

# Autonomic System Evaluation in Non Diabetic ESRD

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## ABSTRACT

**Background:** Cardiac autonomic nervous system dysfunction (CAND) has been associated with an increased risk of ventricular arrhythmias and sudden death in patients with End Stage Renal Disease (ESRD). Autonomic dysregulation, which is common among patients on Hemodialysis even without diabetes, may contribute to dysrhythmias and an increased risk of sudden death in ESRD. **Objective of the study:** This study was done to find out cardiovascular autonomic system dysfunction in non-diabetic ESRD on maintenance hemodialysis (MHD) at a tertiary care center. **Method:** This was a single hospital based cross-sectional study. All non-diabetic ESRD patients of both genders doing maintenance hemodialysis in Shaikh Zayed Hospital from were included by nonprobability purposive sampling technique. Duration of study was 3 month. All 200 participants underwent five standard autonomic function tests as Heart rate (R-R interval) variation during deep breathing, immediate heart rate response to standing (30:15 ratio test), Heart rate response to Valsalva maneuver, Blood pressure response to standing and Blood pressure response to sustained hand grip. **Result:** The early cardiovascular autonomic nervous system dysfunction was found in 30% non-diabetic ESRD. There was significant difference in CAND in patient on longer duration of dialysis ( $p < 0.05$ ) but there were no significant differences of it among gender and age subgroup. **Conclusion:** In conclusion, cardiovascular autonomic dysfunction is not uncommon abnormalities on non-diabetic ESRD patients. Early recognition of the abnormality will prompt clinician predicting prognosis, treatment and better care of patients.

**Keywords:** Cardiovascular Autonomic nervous system dysfunction (CAND), Cardiovascular autonomic neuropathy (CAN), End Stage Renal disease (ESRD), Hemodialysis (HD), Autonomic nervous system tests

## INTRODUCTION

In patients with renal failure on hemodialysis (HD) cardiovascular disease is a major cause of death.<sup>1</sup> Bleyer et al. estimate approximately 42% of death on dialysis is of cardiovascular etiology, of which 22.4% are related to cardiac arrest or arrhythmia.<sup>2</sup> The autonomic nervous system (ANS) controls a variety of fundamental physiological processes in the human body including regulation of breathing, heart rate, blood pressure, temperature, gastrointestinal motility<sup>3</sup> bladder, and sexual function.<sup>4</sup> The autonomic and peripheral nervous system dysfunction is a well-known complication of chronic uremia and nearly 70 % of uremic patients fulfill electrodiagnostic criteria for polyneuropathy including autonomic neuropathy (AN). The

incidence of AN is as high as 46 % where as in non-diabetic ESRD patients AN was found in only 18 % of the patients.<sup>5</sup>

Cardiac autonomic nervous system dysfunction (CAND) leading to depressed arterial baroreflex sensitivity (BRS) has been associated with an increased risk of ventricular arrhythmias and sudden death in patients with CKD on maintenance hemodialysis (MHD).<sup>6</sup> Autonomic dysregulation, which is common among patients on HD even without diabetes, may contribute to dysrhythmias and an increased risk of sudden death in ESRD.<sup>7</sup>

This study will be helpful in determining the presence of CANS dysfunction in non-diabetic ESRD patient with simple tests describe below, so that precaution from sudden cardiac death can be

made, prognosis of patients can be counseled and better treatment could be considered to enhance the patient's care in ESRD patients on MHD economically. Moreover there are no local data so the study will be helpful to find the occurrence of CANS dysfunction in non-diabetic ESRD in local population.

## MATERIAL AND METHODS

This was a single hospital based cross-sectional study. All non-diabetic ESRD patients of both genders from age 18-55 years doing maintenance hemodialysis twice a week for more than 6 months coming to Shaikh Zayed Hospital, Lahore, Hemodialysis Unit having Blood urea nitrogen <70 mg/dl after 24 hour of last dialysis session giving informed consent were included by nonprobability purposive sampling technique. Duration of study was 3 month. Not giving informed consent, uncooperative, Fasting blood sugar level >126mg/dl, History of hematemesis, melena and Per rectal bleeding, Dehydrated (weight less than previous session dry weight), Obese BMI >30, Ischemic heart disease (new changes in ECG or ejection fraction <45%), Unstable patients, like presence of encephalopathy (GCS<15/15), hypotensive- (systolic blood pressure <90 mm Hg), respiratory distress (Respiratory rate >16/min), Abstinence from smoking and alcohol (<6weeks) as may effect CAND, Medication like beta blocker, alpha blocker, nitrate and diuretic within 12 hours were excluded. Sample size of 200 cases was calculated at 95% confidence interval with absolute precision of 5.5% and previous literature showing 18% occurrence of CAND in non-diabetic.<sup>5</sup>

