# Cardiovascular autonomic neuropathy in non-diabetic Nigerian patients with chronic renal failure

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**Summary**

*Aims:* **To determine the frequency of cardiovascular autonomic neuropathy (CAN), its pattern and clinical predictors in Nigerians with non-diabetic chronic renal failure (CRF).**

*Methods:* **A total of 120 subjects comprising 60 pre-dialysis CRF patients and an equal number of age- and sex - matched healthy controls were studied. Five standard cardiovascular reflex (CVR) tests namely: heart rate response to deep breathing, Valsalva manoevre and posture, as well as blood pressure response to hand grip and posture were used to evaluate the cardiac autonomic functions. A pre-tested questionnaire was administered, with neurological examination and serum biochemical investigations also included in the evaluation.**

*Results:* **The frequency of CAN in non-diabetic CRF was 65%. Dysfunction of both the parasympathetic and sympathetic divisions of the ANS occurred in CRF patients. Significant impairment in all the heart rate reflex tests (39%) and blood pressure response to the handgrip tests (28%) occurred in patients with CAN. Symptoms of autonomic neuropathy with clinical correlation with CAN included: constipation (60%), hyposialism (51%) and hypohidrosis (33%), whilst those of peripheral neuropathy were: loss of sensation (50%) and numbness (40%). Of the biochemical parameters, serum creatinine and urea had significant correlation with autonomic neuropathy.**

*Conclusion:* **Autonomic neuropathy is common in Nigerian patients with non-diabetic CRF, especially in those with symptoms of constipation, hypohidrosis, numbness and prickly sensations.**

**Keywords:** ***Autonomic neuropathy, Cardiovascular reflex tests, Non-diabetic chronic renal failure.***

**Résumé**

*Objectifis:* Déterminer la fréquence de neuropathic cardiovasculaire et autonomie (NCA), son modèle et ses pré diseurs clinique chez les Nigérians avec un arrêt rénal chronique et non-diabétique (ARN).

*Approches:* Deux études furent entamées la première consistait en 120 sujets administres a 60 patients souffrant de predialyse en ARN; la deuxième consistait en nombre égal de cas témoins dont les ages et les sexes furent pareils a la première.

Pour évaluer le fonctionnement cardiaque et autonomique, nous avons eu recours a cinq tests standard de réflexe cardiovasculaire (RCV); ces tests consistaient en réaction an degré de vitesse du cour après une profonde respiration, manouvre de Valsalva et a la posture. Un questionnaire préalablement éprouve fut administre, suivi d'un examen neurologie et d'une enquête de sérum biochimique dans l'évaluation.

*Résultants:* La fréquence de NCA dans les ARN non-diabétique fut 65%. Le dysfonctionnement de divisions parasympathique et sympathique du système nerveux autonomique dans les patients de ARN. Une altération importante dans tous les teste de réflexe du degre de vitesse du cour (39%) fut observée. De même l'alteration de réponse de la tension artérielle aux tests prise (28%) fut remarquée dans les patients souffrant de NCA. Voici les symptômes de neuropathie autonomique avec corrélation clinique en NCA: constipation (60%), hyposialism (51%), hypohidrose (33%) alors que ceux en neuropathie périphérique furent: perte de sensation (50%) et engourdissement (40%). Quant aux paramètres biochimiques, seule la creatinine sérum et urée eurent une corrélation importante avec la neuropathie autonomique.

*Conclusion:* La neuropathie autonomique est répandue parmi les patients Nigérians souffrant de ARN, en particulier parmi ceux qui présentent des indices de constipation, d'hypohidrose, d'engouridissement et de sensations de picotement.

