion criteria. The anthropometric parameters such as height, weight, and Body Mass Index (BMI) were recorded

For HRV measurement, patients were asked to rest for 10 minutes before the recording of electrocardiography (ECG). A lead II ECG was recorded for 5 minutes. (Table/Fig1, Table/Fig 2) 17,18,

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STUDY PARAMETERS

HRV is studied under Time domain and frequency domain parameters.

Overview of HRV time-domain parameters. SDNN or SDRR is the Standard deviation of NN intervals**.** SDANN is the Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording. SDNN index is the Mean of the standard deviations of all the NN intervals for each 5 minutes. PNN50 % is the Percentage of successive RR intervals that differ by more than 50 ms HR Max − HR Min bpm Average difference between the highest and lowest heart rates during each respiratory cycle RMSSD is the Root mean square of successive RR interval differences

Overview of HRV frequency domain parameters measures.

Total Power (T.P.) is the Overall potency of cardiac modulation. LF power ms2 is the Absolute power of the low-frequency band. LF power (%) is the % Relative power of the low-frequency band. LF power (nu) is the Relative power of the low-frequency band in normal units (normal units =LF/(TP-VLF)/ 100). HF power ms2 is the absolute power of the highfrequency band. HF power (%) is the % Relative power of the High-frequency band HF power (nu) is the Relative power of the high frequency (HF/(TP-VLF)/ 100)

Study Procedure

Room made dark silent and temperature maintained at 20-260 Celsius. Recordings measured between 9 am to 1 pm to prevent effect of diurnal variation. Consumption of any hot or cold drinks strictly prohibited before test. Subject rested for at least 10 minutes before starting the recording. All the recordings done in lying down position for 5 minutes. Subject made calm No talking allowed during test.

HRV was recorded with a lead II ECG. Five leads were used to record ECG. After recording, we select HRV module whole channel and no ectopic beat in setting. The ECG signals were

continuously amplified, digitalised and stored in the computer for five minutes for offline analysis. Only cycles in which beads had normal morphological characteristics were used for analysis. the computer was confirming that there was no ectopic beats or noises. The NN interval were computed and fed to effective software for analysis (time domain and frequency domain).13

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Statistical Analysis

To analyse the correlation of CKD duration with HRV parameters the Pearson's correlation coefficient "r" value was calculated for HRV parameters with respect to CKD Duration. The values range from -1 to +1. Correlation matrix of HRV parameters was done. The outcome measures for various variables were summarized as Mean±SD and proportion & percentages depending on the nature of the variable. Data was analyzed using Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL) and MS-Excel. P-value < 0.05 was taken to be significant at 95% confidence level.

RESULTS

A total of 92 CRF patients with a mean age of 40.71 years (±13.21) were included in this study. The Baseline characteristic of all participants was obtained at time of enrolment. This included age, sex BMI, D.M., exercise, addiction, lifestyle, socioeconomic status, CKD Duration was recorded. The mean duration of CKD of cases was 2.62 years. (±1.58) with a minimum of 0.33 years and maximum of 6.80 years of CKD.

Table 1/Fig-1: Demographic Data (n=92)

Variable Mean (SD)/Min./Max. or Frequency (%)

Gender

Female 33 (35.9%)

Male 59 (64.1%)

TOTAL 92 (100%)

Mean SD Min. Max

Age (yr) 40.71 13.21 18.00 70.00

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BMI 20.61 2.97 15.38 28.26

CKD (yr) 2.62 1.58 0.33 6.80

Table/Fig -1: Baseline characteristic of study subjects

.

The r (coefficient of correlation) values of all heart rate variability parameters with respect to duration of CKD were calculated. (Table/fig- 2 and 3) and (Table/figure-4). The Correlation matrix of HRV Parameters was also calculated. (Table/fig. 5 and 6).

Correlation of time domain hrv parameters with CKD duration

All the time domain parameters show negative correlation (- r) with CKD duration. Increase in duration of CKD causes all the time domain parameters of HRV to decrease. This decrease is significant for average RR median RR SDSD, RMSSD and PRR50, Showing ANS dysfunction.

Variable

(time domain hrv parameters)

Duration

r-value p-value

aver. RR (ms) -.238 **0.022**

Med.-RR (ms) -.230 **0.027**

SDRR (ms) -.192 0.067

CVRR -.121 0.251

Aver. Rate (BPM) .277 **0.007**

SD Rate (BPM) -.063 0.552

SDSD (ms) -.254 **0.014**

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RMSSD (ms) -.258 **0.013**

pRR50(%) -.234 **0.025**

Table /Fig 2: Correlation of CKD Duration with Time Domain Heart rate variability parameters

"p- value <0.05 was considered as significant

RR: RR interval; SDRR is the Standard deviation of RR intervals**:** PRR50 % is the Percentage of successive RR intervals that differ by more than 50 ms HR Max − HR Min bpm Average difference between the highest and lowest heart rates during each respiratory cycle RMSSD is the Root mean square of successive RR interval differences