All the data were entered into a predesigned performa. Name, age, gender and address were recorded. Weight of the patients was measured by standard weighing Machine, blood pressure was measured by mercurial sphygmomanometer and electrocardiogram by Schiller AT-1 device. All the participants had undergone five standard autonomic function tests:

### Heart rate (R-R interval) variation during deep breathing (HRVIE)

The patient was asked to breathe deeply at 6

breaths per minute for one minute in supine position. Continuous Electrocardiogram (ECG) was recorded throughout the deep breathing and onset of each inspiration and expiration was marked in ECG. The maximum R-R interval during expiration and minimum R-R interval during inspiration was measured with ruler and converted to beats per minute.<sup>8</sup> Heart rate variability during inspiration and expiration of more than 10 bpm is normal and less than 10 bpm is positive for autonomic dysfunction.<sup>9</sup>

### Immediate heart rate response to standing (30:15 ratio test) (for 30th/15th RRR)

The test was performed with the patients lying down quietly in couch while the heart rate continuously recorded in ECG. The patients were asked to stand unaided and the point at starting to stand was marked on ECG paper. The shortest R-R interval at around the 15<sup>th</sup> beat and the longest R-R interval at around the 30<sup>th</sup> beat after starting to stand were marked on ECG paper. The shortest R-R interval at round the 15<sup>th</sup> beat and the longest R-R interval at around the 30<sup>th</sup> beat after starting to stand were measured with a ruler.<sup>8</sup> 30:15 RRI ratio of  $\geq 1$  is considered normal and <1 is positive for autonomic dysfunction.<sup>9</sup>

### Heart rate response to Valsalva maneuver (VR)

The patients were asked to blow into a mouthpiece attached to the mercury sphygmomanometer with nostrils close, holding it at a pressure of 40 mm Hg for 15 seconds while a continuous ECG was recorded. Again ECG was recorded continuously just after the Valsalva. The maneuver was repeated three times with one minute interval. Result was expressed as ratio of longest R-R interval after the maneuver to shortest R-R interval during the maneuver. Mean of three Valsalva Ratio was taken.<sup>8</sup> Normally after Valsalva, RR interval to RR interval during Valsalva is  $\geq 1.1$  if <1.1 is positive for autonomic dysfunction.<sup>9</sup>

### Blood pressure response to standing (PH)

The patient's blood pressure was measured while the patient was in supine position with mercury sphygmomanometer then he was asked to stand, after three minutes the blood pressure was measured in standing position. The posture fall in

blood pressure was taken as difference between the systolic pressure lying and systolic blood pressure in standing position.<sup>8</sup> The test is repeated three times and mean is taken. Postural fall of less than 30 mm Hg is normal and if more than 30 mm Hg is positive for autonomic dysfunction.

### Blood pressure response to sustained hand grip (for HGDBP)

The blood pressures of the patients were taken before the maneuver. A modified sphygmomanometer was used for sustained handgrip maneuver. The patient was asked to grip the inflatable rubber bag of sphygmomanometer and apply maximum voluntary pressure possible. Reading from the attached mercury manometer was taken during the maximum voluntary contraction. Then the patient was asked to maintain the pressure to 30 % of initial voluntary contraction for five minutes. Blood pressure was measured at one minute interval during hand grip. The result was expressed as the difference between the highest diastolic pressure during the hand grip exercise and the diastolic pressure before the handgrip began.<sup>8</sup> Normally the diastolic BP increases by more than 10 mmHg. If it increases less than 10 mm Hg then the test is positive for autonomic dysfunction.<sup>9</sup>

Early Cardiovascular autonomic nervous system dysfunction is said to be present when any one of these test was positive. Definitive when two or more test are positive

### Data analysis procedure

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 17.0. Qualitative data like CAND (present, absent), gender and sub groups of age, BUN level, and duration of dialysis were described using frequency and percentages. Quantitative data like age, BMI were described by mean, standard deviation. Comparison of distribution among sub groups of age, blood urea nitrogen level and duration of dialysis with CAND were done by chi square test. p value<0.05 is said to be significant.