## Introduction

Autonomic nervous dysfunction is a common complication of CRF and may be responsible for the high cardiovascular morbidity and mortality in this group of patients.[1-5] Although, parasympathetic impairment as part of the autonomic neuropathy seen in pre-dialysis and haemodialysis-dependent CRF patients has been well documented, reports differed on sympathetic dysfunctions in chronic renal failure.[1,3,4,6-9] Cardiovascular disorders as the leading cause of death in end-stage renal failure,[9] accounts for nearly 44% of deaths in patients on chronic haemodialysis[10] and may be responsible for the high mortality rate of about 150 times in those within the age range of 15 - 30 years on haemodialysis as compared to general population.[11] CAN is associated with reduction in heart rate variability leading to increased risks of dysrhythmia (such as paroxysmal atria tachycardia and ventricular ectopics), unstable blood pressure, postural hypotension, nocturnal hypoxemia, cardiac hypertrophyy and dialysis-induced hypotension.[12]

In CRF, the symptoms of autonomic dysfunction and peripheral neuropathy are often overshadowed by uremic symptoms and hence they proceed unnoticed. Dysautonomic symptoms that are commonly seen in chronic renal failure include orthostatic light-headedness, altered gastric motility, hypohidrosis (impaired sweating), diarrhoea, constipation, hyposialism, dysphagia, impotence and urinary retention.

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The prevalence of CRF in Nigeria, like other tropical African countries, is estimated to range between 1.6 and 8% from hospital -based data.[13-15] To our knowledge, there is, as yet, no published data on the prevalence and clinical characteristics of autonomic neuropathy amongst Nigerian patients with non-diabetic CRF. An earlier series on the causes of autonomic neuropathy in Nigerians, excluded CRF as an etiological factor amongst Nigerians with autonomic neuropathy.[16] The aim of this study therefore, is to investigate the occurrence of uremic cardiovascular autonomic neuropathy and the clinical characteristics of this disorder in Nigerians with non-diabetic chronic renal failure using a battery of five CVR tests with detailed neurological assessment and biochemical parameters.

## Subjects and methods

### *Subjects*

Sixty pre-dialysis CRF patients (1 month - 7years from the initial diagnosis), referred to the out- and in-patients renal clinics of the department of medicine, University College Hospital, Ibadan were enrolled into the study after obtaining informed consent. An equal number of age - and sex-matched healthy controls were recruited from the medical staff and medical students. The study was carried out between January and December, 2000. Chronic renal failure was defined as creatinine level >2.0mg/dl with supportive renal sonographic and clinical features of chronic uremia. None of the subjects had clinical evidence of diabetic mellitus, coronary heart disease and congestive heart failure. Neither the patients nor the controls were on medications that could influence the cardiovascular and autonomic nervous system. Individuals with history of alcohol consumption of more than 120gm per week and clinical evidence of chronic liver disease were excluded from the study.

A structured questionnaire about symptoms of autonomic impairement was administered blind to all the study subjects, after an initial pilot testing. The study had received approval of the joint University of Ibadan/UCH Ethics Committee.

### *Heart rate viariation to deep breathing*

After an initial 10 minutes supine rest in the laboratory allowiing for cardiovascular stability, all subjects had baseline blood pressure recording using a mercury sphygmomanometer applied to the right arm. Continuous electrocardiographic recordings were made with 5 lead disc electrodes on the chest wall across the cardiac position. The subjects then breathed deeply and evenly at a rate of 6 breaths/min (5s inspiration and 5s expiration) for 2 minutes. The heart rate responses were quantified in beats per minutes. The average heart rate during deep expiration was subtracted from that during inspiration, which gave the maximum-minimum response.[4,17-20]

### *Valsalva manoeuvre*

The subjects were asked to sit quietly and blow into a mouthpiece attached to a pressure guage to a pressure of 40mmHg, and to maintain that pressure for 15s. The ratio of the longest R-R interval shortly after the manoeuvre to the shortest R - R interval immediately after the strain period was calculated and expressed as the Valsalva ratio.[4,9,21,22]