Correlation of Frequency domain parameters with CKD duration

The TP r value is -0.155 but the P value is insignificant(P>.05). The relative values LF (%) and LF (nu) shows positive (+ r) which is significant. (P<0.05). The high frequency (HF) values show negative (-r) value which is significant both in absolute and in relative values. The LF/HF ratio denotes sympathovagal balance. The r value is (+0.543) and most significant(P<0.05)

Table /Fig 3: Correlation of CKD Duration with Frequency Domain Heart rate variability parameters

Variable

(frequency domain hrv parameters)

Duration

r-value p-value

TP -.155 **.140**

LF (ms2) -.059 **.575**

HF (ms2) -.326 **.002**

(%)-LF .343 **.001**

(%)-HF -.074 **.484**

LF(nu) .405 **.000**

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HF(nu) -.386 **.000**

LF/HF .543 **.000**

Table/Fig 3: Correlation of CKD Duration with Frequency Domain Heart rate variability parameters

Total Power (T.P.) is the Overall potency of cardiac modulation: LF power ms2 is the Absolute power of the low-frequency band: LF power (%) is the % Relative power of the low-frequency band: LF power (nu) is the Relative power of the low-frequency band in normal units (normal units =LF/(TP-VLF)/ 100): HF power ms2 is the Absolute power of the high-frequency band: HF power (%) is the % Relative power of the High-frequency band: HF power (nu) is the Relative power of the high frequency (HF/(TP-VLF)/ 100)

All the time domain parameters show negative correlation with CKD duration (r value in negative) this means as the duration of CKD increases all the time domain parameters of HRV decrease. this decrease is significant for average RR, median RR, SDSD, RMSSD and pRR50. Similarly, all the HF parameters of frequency domain parameters decreased meaning parasympathetic function decrease with CKD duration. LF parameters values increase meaning as the CKD duration increases there is relative increased sympathetic component of sympathovagal balance.

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Table/Figure 4: Correlation of CKD Duration with Heart rate variability Parameters

Table 5: Correlation Matrix of Time Domain HRV parameters

aver.R

R

Med.-

RR

SDRR CVRR

Aver.

Rate

SD

Rate

SDSD

RMSS

D

pRR5

0

FREQDom.

PLF(

ms2)

r-value 1

p-value

r-value .999 1

p-value **.000**

r-value .344 .333 1

p-value **.000 .000**

r-value -.086 -.087 .053 1

p-value .247 .239 .477

r-value -.904 -.900 -.353 -.069 1

p-value **.000 .000 .000** .351

r-value -.024 -.031 .501 .411 -.294 1

p-value .745 .674 **.000 .000 .000**

r-value .333 .322 .903 -.084 -.228 .228 1

p-value **.000 .000 .000** .258 **.002 .002**

r-value .330 .319 .941 .038 -.353 .531 .936 1

p-value **.000 .000 .000** .605 **.000 .000 .000**

r-value .452 .446 .663 .127 -.429 .362 .584 .626 1

p-value **.000 .000 .000** .085 **.000 .000 .000 .000**

r-value .472 .465 .777 .116 -.417 .313 .680 .676 .760 1

p-value **.000 .000 .000** .117 **.000 .000 .000 .000 .000**

r-value .351 .342 .751 .053 -.324 .377 .620 .634 .730 .853 p-value **.000 .000 .000** .474 **.000 .000 .000 .000 .000 .000**

r-value .474 .478 .741 -.009 -.426 .332 .658 .696 .804 .706 .720 p-value **.000 .000 .000** .908 **.000 .000 .000 .000 .000 .000 .000**

FREQDom.

PLF(ms2)

PHF(ms2)

CVRR

Aver.Rate

SD Rate

SDSD

RMSSD

pRR50

Pearson's

Correlation

aver.RR

(ms)

Med.-RR

SDRR

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The correlation matrix shows that LF and HF relative values(nu) are strongly correlated in negative (r= -0.952) this means that as the high frequency or parasympathetic power decreases there is correspondent increase in low frequency power and vice versa so whenever there is decrease in parasympathetic arm there is relative increase in sympathetic arm.

variables

Values Total

Power

(TP)

Absolute

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LF (ms2)

Absolute

HF

(ms2)

P(%)

LF

P(%)

HF

P(nu)

LF

P(nu)

HF

LF/HF

Total

Power

(TP)

r-

Value

1

pvalue

Absolute

LF (ms2)

r-

Value

.853 1

pvalue

.000

Absolute

HF (ms2)

r-

Value

.706 .720 1

pvalue

.000 .000

Power(%)

LF

r-

Value

-0.42 .118 -.214 1

pvalue

.568 .110 .004

Power(%)

HF

r-

Value

.230 .427 .034 .029 1

pvalue

.002 .000 .647 .700

Power(nu)

LF

r-

Value

-.233 -.069 -.383 .699 .065 1

pvalue

.001 .350 .000 .000 .378

P(nu)