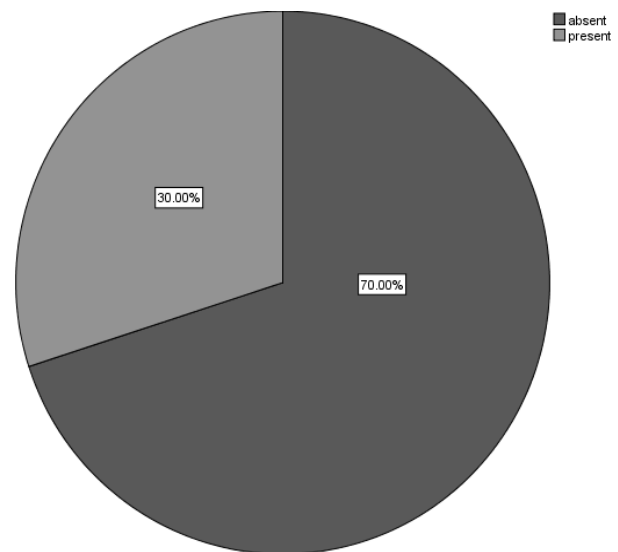
## RESULTS

Mean age of patient was 38.95±11.47 years.

There were 121 males (60.5%) and 79 females (39.5%) patients. Mean blood urea nitrogen level was 45.32±11.74. Mean duration of dialysis of patients was 54.94± 51.0 months and median was 41.50 months. Mean body mass index of the patients was 23.53± 3.72 (Table 1).

**Table 1: Baseline character of the patients**

Particular	Mean/percentage
Age (years)	38.95± 11.47
Gender (%)	
Male	60.5
Female	39.5
Blood nitrogen level (mg/dl)	45.32± 11.74
Duration of dialysis (months)	
Mean	54.94± 51.0
Median	41.50
BMI	23.53± 3.72



**Fig. 1: Percentage having CAND**

Cardiovascular autonomic system dysfunction was found to be 30% indicating early autonomic dysfunction and CAND with two or more than 2 test positive was found in 19.5 % cases. Comparison of distribution among subgroup of age, gender, BUN level and duration of dialysis was done by chi square test. Comparison of Age, Gender and BUN level distribution with frequency of CAND was not statistically significant. (p value>0.05) But comparison of duration of dialysis

between less than 60 months and more than 60 months of dialysis shows frequency of CAND in more than 60 months of dialysis was significantly higher with p value of 0.0001 (<0.05) (Table 2).

**Table 2: Sub-group analysis (n=200).**

Particular	CAND present	P value
Age		
18-39(50.5%)	26(43.3%)	0.184
40-55(49.5%)	34(56.7%)	
Gender		
Male (60.5%)	37(61%)	0.825
Female(39.5%)	23(38%)	
Duration of dialysis (months)		
<=60(66.5%)	8(30%)	0.0001
>60(33.5%)	42(70%)	
BUN level(mg/dl)		
<=50(71%)	45(75%)	0.414
51-70(29%)	15(25%)	

## DISCUSSION

Autonomic neuropathy is a common problem. In some of the studies the incidence of AN was as high as 46%.<sup>10</sup> Michał Nowick et al study which included only non-diabetic ESRD patients, AN was diagnosed in only 18% of the patients by similar modified Ewing and Clarke's test.<sup>5</sup> In our study we found 30% frequency of CAND in non-diabetic ESRD patients which indicate early autonomic nervous system involvement. This frequency is lower from previous studies because diabetic patients were excluded in our study. Whereas this frequency is higher from previous study in non-diabetic, as this study include more number of patients and more patients are on longer duration of dialysis.