### *Heart rate and Blood pressure response to standing*

After an initial 5 minutes supine rest, subjects were requested to stand-up quickly as possible and remain standing for 2 minutes while the ECG was being recorded. The shortest RR-interval at the 15th beat after the standing and the widest RR-interval at the 30th beat were measured from the recordings and the 30:15 ratio was calculated to give the max/min ratio. Blood pressure after 1 minute of standing was taken from the right arm at the level of the heart in an horizontally outstretched position. The erect diastolic value was substracted from the resting diastolic blood pressure.[20,21]

### *Blood pressure response to sustained hand grip*

The subjects were trained to sustain hand grip at 30% of maximum voluntary contraction with a handgrip dynamometer using the dominant hand. Blood pressures were recorded at one-minute intervals to a maximum of 5 minutes. The average of 3 diastolic blood pressures was calculated from which the resting diastolic blood pressure was subtracted.[20,21]

### *Cardiac autonomic neuropathy and neurological assessment*

The patients were divided into two groups depending on the number of abnormalities found in the 5 cardiovascular reflex tests. Those with 3 or more abnormal results were considered as having definite cardiovascular autonomic neuropathy (CAN+), while those with abnormalities in less than 3 tests were classified as not having cardiovascular autonomic neuropathy (CAN-).[4,6,20] General physical examination and detailed neurological assessment including higher mental function, cranial nerves and peripheral nerve function (sensory and motor) were also carried out.

### *Statistics*

All measures were expressed as mean values $\pm$ SD. Student's t test was used for comparison of measures between controls and CRF patients. Chi square test was used to test for association between discrete variables. The correlation between two variables was examined using multivariate analysis. A p value $< 0.05$ was considered significant.

## Results

The baseline characteristics of the patients and controls are shown in table 1.

### *Cardiovascular autonomic reflex tests.*

Thirty-nine patients (65%) and 5 controls (8.3%) had abnormal values in three or more tests, which indicated autonomic neuropathy. A significant number of CRF patients had abnormalities in four of five CVR tests compared to the healthy controls (table 2). The two most frequently abnormal CVR tests were heart rate variation to deep breathing (sinus arrhythmia) and Valsalva manuouvre. They both occurred in 58% of the patients and 7% controls ($p < 0.001$). A significant number of patients with CAN+ had abnormalities in all the three cardio-vagal heart rate tests compared to those without

**Table 1 Clinical characteristics of patients and controls (NS = not significant)**

| Variables | Patients | Controls | P value |
|---|---|---|---|
| Age (years) | | | |
| Mean | 39 ± 13 | 38 ± 14 | NS |
| Range | 18 - 57 | 18 - 54 | |
| Weight (Kg) | | | |
| Mean | 62 ± 11 | 67 ± 10 | NS |
| Range | 52 - 74 | 47 - 89 | |
| Height (m) | | | |
| Mean | 1.65 ± 0.07 | 1.68 ± 0.08 | NS |
| Range | 1.7 - 1.82 | 1.5 - 1.9 | |
| BMI ($Kg/m^2$) | | | |
| Mean | 23 ± 2 | 23 ± 1 | NS |
| Range | 20 - 24 | 22 - 25 | |
| Systolic BP (mmHg) | | | |
| Mean | 155 ± 29 | 125 ± 22 | <0.05 |
| Range | 110 - 210 | 95 - 160 | |
| Diastolic BP (mmHg) | | | |
| Mean | 95 ± 24 | 77 ± 14 | <0.05 |
| Range | 60 - 120 | 50 - 100 | |