HF

r-

Value

.202 .048 .344 -.682 -.067 -.952 1

pvalue

.006 .522 .000 .000 .363 .000

LF/HF r-

Value

-.208 -.059 -.283 .619 .075 .829 -.851 1

pvalue

.005 .425 .000 .000 .314 .000 .000

Table 6: Correlation Matrix of Frequency Domain HRV parameters

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DISCUSSION:

The present study was done to assess the correlation between CKD duration and HRV parameters. Among the time domain variables of resting HRV, a high variability of RR interval is considered an index of the ability of the cardiovascular system and ANS to cope with environmental challenges. RMSSD reflects the vagal modulation of heart rate and is therefore an important short-term measure of parasympathetic drive. The percentage of adjacent NN intervals that differ from each other by more than 50 ms, known as pNN50, is closely related to parasympathetic activity.7,8

In table/Fig.2 different time domain parameters showed negative correlation (- r) with CKD duration. Inference is increase in duration of CKD decreases time domain parameters leading to less variability in HRV. This decrease is significant for average RR median RR SDSD RMSSD and PRR50, Showing ANS imbalance. 9

The r values are in lower range (r value less than 0.3) implying weak correlation. The Correlation matrix shows a high positive correlation between SDRR and TP (r value 0.777) which is highly significant. For this reason, TP is considered as Frequency equivalent of SDRR time domain.

Time domain parameters could not separately differentiate effect on sympathetic and parasympathetic arms of Autonomic Nervous System. The frequency domain parameters can throw light separately on sympathetic and parasympathetic arm of ANS showing differential

change and can be understood more clearly by studying correlation matrix between the HRV parameters. Total power (TP) represents the total variance. influencing the LF and HF values. To minimise this effect, normalised HF and LF values are used.

Table/Fig. 3 shows correlation of CKD duration with frequency domain HRV parameters, The TP r value is -0.155 and the P value is insignificant(P>0.05). The table/Fig. 6 of correlation matrix shows that this TP is highly positively correlated with both LF and HF (ABSOLUTE POWER) since the total power (TP) is sum of all the changes (modulations) TP=LF +HF+V.L.F. (which are in different directions).

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The r value of absolute Frequency of LF parameter is negative though it is non-significant. Though it gives a vital clue that the low frequency LF arm which denotes sympathetic impulse may also decrease with CKD duration in absolute values.

In relative values that is LF (%) and relative value LF (nu) the value of LF parameter shows positive correlation (+ r) with CKD duration. As CKD duration increases there is relative increased sympathetic drive leading to sympathovagal imbalance which is significant. (P<0.05). The high frequency (HF) values show negative r value which is significant both in absolute values and in relative values implying decreased parasympathetic drive with increased CKD duration.

The correlation matrix shows that LF and HF relative values(nu) are strongly correlated in negative (r= -.952) this means that as the high frequency or parasympathetic power decreases there is correspondent increase in low frequency power and vice versa so whenever there is decrease in parasympathetic arm there is relative increase in sympathetic arm.

The LF/HF ratio which denotes sympathovagal balance the r value is (+0.543) which is in medium range and is positive and it's significant(P<0.05) this means that LF/HF ratio is most strongly and positively correlated with CKD duration.

LF/HF ratio denotes sympathovagal balance meaning there is definite decrease in sympathovagal balance with CKD duration. The correlation matrix shows that LF/HF ratio is highly negatively correlated with HF (r = -0.851) and highly positively correlated with low

frequency LF (r = +0.829). It clears that with CKD duration there is decrease in parasympathetic impulse and relative increase in sympathetic impulse.

The proper functioning of autonomic nervous system is affected by many factors such as age, malnutrition, presence of diseases, duration of the disease, creations of toxic substances in the body and other factors. Autonomic nervous system comprises of sympathetic and parasympathetic arm which are finely balanced. The parasympathetic supply to heart is vagus nerve which is long while the sympathetic nerve to heart is shorter. Vagus is the longest Autonomic nerve in the body so the parasympathetic component of HRV is more affected by toxins and other detrimental factors than the sympathetic component resulting in sympathovagal imbalance denoted by deranged LF/HF ratio favouring relatively increased sympathetic activity and reduced parasympathetic function29.

Sympathetic and parasympathetic nerves activity are difficult to be measured directly except invasive method such as recording of muscle sympathetic-nerve activity (MSNA).

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In our study both time domain and frequency domain parameters had inverse correlation with CKD duration. The “r” coefficient of correlation value is less than 3 in all time domain variables It is a weak correlation. The reason may be because the time domain analysis cannot differentiate between sympathetic and parasympathetic arm which are in opposite direction. LF (nu) values are +0.405 and $P<0.05$. HF (nu) value is -0.386 and it is also significant ($P<0.05$) which shows that the sympathetic system and parasympathetic system are separately affected by the CKD duration. There is relative increase in low frequency and decrease in high frequency26. So, the frequency domain parameters give a better view of effect of CKD duration on heart rate variability parameters48,49.

