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A Study of Cardiovascular Autonomic Neuropathy in Adult Patients with Diabetes Mellitus at Levy Mwanawasa University Teaching Hospital

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is the diminished capacity of autonomic regulation of the cardiovascular system occurring in the presence of diabetes mellitus (DM) and in the absence of other aetiologies. Diabetes mellitus is a well-known cause of peripheral neuropathy. However, in comparison to somatic neuropathy, autonomic neuropathy is an under-diagnosed and under-treated chronic complication of diabetes mellitus despite its serious and significant contribution to morbidity and mortality in the diabetes mellitus population. A variety of tests, based on evaluation of the cardiovascular reflexes triggered by performing specific provocative manoeuvres, have been proposed to measure autonomic function. This study used four cardiovascular reflex tests to estimate appropriate autonomic function by examining heart rate, heart rate variation and the baroreceptor reflex. The aim of this study was to determine the presence of cardiovascular autonomic neuropathy in adult patients with diabetes mellitus at Levy Mwanawasa University Teaching Hospital in Lusaka, Zambia. Adult patients with diabetes mellitus, aged between 21 and 70 years, participated in this cross-sectional study. Four, non-invasive, cardiac autonomic reflex tests to assess for cardiac autonomic neuropathy were employed according to Ewing's method. The parasympathetic function was analysed based on the heart rate response to paced deep breathing and to Valsalva manoeuvring. The sympathetic function was assessed by measuring heart rate and blood pressure response to postural change. Ewing`s criteria was used for the categorisation of cardiac autonomic neuropathy. Data were analysed using SPSS version 20. Continuous data were presented as means and standard deviation. Categorical data were analysed using a Fishers' Exact Test (χ^2) and a logistic regression was performed to verify the effects of diabetes mellitus' duration, sex and age on the probability that the participants have cardiac autonomic neuropathy. A total

of 52 patients participated in the study. The prevalence of Cardiac autonomic neuropathy was 48.1%. Out of 52 patients, 42.3% had definite cardiac autonomic neuropathy and 5.8% had severe cardiac autonomic neuropathy. Early cardiac autonomic neuropathy was observed in 34.6% of patients while 17.3% had no signs of cardiac autonomic neuropathy. The mean age of patients with cardiac autonomic neuropathy was 54.44 ± 10.90 years and the mean duration of diabetes mellitus from diagnosis was 5.36 ± 6.78 years. The probability of developing cardiac autonomic neuropathy increased with increasing age and hypertensive participants were more likely develop cardiac autonomic neuropathy (v = 5.82, p = .001). In conclusion, cardiac autonomic neuropathy was present in a significant proportion of adult patients with diabetes mellitus at Levy Mwanawasa University Teaching Hospital, reflecting the increased morbidity encountered by this population. In order to improve patient quality of life and reduce disease burden, screening for cardiac autonomic neuropathy should be implemented using cardiovascular autonomic reflex tests which are relatively simple, safe and affordable.

Keywords: *cardiovascular autonomic neuropathy, cardiovascular autonomic reflex tests, diabetes mellitus*

INTRODUCTION

Cardiovascular autonomic neuropathy (CAN) is defined as impairment of the autonomic control of the cardiovascular system (CVS), specifically occurring in the presence of diabetes mellitus (DM) and in the absence of other aetiologies[1]. Diminished autonomic regulation of the CVS can have devastating consequences because the primary extrinsic control mechanism that regulates cardiac performance occurs via autonomic innervation of the CVS, thus, facilitating modulation of cardiovascular structures through sympathetic-parasympathetic balance[2,3]

Neuropathies occur, with a high prevalence, in individuals with DM but despite this, they are the most under-diagnosed and under-treated chronic complications of diabetes (Rolim *et al.,* 2013). CAN, in particular, is known to be an early and common complication, affecting 7 to 15% of newly diagnosed patients with DM. The chronic hyperglycaemic state characteristic of DM induces complex pathological processes involving the autonomic system nerve fibres that result in neural degeneration and diminished or loss of function. This, ultimately, leads to a decline in the appropriate regulation of the cardiovascular system.

In relation to the quality of life and life expectancy, CAN is among the most disabling of complications of DM[4]. Many previous studies conducted have associated CAN with increased risk of: exercise intolerance, cerebrovascular accident (stroke), silent myocardial ischemia, atrial and ventricular arrhythmias, coronary artery disease, perioperative instability, orthostatic hypotension and sudden death[5,6]. In the absence of hypertension, coronary vessel disease and structural or valvular disease, CAN was also reported to be associated with diabetic cardiomyopathy leading to systolic and diastolic dysfunction[7].