**Table 2 Tests of cardiovascular autonomic neuropathy in patients and controls (NS = not significant)**

| Autonomic function Tests | Patients (N = 60 (%)) CAN+ | CAN- | Total | Controls N = 60 % | P values |
|---|---|---|---|---|---|
| **Heart rate response to:** | | | | | |
| (1) Deep breathing | 26(43.3) | 14(23.3) | 40(66.7) | 3(5) | < 0.01 |
| (2) Valsalva manoeuvre | 24(40) | 5(8.3) | 29(48.3) | 5(8.3) | < 0.01 |
| (3) Posture | 20(33.3) | 3(5) | 23(38.3) | 7(11.7) | <0.01 |
| Blood pressure response to: | | | | | |
| (4) Handgrip | 17(28.3) | 7(11.7) | 24(40) | 4(6.7) | <0.05 |
| (5) Posture | 1(1.7) | 0 | 1(1.7) | 0 | NS |
| Number of abnormal tests | | | | | |
| ≥ 3 | 39(65) | - | 39(65) | 5(8.3) | |
| ≤ 2 | - | 21(35) | 21(35) | 55(91.7) | |

**Table 3 Serum biochemistry in uremic patients with and without CAN (mean ± SD, NS = not significant)**

| Parameter | CAN+ | CAN- | P Value |
|---|---|---|---|
| Urea (mg/dl) | 164.3 ± 89.34 | 106 ± 34.11 | <0.05 |
| Creatinine (mmol/L) | 5.5 ± 2.5 | 3.6 ± 1.1 | < 0.05 |
| Calcium (mmol/L) | 7.74 ±1.5 | 8.2 ± 1.9 | NS |
| Sodium (mmol/L) | 132.5 ± 6 | 132.8 ± 6.3 | NS |
| Potassium (mmol/L) | 4.7 ± 0.9 | 4.3 ± 0.8 | NS |
| Chloride (mmol/L) | 99.4 ± 3.2 | 100.8 ± 3 | NS |
| Bicarbonate (mmol/L) | 21.4 ± 3.8 | 19.7 ± 5.4 | NS |
| Phosphate (mmol/L) | 12.3 ± 5.1 | 6.3 ± 2.6 | NS |
| Hematocrit (%) | 26.6 ± 6.4 | 34.5 ± 3.5 | NS |

(p < 0.01). Of the two tests used to assess sympathetic function, only the handgrip was significantly abnormal in the 24 CRF patients as compared with 4 controls (P < 0.05). The blood pressure response to posture was only abnormal in one patient with cardiovascular autonomic neuropathy.

### *Symptoms of autonomic neuropathy*

Generally, the clinical symptoms and signs suggestive of dysautonomia occurred in 33.4% of CRF patients. These symptoms were present in 70% of those with definite autonomic neuropathy (especially constipation (60%); hypohidrosis (51.3%); and hyposialism (33.3%) (Figure 1).

**Table 4 Clinical signs and symptoms in CRF patients and controls (NS = not significant)**

| Signs and symptoms | Patients (N = 60 (%)) CAN+ | CAN- | Total | Controls N = 60 % | P values |
|---|---|---|---|---|---|
| Loss of tendon reflexes | 17(28.3) | 8(13.3) | 25(41.7) | 15(25) | NS |
| Impaired temperature sensitivity | 10(16.7) | 1(1.7) | 11(18.3) | 3(5) | <0.01 |
| Impaired vibratory sensitivity | 10(16.7) | 4(6.7) | 14(23.3) | 4(6.7) | <0.05 |
| Impaired sensation to pin prick | 9(15) | 2(3.3) | 11(18.3) | 2(3.3) | <0.01 |
| Impaired tactile sensitivity | 11(18.3) | 4(6.7) | 15(25) | 4(6.7) | <0.01 |
| Loss of sensation | 30(50) | 7(11.7) | 37(61.7) | 8(13.3) | <0.05 |
| Paraesthesia (Prickly sensation) | 24(40) | 6(10) | 30(50) | 7(11.7) | <0.05 |
| Muscular fatigabilities | 2(3.3) | 0 | 2(3.3) | 0 | NS |
| Cranial nerve palsy | 1(1.7) | 1(1.7) | 2(3.3) | 0 | NS |

### *Laboratory parameters.*

The mean ± SD values of serum creatinine and urea in patients with CAN+ were 5.5± 2.5mg/dl and 164 ± 89.34mg/dl respectively, compared to 3.6± 1.1 mg/dl and 106 ± 34.11mg/dl in those without (CAN-) and the differences were significant, P <0.05 (Table 3).