The r value of +0.543 of LF/HF is highly significant. Many studies show that LF /HF ratio is an independent Marker of rapid CKD deterioration.

The reason of decreasing HRV variability parameters with CKD duration are many. it may be due to uremic toxins which directly damage the Axon by inhibiting nerve fibre enzymes required for maintenance of energy production. These unknown neurotoxin compounds enter

the endoneural space and cause hydro electrolytic changes producing shrinkage or expansion of endoneural space.31

Sympathetic nerve innervates kidney directly and affects tubular and vascular function of glomeruli. Their overactivity can lead to renal damage through increasing activity of reninangiotensin system and impaired vascular autoregulation due to decreased nitric oxide synthesis, sodium retention with hypovolemia and high blood pressure.32

Additionally depressed parasympathetic activity results in renal damage caused by type 2 cardiorenal syndrome. Improving autonomic dysfunction maybe beneficial for the preservation of renal function.

LIMITATIONS

The speed of progression of CKD with time has individual variation. Apart from associated ANS dysfunction; noncompliance to treatment, poor socioeconomic condition, effect of dialysis, associated HTN, effect of drugs all affect the HRV parameters. Heart Rate Variability is not a univariate association but multivariate association. More study is needed for more direct correlation. In further studies other factors may be taken into account.

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CONCLUSION:

Our study provides evidence that CKD duration and HRV are correlated. The Heart Rate variability decreases with CKD duration. Frequency domain parameters are more significantly correlated with the duration of HRV than the time domain parameters because the effect on sympathetic (LF) and parasympathetic arms (HF) of ANS shows separately in frequency domain parameters. The ratio of LF/ HF is most strongly and significantly associated which CKD duration.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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CORRELATION OF HEART RATE VARIABILITY PARAMETERS

WITH CHRONIC KIDNEY DISEASE DURATION

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ABSTRACT

Introduction- Autonomic dysfunction commonly presents with Chronic Renal Failure. Its pathophysiology is obscure. Autonomic dysfunction contributes to cardiovascular morbidity and mortality and can be evaluated with heart rate variability (HRV).

AIM- To evaluate the correlation of chronic kidney disease duration with Heart Rate Variability parameters to better understand autonomic dysfunction in chronic renal failure

Materials and Method

The present cross sectional observational study was carried out in Department of Physiology at King George's Medical University, Lucknow UP from April 2019 to march 2020, on 92 patients of chronic kidney disease. Heart rate variability of the subjects was assessed from five-minute digitalized Electrocardiography. The Coefficient of correlation (r value) of heart rate variability parameters (both time and frequency domain) with respect to duration of CKD

were calculated. The data was analyzed for changes in HRV parameters in relation to CKD duration.

Results

The analysis showed Time domain HRV parameters had negative Coefficient of correlation (-r value) with respect to CKD duration indicating deteriorating autonomic balance with CKD

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duration. Frequency domain parameters showed differential change. The relative low frequency (LF) component showed + r value. The high frequency (HF) showed -r values. The LF mainly corresponds to sympathetic and HF Parasympathetic arm of Autonomic Nervous System. The result emphasize that CKD duration causes relative increased sympathetic and decreased parasympathetic effect (sympathovagal imbalance).

Conclusion:

This study showed that CKD duration have negative impact on HRV parameters implying deterioration of autonomic system.

Keywords: Heart Rate Variability, Chronic kidney disease, Chronic renal failure, sympathetic arm, parasympathetic arm.

INTRODUCTION

Chronic Kidney Disease (CKD) is a scourge of modern times. Its incidence and prevalence is increasing. About 860 million people are now suffering from CKD. The exact etiopathology of CKD and its complications is still obscure1.

CKD has been divided into five stages based on Glomerular Filtration Rate (GFR).

Stage 5 CKD is End-stage renal disease (ESRD) needing dialysis or Renal transplant. Moderate to severe CKD (stage 3–5) is associated with a significantly higher risk of cardiovascular morbidity and mortality. Majority of CRF patients succumb before reaching the last stage (ESRD). Cardiovascular system (CVS) complications are one of the main reasons of morbidity and mortality in these CRF patients. The etiopathology of CVS complications in CKD is unclear. 2,3,15,16

“Why and how CKD patients develop CVS consequences?” is a clinically significant question.

Autonomic dysfunction in the form of relatively increased sympathetic and decreased parasympathetic arm of Autonomic Nervous System (ANS) is a frequent accompaniment of CRF which may contribute to comorbid cardiovascular morbidity and mortality 4,5,10,11 The underlying mechanism of autonomic changes in CKD patients remains elusive. Correlation of Autonomic Nervous system (ANS) changes with CKD duration may be an important clinical parameter. Heart Rate Variability (HRV) derived from digitalized ECG signals is an easy way to study ANS. It is non-invasive and easily applied technique. It does not need patient's effort which may be cumbersome to get. Advanced CRF patients often fail

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or unwilling to perform Cardiac autonomic reflex test (CART), such as Valsalva which needs patient's effort. HRV in such patients is an easy way to study cardiac ANS. The short-term gathering (5 minutes) of Heart Rate signals is a well-known and practical approach to study HRV at any setting (clinic or lab)7,13.