The difficulties that are faced in diagnosing CAN early are due to its clinical manifestation appearing in the

late stages of the condition, as well as presenting with a myriad of signs and symptoms that are non-specific. The condition may be present in the early stages of DM, but it is often subclinical and only detectable using objective autonomic tests.

A variety of markers have been proposed to measure autonomic function including heart rate (HR), heart rate variation (HRV), baroreflex sensitivity and others[7]. Most tests are based on evaluation of the cardiovascular reflexes triggered by performing specific provocative manoeuvres[8]. Evaluation of CAN may be sufficiently done by use of cardiac autonomic reflex tests (CARTs). Time-domain HRV analysis has the widest application in routine clinical evaluation and some of its indices have become well-documented independent risk factors of cardiovascular events.

Ewing *et al.* (1982) recommended five relatively simple tests that could be applied to measure autonomic function. These tests examine: (1) HR response to paced deep breathing; (2) HR response during the Valsalva manoeuvre; (3) HR response to standing from supine; (4) systolic BP response to standing from a supine position and (5) BP response to sustained handgrip caused by muscle contraction using a handgrip dynamometer. The first two tests measure, mainly, the ability of the vagal nerve to slow the HR during procedures which increase HR (parasympathetic function) and the last three tests measure baroreceptor reflex-mediated HR and BP fluctuations (sympathetic function).

Ewing's battery of tests is considered the gold standard of evaluation of the autonomic system and these tests were determined as suitable for both routine screening and monitoring of the progress of autonomic neuropathy[9, 10]. Also, the American Diabetes Association recommends the use of these tests in the diagnosis of CAN. These tests are an attractive option in low-resource settings because they are relatively simple to perform, safe, require minimal patient preparation and cooperation, do not require expensive, specialised equipment and may be conducted in a practitioner's office or by the bedside. They are not excessively time-consuming, making them feasible to perform in Zambia where clinicians are a strained resource, and the low doctor-to-patient ratio causes severe time constraints with regards to exhaustively be investigating diabetic patients and the many complications they are prone to.

CAN has been investigated widely within North America and Europe, with few studies conducted in Asia and the Middle East[11]. Fewer still in sub-Saharan Africa. Currently, in Zambia, a low-middle-income country, there are no known reports of CAN are available. Nsakashalo *et al*. (2011), reported a prevalence of type 2 diabetes mellitus of 2.1% and 3.0% for males and females respectively, following a comprehensive general population-based survey, conducted in 2011, among persons aged 25 years and above in Lusaka urban district[12].

Although CAN is known to be a complication of DM, screening is not widely done in the clinical setting, and this may be due to the lack of sufficient information regarding its presence among the diabetic population. Its prevalence within the diabetic community is obscure, as is the use of autonomic tests as a clinical tool for diagnosis or screening. Making intentional efforts to curb CAN as one of the more serious

but most underrated complications of diabetes may result in improved quality of life and some alleviation of the disease burden that DM incurs upon patients. This process may begin with recognising CAN by carrying out appropriate clinical research on the diabetic population in Zambia.

This study used cardiac autonomic reflex tests to estimate autonomic function and investigate for CAN by examining HR, HRV and baroreceptor reflex in adult DM patients at Levy Mwanawasa University Teaching Hospital in Lusaka, Zambia.

MATERIALS AND METHODS

Study type: Cross-sectional observational study conducted at the Levy Mwanawasa University Teaching Hospital in Lusaka, Zambia from September to December 2019. Adult DM patients, between 21 and 70 years, were enrolled irrespective of disease duration and therapeutic status.

Sample size and sampling method: Convenience sampling was used to recruit a total of 52 patients.

Case definition: The presence of DM, during recruitment, was defined by current usage of insulin or oral hypoglycaemic medication. These patients were previously diagnosed by their primary care clinicians according to standard definitions of DM and subsequently instituted on insulin/oral hypoglycemics.

Non-eligibility criteria included any patient that had: (1) an acute illness; (2) other conditions that are associated with the autonomic nervous system such as thyroid disease; (3) a severe systemic disease [pulmonary, renal and malignancy] (4) a history of regular alcohol consumption (defined as drinking one or two drinks per day for six months or longer), since these would possibly be confounders to autonomic neuropathy; (5) a history of underlying cardiovascular diseases such as myocardial infarction, coronary artery disease, rheumatic heart disease and heart failure, since there was the potential of interference with the interpretation of the electrocardiogram; (6) a physical disability or was uncooperative as this patient would not be able to perform the manoeuvres properly and within the time limits and thus may result in erroneous results; (7) declined to participate in the study.