### *Neurological assessment*

Amongst the patients, clinical signs of sensory impairment were demonstrable in 25.3%; notably those with impaired tactile perception (25%), impaired vibratory sensitivity (23.3%) and

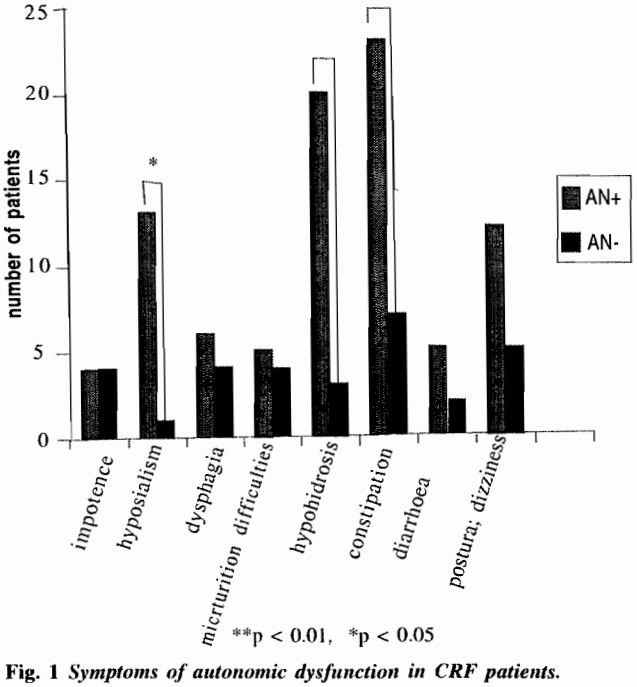


**Fig. 1** ***Symptoms of autonomic dysfunction in CRF patients.***

impaired pin-prick perception (18.3%). Diminution/loss of deep tendon reflex occurred in 41.7% of the patients while only 3.3% experienced muscular fatigability. Table 4 shows the distribution of these sign and symptoms amongst patients with and without CAN and the controls.

## Discussion

Amongst the various modalities available for assessing cardiac autonomic neuropathy, the non-invasive conventional cardiovascular reflex tests have been shown to be simple and reliable with good reproducibility and diagnostic yield of up to 70% in diabetic mellitus and CRF patients.[2, 19 - 23] The standard assessment of the integrity of the parasympathetic (cardiovagal) nervous system includes the measurement of the heart rate responses to respiration, valsalva manoeuvre and orthostatic change.[4, 20] The functional integrity of the sympathetic nervous system is evaluated by blood pressure responses to orthostatic change and pressure stimuli like the handgrip, mental arithmetic and cutaneous cold test.[1, 20, 21] Abnormalities in more than two of the cardiac reflex tests are indicative of cardiovascular autonomic neuropathy.[4, 5, 20]

Our study has shown that in Nigerian patients with non-diabetic CRF, cardiovascular autonomic neuropathy is a common complication. It was significantly more common in the CRF patients than in controls. Secondly, parasympathetic dysfunction was also found to occur more in CRF patients (39%) than sympathetic dysfunction (28%). Thirdly, the symptoms of autonomic impairment that have significant correlation with autonomic neuropathy were those of hypohidrosis, hyposialism and constipation.