HRV is the difference in duration (in ms) of RR interval between adjacent heart beats. HRV shows two types of parameters. "Time domain parameters" and "frequency domain parameters". Time domain indices of HRV measure the inter beat interval variability. Frequency domain indices mainly considers the power which is the signal energy found within a frequency band. This makes the power spectral analysis a quantitative marker of autonomic function of the heart. In frequency domain parameters, the effect on sympathetic and parasympathetic arms of ANS can be studied separately through Low frequency (LF) and high frequency (HF) variables and is more elaborative. The changes in HRV parameters with CKD duration was assessed in the present study. The present study was part of the larger study. The objective of present study was to compare the coefficient of correlation (r-value) of various HRV parameters with CKD duration as HRV is a marker of autonomic activity. The hypothesis of the present study was "HRV decrease with CKD duration." 6,9

Materials and Methods:

This cross-sectional study was conducted in the Autonomic Nervous System (ANS) lab of Department of physiology in collaboration with the Medicine department at King George's

Medical University, Lucknow, Uttar Pradesh (KGMU). The study was carried on 92 CKD outpatients enrolled at the Outpatient Department (OPD) of General Medicine of King George's Medical University at Lucknow, over a period of one year from April 2019 to March 2020. The study protocol was approved by the Institutional ethical committee of KGMU. The IEC no. is 96th ECM II B-thesis/P23. Informed written consent was obtained from all participants8,12

I**NCLUSION CRITERIA:** CKD patients both male and female aged between 18 to 70 years old enrolled at KGMU Medicine OPD.

Exclusion Criteria: Subject with previous cardiac events and diabetic patients, as these conditions may affect HRV parameters.

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Sample size Calculation: Sample size calculated by formula (As the population in question is infinite population)

P = 6% = .06

Q = 1-p = 1-0.06 = 0.94

n =

1.96 X 1.96 X 0.06 X 0.94

0.0025

= 87

z= Z score 1.96 for 95% confidence level

p= prevalence of CRF (. According to SEEK (Screening and Early Evaluation of Kidney Disease) study, the prevalence of CRF ~ 6% having CKD stage 3 or worse (eGFR less than 60ml per minute) per 1.73 mt/sq (CKD stages using NKF-KDOQI guidelines)) in Indian population.

Q=1- P

d= .05 (Margin of error or confidence interval.)

type1 error =5% corresponds to 95% confidence interval

Random sampling was done to choose the study population.

The calculated sample size was 87 subjects.

Pro Lab Chart data analysis software (Power Lab 8 Pro) of AD instrument was used for HRV processing and analysis.

Data Collection: Once the subjects were selected, informed written consent was obtained from all the participants. They were instructed to report to the Autonomic Nervous System (ANS) research lab of the department of physiology KGMU, at around 10 AM, with instructions to have breakfast before 8 AM and to avoid coffee or tea for at least two hours prior to the test. A detailed history, general, and systemic examination of the subjects were conducted to follow the inclusion/exclusion criteria. The anthropometric parameters such as height, weight, and Body Mass Index (BMI) were recorded

For HRV measurement, patients were asked to rest for 10 minutes before the recording of electrocardiography (ECG). A lead II ECG was recorded for 5 minutes. (Table/Fig1, Table/Fig 2) 17,18,

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STUDY PARAMETERS

HRV is studied under Time domain and frequency domain parameters.

Overview of HRV time-domain parameters. SDNN or SDRR is the Standard deviation of NN intervals**.** SDANN is the Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording. SDNN index is the Mean of the standard deviations of all the NN intervals for each 5 minutes. PNN50 % is the Percentage of successive RR intervals that differ by more than 50 ms HR Max − HR Min bpm Average difference between the highest and lowest heart rates during each respiratory cycle RMSSD is the Root mean square of successive RR interval differences

Overview of HRV frequency domain parameters measures.

Total Power (T.P.) is the Overall potency of cardiac modulation. LF power ms2 is the Absolute power of the low-frequency band. LF power (%) is the % Relative power of the low-frequency band. LF power (nu) is the Relative power of the low-frequency band in normal units (normal units =LF/(TP-VLF)/ 100). HF power ms2 is the absolute power of the highfrequency

band. HF power (%) is the % Relative power of the High-frequency band HF power (nu) is the Relative power of the high frequency (HF/(TP-VLF)/ 100)

Study Procedure

Room made dark silent and temperature maintained at 20-260 Celsius. Recordings measured between 9 am to 1 pm to prevent effect of diurnal variation. Consumption of any hot or cold drinks strictly prohibited before test. Subject rested for at least 10 minutes before starting the recording. All the recordings done in lying down position for 5 minutes. Subject made calm No talking allowed during test.