According to some authors in non-diabetic patients with ESRD the parasympathetic nervous system dysfunction is the most common but usually subsides with increasing time on dialysis what is in opposition to the diabetic AN in which the signs and symptoms tend to increase with time.<sup>11, 12</sup> In contrast our study shows statistically significant more CAND in patients with longer duration of dialysis. Our results contrast with other authors observations

but a relatively larger number of patients were included and the selection of non-diabetic subjects may speak in favor of our findings.

The efficient dialysis may reduce the concentration of uremic toxins responsible for autonomic neuropathy manifestation<sup>13</sup>. Some investigators have found a positive association between the severity of autonomic function and the severity of uremia, while others found no such relationship.<sup>14</sup> For minimizing the effect of uremic toxin, we have included the patients with low urea load BUN < 70mg/dl and most of patient have BUN < 50mg/dl, ensuring good adequacy of dialysis along with good nutrition status with mean BMI of  $23.54 \pm 3.72$ . However the study also shows no significant difference of CAND in urea level. It is however of note that even the efficient dialysis treatment does not provide a definite cure for AN of which pathogenesis is multifactorial<sup>15, 16</sup>

The gold standard in evaluating tests of autonomic neuropathy should ideally be the biopsies from the autonomic nervous system. But because such biopsies cannot be achieved from healthy living persons, another tool must be sought.<sup>8</sup> Amongst the various modalities available for assessing cardiac autonomic neuropathy, the noninvasive conventional cardiovascular reflex tests have been shown to be simple and reliable with good reproducibility and diagnostic yield of up to 70 % in diabetic and CRF patients.<sup>17</sup>

Other tests for autonomic dysfunction includes amyl nitrate inhalation test,<sup>18</sup> cold pressor test,<sup>19</sup> Quantitative Sudomotor Axon Reflex Test (QSART), Thermoregulatory Sudomotor Test (TST), Head up tilt is used for baroreflex function, Cardiac MIBG (meta-idobenzylguanidine) and plasma norepinephrine for adrenergic function.<sup>4</sup> Newer methods for detecting cardiovascular autonomic dysfunction include baroreflex sensitivity<sup>20, 21</sup> and power spectral analysis of heart rate variability (HRV).<sup>20, 22</sup> Pupillometry is another widely used tool for detection of autonomic neuropathy.<sup>23</sup> Recently task force monitor has been developed with the ability to collect beat to beat data for heart rate, blood pressure and baroreceptor sensitivity using novel, noninvasive technology.

Sahin et al. report most abnormal parasympathetic and sympathetic tests are heart rate

variation during deep breathing and the blood pressure response to hand grip exercise test, respectively, and the positive predictive value for each test is 97 and conclude that performing only one test instead of five has a high sensitivity and positive predictive value and is more practicable in terms of determining autonomic neuropathy.<sup>16</sup> In our study also those having autonomic nervous system dysfunction have heart rate variability in 96 % cases and grip test occurring in 58 % cases.

For patients with autonomic neuropathy, specific treatments, including sildenafil for impotence and midodrine for intradialytic hypotension, are effective and well tolerated.<sup>24</sup> In addition, selective serotonin reuptake inhibitors (SSRIs)<sup>25</sup> and phenobarbital<sup>26</sup> have been shown to benefit specific patients.

There are few limitations to the present study. Firstly, it is a single center study. Secondly, this is not a case controlled study, so the evidence obtained is not strong. Other limitation include, we didn't establish a relationship between autonomic neuropathy and albumin, ferritin, calcium, inorganic phosphorus, intact parathyroid hormone (iPTH), hemoglobin levels, treatment with vitamin D and erythropoietin. Correlation with symptoms was also not done. Although spectral analysis of the ambulatory ECG has been described as best alternative, this facility is still not available in our set-up.

## CONCLUSION

Cardiovascular autonomic system dysfunction is not uncommon complication in ESRD patients. Patients suffer from severe orthostasis, postural hypotension, exercise intolerance, enhanced intradialysis instability, and an increased incidence of silent myocardial infarction and ischemia. There are simple bedside tests to diagnose CAND. Several agents have become available for the correction of functional defects in the autonomic nervous system.

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