Study procedure: Approval for all research procedures, including examination during tests, was sought and approved by the University of Zambia Biomedical Ethics Committee (UNZABREC), Ref no 111-2019. No participants were subjected to harm. There was a slight risk of severe hypotension possibly causing syncope during the orthostatic test. However, medical assistance was immediately available, and this was explicitly explained to the patients.

Patients were recruited from the out-patient department and DM clinic on a voluntary basis. Details of the study were explained including assurance of anonymity and confidentiality. It was explained that the results would not alter their treatment and the results of the tests would be communicated to the patients via telecommunication, if possible. Written informed consent, to carry out further examination, was obtained.

Four non-invasive cardiovascular autonomic reflex tests were performed

on all patients from 08:00hrs to 11:00hrs. The tests were performed with patients in a fasted state (i.e., not less than 8 hours and not more than 12-14 hours without food or drink). No prior preparation was needed before examination apart from ensuring adequate exposure. Women were appropriately covered during the examination. The patients were allowed to rest in a slightly reclined position for five minutes, after which a 12-lead electrocardiogram was performed using a Fukuda Denshi FX – 8222 CardiMax device. The ECG was connected to the patient for the whole duration of conducting the tests.

All patients were examined by one examiner according to Ewing's method. Patients were given clear instructions on how to perform the procedures in addition to the examiner demonstrating. All procedures involved the patient supine, except for the orthostatic test which required the patient to stand up from a supine position.

Parasympathetic Nervous System Examination

1. The patient was instructed to lie quietly and breathe normally. Beat-to-beat heart rate variation was obtained from the continuous ECG tracing as the patient carried out paced breathing for one minute at a rate of 6 deep breaths per minute (as guided by the examiner, the rate at which respiratory arrhythmia is most pronounced. The HRV is computed as the expiration-to-inspiration (E/I) ratio.

E/I ratio = $\frac{\text{Mean of the longest R-R interval during expiration (E)}}{\text{Mean of the shortest R-R interval during inspiration (I)}}$

An E/I ratio of more than or equal to 1.21 is considered normal; a ratio from 1.11 to 1.20 is considered borderline while a ratio of less than or equal to 1.10 is considered abnormal[1, 9, 13].

2. The Valsalva ratio also measures HRV. The Valsalva manoeuvre was performed by the patient exhaling forcefully against a closed mouth for 15 seconds then breathing normally. An ECG tracing was run concurrently and recorded at:
   (i) 1 minute, before manoeuvre – resting period
   (ii) 15 seconds, during manoeuvre – strain period and;
   (iii) 1 minute, after manoeuvre – recovery period,

   This was performed 3 times with one-minute intervals in between and the mean of the last two Valsalva ratio computations was taken as the final value. From the ECG tracing, the ratio is computed as:

   Valsalva ratio = Longest R-R interval after the manoeuvre (maximal tachycardia)
   Shortest R-R interval during the manoeuvre (maximal bradycardia)
   A Valsalva ratio of more than or equal to 1.21 is considered normal; a ratio from 1.11 to 1.20 is considered borderline and a ratio of less than or equal to 1.10 is considered abnormal[1, 9, 13].

Sympathetic Nervous System Examination

3. The orthostatic test was performed by asking the patient to lie down quietly for three minutes. During continuous

ECG monitoring, the patient stood up for another two minutes. The immediate heart rate response to change of posture was determined as the heart rate immediately after the patient was fully upright and comparison was made in supine and upright position in terms of the direction and magnitude of difference of heart beats per minute. An immediate increase in the heart rate (of appropriate magnitude), following postural change from supine to standing upright, is a positive sign of sympathetic activity. An increase in heart rate by more than 15 beats per minute from supine to standing up is considered normal, 11-14 beats per minute is borderline, while less than 10 beats per minute is considered abnormal[1, 9, 13].

Blood pressure (BP) response to postural change: the initial BP was taken with the patient supine and another reading was taken after two minutes of standing. The postural fall in BP was taken by calculating the difference in systolic BP when the patient was supine and the when the patient was standing.

4. A difference in systolic BP that occurs following postural interchange assesses sympathetic activity. Postural change from lying to supine, resulting in a drop in the systolic BP of less than 10mmHg is normal. A systolic drop of between 11mmHg to 29mmHg is borderline and a systolic BP drop of more than 30mmHg is considered abnormal[1, 9, 13]. The blood pressure was obtained using a Medigenix Deluxe Upper Arm Blood Pressure Monitor.