HRV was recorded with a lead II ECG. Five leads were used to record ECG. After recording, we select HRV module whole channel and no ectopic beat in setting. The ECG signals were continuously amplified, digitalised and stored in the computer for five minutes for offline analysis. Only cycles in which beads had normal morphological characteristics were used for analysis. the computer was confirming that there was no ectopic beats or noises. The NN interval were computed and fed to effective software for analysis (time domain and frequency domain).13

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Statistical Analysis

To analyse the correlation of CKD duration with HRV parameters the Pearson's correlation coefficient "r" value was calculated for HRV parameters with respect to CKD Duration. The values range from -1 to +1. Correlation matrix of HRV parameters was done. The outcome measures for various variables were summarized as Mean±SD and proportion & percentages depending on the nature of the variable. Data was analyzed using Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL) and MS-Excel. P-value < 0.05 was taken to be significant at 95% confidence level.

RESULTS

A total of 92 CRF patients with a mean age of 40.71 years (±13.21) were included in this study. The Baseline characteristic of all participants was obtained at time of enrolment. This included age, sex BMI, D.M., exercise, addiction, lifestyle, socioeconomic status, CKD Duration was

recorded. The mean duration of CKD of cases was 2.62 years. (±1.58) with a minimum of 0.33 years and maximum of 6.80 years of CKD.

Table 1/Fig-1: Demographic Data (n=92)

Variable Mean (SD)/Min./Max. or Frequency (%)

Gender

Female 33 (35.9%)

Male 59 (64.1%)

TOTAL 92 (100%)

Mean SD Min. Max

Age (yr) 40.71 13.21 18.00 70.00

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BMI 20.61 2.97 15.38 28.26

CKD (yr) 2.62 1.58 0.33 6.80

Table/Fig -1: Baseline characteristic of study subjects

.

The r (coefficient of correlation) values of all heart rate variability parameters with respect to duration of CKD were calculated. (Table/fig- 2 and 3) and (Table/figure-4). The Correlation matrix of HRV Parameters was also calculated. (Table/fig. 5 and 6).

Correlation of time domain hrv parameters with CKD duration

All the time domain parameters show negative correlation (- r) with CKD duration. Increase in duration of CKD causes all the time domain parameters of HRV to decrease. This decrease is significant for average RR median RR SDSD, RMSSD and PRR50, Showing ANS dysfunction.

Variable

(time domain hrv parameters)

Duration

r-value p-value

aver. RR (ms) -.238 **0.022**

Med.-RR (ms) -.230 **0.027**

SDRR (ms) -.192 0.067

CVRR -.121 0.251

Aver. Rate (BPM) .277 **0.007**

SD Rate (BPM) -.063 0.552

SDSD (ms) -.254 **0.014**

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RMSSD (ms) -.258 **0.013**

pRR50(%) -.234 **0.025**

Table /Fig 2: Correlation of CKD Duration with Time Domain Heart rate variability parameters

"p- value <0.05 was considered as significant

RR: RR interval; SDRR is the Standard deviation of RR intervals**:** PRR50 % is the Percentage of successive RR intervals that differ by more than 50 ms HR Max − HR Min bpm Average difference between the highest and lowest heart rates during each respiratory cycle RMSSD is the Root mean square of successive RR interval differences

Correlation of Frequency domain parameters with CKD duration

The TP r value is -0.155 but the P value is insignificant(P>.05). The relative values LF (%) and LF (nu) shows positive (+ r) which is significant. (P<0.05). The high frequency (HF) values show negative (-r) value which is significant both in absolute and in relative values. The LF/HF ratio denotes sympathovagal balance. The r value is (+0.543) and most significant(P<0.05)

Table /Fig 3: Correlation of CKD Duration with Frequency Domain Heart rate variability parameters

Variable

(frequency domain hrv parameters)

Duration

r-value p-value

TP -.155 **.140**

LF (ms2) -.059 **.575**

HF (ms2) -.326 **.002**

(%)-LF .343 **.001**

(%)-HF -.074 **.484**

LF(nu) .405 **.000**

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HF(nu) -.386 **.000**

LF/HF .543 **.000**

Table/Fig 3: Correlation of CKD Duration with Frequency Domain Heart rate variability parameters

Total Power (T.P.) is the Overall potency of cardiac modulation: LF power ms2 is the Absolute power of the low-frequency band: LF power (%) is the % Relative power of the low-frequency band: LF power (nu) is the Relative power of the low-frequency band in normal units (normal units =LF/(TP-VLF)/ 100): HF power ms2 is the Absolute power of the high-frequency band: HF power (%) is the % Relative power of the High-frequency band: HF power (nu) is the Relative power of the high frequency (HF/(TP-VLF)/ 100)

All the time domain parameters show negative correlation with CKD duration (r value in negative) this means as the duration of CKD increases all the time domain parameters of HRV decrease. this decrease is significant for average RR, median RR, SDSD, RMSSD and pRR50. Similarly, all the HF parameters of frequency domain parameters decreased meaning parasympathetic function decrease with CKD duration. LF parameters values increase meaning as the CKD duration increases there is relative increased sympathetic component of sympathovagal balance.