The frequency of autonomic neuropathy in non-diabetic CRF patients varied between 26- 67% depending on whether the patients were dialysis-dependent or not.[8, 10, 18, 25, 26] In this study, we found the frequency of autonomic neuropathy in pre-dialysed, non-diabetic CRF patients to be 65% and it involved both parasympathetic and sympathetic functions early in the course of the disease. This differs from the pattern in diabetes mellitus where the parasympathetic function is majorly impaired, while the sympathetic control is rarely involved or is minimally involved late in the course of the disease.[19, 20, 27] Our finding is consistent with that of Miyanaga et al, who showed an early impairement of the sympathetic nervous system in uremic dysautonomia using radionuclear MIBG myocardial scintigraphy.[28] The occurence of sympathetic impairment in 28% of our patients is within the range of 13 - 45% of what was previously reported using similar CVR tests.[2, 4, 22] Our findings corroborate the view of Vita et al which indicated that the current opinion held by many clinicians, of mainly parasympathetic damage in chronic uremic state needs to be modified to accommodate the widespread damage involving the sympathetic and parasympathetic impairments.[2]

The clinical implications and prognostic relevance of cardiovascular autonomic failure in chronic uremic conditions is increasingly being studied. Jassal and colleagues using the standard CVR tests reported higher incidence of cardiac arrhythmias in haemodialysis patients with associated autonomic dysfunction.[29] In another series, abnormality in 24-hour heart rate variabilities was demonstrated using spectral analysis in dialysis-dependent and non-dialysis dependent diabetics as well as non-diabetic patients awaiting renal transplant. A total of five sudden deaths were reported to have occurred during the 6 months study period amongst those with demonstrable autonomic neuropathy.[30]

The impairment in autonomic functions results in alteration of the parasympathetic: sympathetic balance and hence predisposes patients to a higher risk of developing cardiac arrhythmias due to the unopposed sympathetic acitviity.[31 32] Although in uremic conditions the disturbed autonomic nervous function is unlikely to be the sole determinant, it is possibly a contributing mechanism that increased the propensity for other triggering events to cause a disturbed rhythm. Also, the postural hypotension which often complicates haemodialysis has been shown to be accompanied by acute withdrawal of the sympathetic activity, vasodilatation and relative bradycardia, known as Bezold-Jarisch reflex.[33] This reflex is often elicited by subtle change in the vasomotor tone in hypovolemic state, and so reduction in blood volume may play a crucial role in the dialysis-related hypotension as well as the neurological impairment. Recently, Nashimura et al suggested enhanced nitric oxide production to be responsible for the inhibition of sympathetic activity in chronic uraemia[34] and so plasma concentration of nitrate anion $NO_3$, a stable metabolite of NO before dialysis may be used as a predictor of dialysis related hypotension.

We found no correlation between biochemical parameters and autonomic neuropathy in CRF patients, confirming previous reports that showed no relationship between serum calcium, phosphate and hematocrit and the development of autonomic neuropathy.[35] It can be argued that dehydration might be responsible for symptoms like constipation and hyposialism observed in the patients. However, this is unlikely as there was no significant difference in the hydration status between the patients and controls. Also the occurrence of normal pulse volume in the patients suggested that autonomic impairment rather than dehydration was responsible for the observed symptoms.

In conclusion, our study has demonstrated the occurrence of parasympathetic and sympathetic autonomic nervous impairments in CRF patients. Therefore, chronic uremia is an important cause of autonomic neuropathy in Nigerians. The tests of heart rate response to Valsalva manoeuvre and deep breathing and the blood pressure handgrip test were found to be most sensitive in detecting autonomic neuropathy in the Nigerians with non-diabetic CRF. Neuropathic symptoms such as constipation, persistent dry mouth, hypohidrosis, loss of sensation and numbness in the limbs have significant clinical correlation with CAN in CRF patients.

Further studies may be necessary to look at the prognostic implications of autonomic neuropathy in Nigerians with chronic renal failure and possibly compare the finding to those with congestive cardiac failure.

## Appreciation

The authors are grateful to Professor S. Kadiri, Dr A Arije and Dr B L Salako of the renal unit for permission to

enrol the patients under their care into this study.

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