Data analysis plan (and statistical methods): The data collected was entered into Microsoft Excel, and then transferred to statistical software package SPSS version 20 for analysis.

The Shapiro-Wilk's test for normality was performed. Continuous data were presented as means ± standard deviation (SD). Categorical data were presented as frequencies and percentages (n and %) and analysed using a Fishers' Exact Test (χ^2) at a p value of < 0.01. A logistic regression was also performed at a p-value level of < 0.05 to verify the effects of duration of DM, age and sex on the participants who had CAN.

RESULTS

A total of 52 patients were enrolled into the study. The mean age of the patients was 47.37 years with a standard deviation (SD) of ± 15.07 years and the mean duration of diabetes mellitus from diagnosis was 4.41 years with a SD of ± 6.16 years. There were 29 females (55.8%) and 57.7% of the patients had hypertension. Refer to Table 1.

Parasympathetic activity

Thirteen patients (25.0%) with an E/I ratio of more than or equal to 1.21, 14 patients (26.9%) had an E/I ratio of between 1.11 – 1.20 and 25 patients (48.1%) had an E/I ratio of less than or equal to 1.10. Refer to Table 2.

Thirteen patients (25.0%) had a Valsalva ratio of more than or equal to 1.21. Eleven patients (21.2%) had a Valsalva ratio of between 1.11 – 1.20 and 28 patients (53.8%) exhibited a Valsalva ratio of less than or equal to 1.10. Refer to Table 3.

Sympathetic activity

Following postural change from supine to standing upright, 21 patients (40.4%) had an increase in HR of more than 15 beats/min, 10 patients (19.2%) with a HR increase of 11-14 beats/min and 21 patients (40.4%) with HR increase of less than 10 beats/min. Refer to Table 4.

Postural change yielded 36 patients (69.2%) with a systolic BP drop of less than or equal to 10mmHg and 12 patients (23.1%) with a systolic BP drop of between 11 – 14mmHg. Four patients (7.7%) had a systolic BP drop of more than or equal to 30mmHg. Refer to Table 5.

The diagnosis of CAN is made based on the results of these autonomic tests. Ewing's criterion (Table 6) is used to classify CAN. In this study, only normal and abnormal variables for the test results were used as criterion in the categorisation and diagnosis of CAN. A borderline result was, therefore, considered as normal. The prevalence of CAN in adults with DM at Levy Mwanawasa University Teaching Hospital was 48.1% (n = 25) 42.3% (n = 22) had definite CAN, while 5.8% (n = 3) had severe CAN; 34.6% (n = 18) were identified with possible CAN and 17.3% (n = 9) had no signs of CAN. Refer to Table 7. The distribution of findings is as illustrated in Figure 1.

The results were analysed further for patients with and without CAN (classified as 'definite and severe CAN' and 'no CAN', respectively) with reference to Table 7. Thus, 34 patients were included in the subsequent sub-analysis. The mean age of patients with CAN was 54.44 years with a SD of ± 10.90 years. The mean DM duration was 5.36 years with a SD of ± 6.78 years. Fourteen patients (41.2%) were males and 20 (58.8%) of the patients were hypertensive. Refer to Table 8.

A Fishers' Exact Test (χ^2) was performed to examine the relation between hypertension and CAN. The test was conducted at a significance level of 0.01. The relation between these variables was significant, χ^2 (df =1, n = 34) = 11.504, p <.01). Based on the results of this test, hypertensive participants were more likely develop CAN (ν = 5.82, p = .001). Refer to Table 9.

To verify the effects of DM duration, sex and age on the probability that the participants have CAN, a logistic regression was performed. The model was statistically significant ($p<0.05$) and explained the 54.6% variance in CAN, and correctly classified 88.2% of cases. Two of the predictor variables were statistically significant: age and sex. For every unit increase of age, the log odds of CAN increased by 1.096. The odds of CAN of males decreases by 0.082 compared to females (here, female is the reference category) i.e., the odds are males are 8.2% less likely to develop CAN than females. However, there was no significant association between duration of DM and developing CAN. Refer to Table 10.