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Table/Figure 4: Correlation of CKD Duration with Heart rate variability Parameters

Table 5: Correlation Matrix of Time Domain HRV parameters

aver.R

R

Med.-

RR

SDRR CVRR

Aver.

Rate

SD

Rate

SDSD

RMSS

D

pRR5

0

FREQDom.

PLF(

ms2)

r-value 1

p-value

r-value .999 1

p-value **.000**

r-value .344 .333 1

p-value **.000 .000**

r-value -.086 -.087 .053 1

p-value .247 .239 .477

r-value -.904 -.900 -.353 -.069 1

p-value **.000 .000 .000** .351

r-value -.024 -.031 .501 .411 -.294 1

p-value .745 .674 **.000 .000 .000**

r-value .333 .322 .903 -.084 -.228 .228 1

p-value **.000 .000 .000** .258 **.002 .002**

r-value .330 .319 .941 .038 -.353 .531 .936 1

p-value **.000 .000 .000** .605 **.000 .000 .000**

r-value .452 .446 .663 .127 -.429 .362 .584 .626 1

p-value **.000 .000 .000** .085 **.000 .000 .000 .000**

r-value .472 .465 .777 .116 -.417 .313 .680 .676 .760 1

p-value **.000 .000 .000** .117 **.000 .000 .000 .000 .000**

r-value .351 .342 .751 .053 -.324 .377 .620 .634 .730 .853 p-value **.000 .000 .000** .474 **.000 .000 .000 .000 .000 .000**

r-value .474 .478 .741 -.009 -.426 .332 .658 .696 .804 .706 .720 p-value **.000 .000 .000** .908 **.000 .000 .000 .000 .000 .000 .000**

FREQDom.

PLF(ms2)

PHF(ms2)

CVRR

Aver.Rate

SD Rate

SDSD

RMSSD

pRR50

Pearson's

Correlation

aver.RR

(ms)

Med.-RR

SDRR

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The correlation matrix shows that LF and HF relative values(nu) are strongly correlated in negative (r= -0.952) this means that as the high frequency or parasympathetic power decreases there is correspondent increase in low frequency power and vice versa so whenever there is decrease in parasympathetic arm there is relative increase in sympathetic arm.

variables

Values Total

Power

(TP)

Absolute

LF (ms2)

Absolute

HF

(ms2)

P(%)

LF

P(%)

HF

P(nu)

LF

P(nu)

HF

LF/HF

Total

Power

(TP)

r-

Value

1

pvalue

Absolute

LF (ms2)

r-

Value

.853 1

pvalue

.000

Absolute

HF (ms2)

r-

Value

.706 .720 1

pvalue

.000 .000

Power(%)

LF

r-

Value

-0.42 .118 -.214 1

pvalue

.568 .110 .004

Power(%)

HF

r-

Value

.230 .427 .034 .029 1

pvalue

.002 .000 .647 .700

Power(nu)

LF

r-

Value

-.233 -.069 -.383 .699 .065 1

pvalue

.001 .350 .000 .000 .378

P(nu)

HF

r-

Value

.202 .048 .344 -.682 -.067 -.952 1

pvalue

.006 .522 .000 .000 .363 .000

LF/HF r-

Value

-.208 -.059 -.283 .619 .075 .829 -.851 1

pvalue

.005 .425 .000 .000 .314 .000 .000

Table 6: Correlation Matrix of Frequency Domain HRV parameters

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DISCUSSION:

The present study was done to assess the correlation between CKD duration and HRV parameters. Among the time domain variables of resting HRV, a high variability of RR interval is considered an index of the ability of the cardiovascular system and ANS to cope with environmental challenges. RMSSD reflects the vagal modulation of heart rate and is therefore an important short-term measure of parasympathetic drive. The percentage of adjacent NN intervals that differ from each other by more than 50 ms, known as pNN50, is closely related to parasympathetic activity.7,8

In table/Fig.2 different time domain parameters showed negative correlation (- r) with CKD

duration. Inference is increase in duration of CKD decreases time domain parameters leading to less variability in HRV. This decrease is significant for average RR median RR SDSD RMSSD and PRR50, Showing ANS imbalance. 9

The r values are in lower range (r value less than 0.3) implying weak correlation. The Correlation matrix shows a high positive correlation between SDRR and TP (r value 0.777) which is highly significant. For this reason, TP is considered as Frequency equivalent of SDRR time domain.

Time domain parameters could not separately differentiate effect on sympathetic and parasympathetic arms of Autonomic Nervous System. The frequency domain parameters can throw light separately on sympathetic and parasympathetic arm of ANS showing differential change and can be understood more clearly by studying correlation matrix between the HRV parameters. Total power (TP) represents the total variance. influencing the LF and HF values. To minimise this effect, normalised HF and LF values are used.

Table/Fig. 3 shows correlation of CKD duration with frequency domain HRV parameters, The TP r value is -0.155 and the P value is insignificant(P>0.05). The table/Fig. 6 of correlation matrix shows that this TP is highly positively correlated with both LF and HF (ABSOLUTE POWER) since the total power (TP) is sum of all the changes (modulations) TP=LF +HF+V.L.F. (which are in different directions).

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The r value of absolute Frequency of LF parameter is negative though it is non-significant. Though it gives a vital clue that the low frequency LF arm which denotes sympathetic impulse may also decrease with CKD duration in absolute values.

In relative values that is LF (%) and relative value LF (nu) the value of LF parameter shows positive correlation (+ r) with CKD duration. As CKD duration increases there is relative increased sympathetic drive leading to sympathovagal imbalance which is significant. (P<0.05). The high frequency (HF) values show negative r value which is significant both in absolute values and in relative values implying decreased parasympathetic drive with increased CKD duration.

The correlation matrix shows that LF and HF relative values(nu) are strongly correlated in negative (r= -.952) this means that as the high frequency or parasympathetic power decreases there is correspondent increase in low frequency power and vice versa so whenever there is decrease in parasympathetic arm there is relative increase in sympathetic arm.

The LF/HF ratio which denotes sympathovagal balance the r value is (+0.543) which is in medium range and is positive and it's significant(P<0.05) this means that LF/HF ratio is most strongly and positively correlated with CKD duration.

LF/HF ratio denotes sympathovagal balance meaning there is definite decrease in sympathovagal balance with CKD duration. The correlation matrix shows that LF/HF ratio is highly negatively correlated with HF (r = -0.851) and highly positively correlated with low frequency LF (r = +0.829). It clears that with CKD duration there is decrease in parasympathetic impulse and relative increase in sympathetic impulse.

The proper functioning of autonomic nervous system is affected by many factors such as age, malnutrition, presence of diseases, duration of the disease, creations of toxic substances in the body and other factors. Autonomic nervous system comprises of sympathetic and parasympathetic arm which are finely balanced. The parasympathetic supply to heart is vagus nerve which is long while the sympathetic nerve to heart is shorter. Vagus is the longest Autonomic nerve in the body so the parasympathetic component of HRV is more affected by toxins and other detrimental factors than the sympathetic component resulting in sympathovagal imbalance denoted by deranged LF/HF ratio favouring relatively increased sympathetic activity and reduced parasympathetic function29.

Sympathetic and parasympathetic nerves activity are difficult to be measured directly except invasive method such as recording of muscle sympathetic-nerve activity (MSNA).

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In our study both time domain and frequency domain parameters had inverse correlation with CKD duration. The "r" coefficient of correlation value is less than 3 in all time domain variables It is a weak correlation. The reason may be because the time domain analysis cannot differentiate between sympathetic and parasympathetic arm which are in opposite direction.

LF (nu) values are +0.405 and P<0.05. HF (nu) value is -0.386 and it is also significant (P<0.05) which shows that the sympathetic system and parasympathetic system are separately affected by the CKD duration. There is relative increase in low frequency and decrease in high frequency26. So, the frequency domain parameters give a better view of effect of CKD duration on heart rate variability parameters48,49.

The r value of +0.543 of LF/HF is highly significant. Many studies show that LF /HF ratio is an independent Marker of rapid CKD deterioration.

The reason of decreasing HRV variability parameters with CKD duration are many. it may be due to uremic toxins which directly damage the Axon by inhibiting nerve fibre enzymes required for maintenance of energy production. These unknown neurotoxin compounds enter the endoneural space and cause hydro electrolytic changes producing shrinkage or expansion of endoneural space.31

Sympathetic nerve innervates kidney directly and affects tubular and vascular function of glomeruli. Their overactivity can lead to renal damage through increasing activity of reninangiotensin

system and impaired vascular autoregulation due to decreased nitric oxide

synthesis, sodium retention with hypovolemia and high blood pressure.32

Additionally depressed parasympathetic activity results in renal damage caused by type 2 cardiorenal syndrome. Improving autonomic dysfunction maybe beneficial for the preservation of renal function.

LIMITATIONS

The speed of progression of CKD with time has individual variation. Apart from associated ANS dysfunction; noncompliance to treatment, poor socioeconomic condition, effect of dialysis, associated HTN, effect of drugs all affect the HRV parameters. Heart Rate Variability is not a univariate association but multivariate association. More study is needed for more direct correlation. In further studies other factors may be taken into account.

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CONCLUSION:

Our study provides evidence that CKD duration and HRV are correlated. The Heart Rate

variability decreases with CKD duration. Frequency domain parameters are more significantly correlated with the duration of HRV than the time domain parameters because the effect on sympathetic (LF) and parasympathetic arms (HF) of ANS shows separately in frequency domain parameters. The ratio of LF/ HF is most strongly and significantly associated which CKD duration.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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