DISCUSSION

This study showed that CAN is a common complication in patients with DM. Overall, the prevalence for CAN was 48.1% in a population with a mean age of 53.4(± 11.8 SD) years who had DM for a mean duration of 6.9 (± 5.7 SD) years. These findings align with those of several other studies investigating CAN prevalence. Fisher and Tahrani (2017), as well as Bissinger (2017) reviewed thirteen and ten studies, respectively, which were

conducted previously and they reported prevalence ranging from 17% to 73%[5,14]. This wide range is likely due to factors such as differences in diagnostic criteria, tests, and study populations, type of diabetes mellitus and disease stage as suggested by Dimitropoulos *et al.* (2014) who conducted a review of studies in 2013 and reported a wide range in the prevalence of CAN (1% - 90% and 20% - 70% in T1DM and T2DM, respectively).

Two previous studies, in Type 2 DM (T2DM) patients which employed the same four reflex tests with similar CAN diagnostic criteria as used in this study, reported prevalence values of 42.2% and 40.9% in patients with a mean age of 59.5 years and 59.2 years, and mean duration of T2DM of 15 and 11 yeas respectively[15,16]. Lerner *et al*. (2015) determined a prevalence of 37% in T2DM patients, with a mean age of 57.6 years, and mean duration of disease burden of 10.4 years[17]. Results very similar to this study were reported by Eze *et al.* (2013) who conducted a study in Nigeria, observing a prevalence of 44.3% among patients with a mean age of 55.76 years and a duration of T2DM of 7.67 years[18]. Menon *et al*. (2017) observed that 66.2% had definite CAN in patients with a mean age of 61.1 years with a mean duration of T2DM of 10.2 years[5].

In the study the mean duration of diabetes observed in these patients indicate that a large proportion of patients had had diabetes for a relatively short duration when compared to other studies that reported disease duration in the ranges of 14 – 26 years[14,15,16,17].

An abnormally reduced E/I ratio was noted in 25 (48.1%) patients, denoting diminished heart rate variability during paced deep breathing[1,9,13]. A Valsalva ratio of ≤1.10 seen in 28 (53.8%) patients reflects a lack of appropriate parasympathetic influence[1,9,13].

In our cohort, 20 patients (38.5%) had an abnormal HR response indicating an inadequate increase in the HR. Systolic BP change was abnormal in only 4 patients (7.7%) who exhibited an excessive drop in their systolic BP due to the absence of the regulatory influence of the sympathetic system to minimise the effects of gravity on the dynamics of blood flow.

There was a significant difference between the patients that had CAN (patients categorised with definite and severe CAN) and those patients without CAN patients (categorised as 'no CAN') with regard to age according to the results shown in Table 8 ($p < 0.05$). This reflects the findings from other studies which observe that older patients with DM are more likely to be diagnosed with CAN[19, 20, 21]. Table 10 also showed that increasing age was associated with developing CAN. For every unit increase of age, the log odds of CAN increased by 1.096. This reflects the findings from previous studies which observed that autonomic neuropathy is common in older persons, particularly if they have DM[22]. Increasing age may also imply that the patient has had DM for a longer duration, of which, the latter is a risk factor for CAN due to longer exposure of the patient to the pathological processes associated with DM. With regards to CAN and duration of DM, the patients that had CAN in this study were found to have DM for a longer duration compared to those that did not have CAN (5.36years ± SD 6.78 years versus 2.78 ± SD 2.28 years) as

shown in Table 8. However, there was no significant difference between the two groups [p (0.106) > 0.05]. This finding was similar to what was observed after a logistic regression was conducted to verify the effects of DM duration on the probability that the patients have CAN. There was no significant association between DM duration and developing CAN (Table 10, p = 0.663). This observation contrasted with what other similar studies have shown which observe that increased DM duration is associated with development of CAN[10, 19, 20]. However, Mansour and Odea (2013) did not observe increased duration of DM to be a predictor of autonomic neuropathy. The patients who had CAN in this study had DM for a remarkably shorter period compared to other studies and this may be the reason as to why there was no significant association observed between DM duration and development of CAN.

Furthermore, this study found hypertension to be an independent factor for the development of CAN. A Fishers' Exact Test (χ^2) was performed to examine the relation between hypertension and CAN (conducted at a significance level of 0.01) and the relation between these variables was significant, χ^2 (df=1, n=34) = 11.504 (Table 9). Based on the results of this test, hypertensive participants were more likely develop CAN. This finding is comparable to other studies which demonstrated CAN to be significantly associated with hypertension[19, 23, 24]. Hypertension is widely known to co-exist with DM[14]. Hypertension and CAN, within the same individual, may contribute to a reduction in the quality of life and increase morbidity.

The results from Table 10 showed that female gender was significantly associated with the development of CAN. The odds of CAN of males decreases by 0.082 compared to females (here female is the reference category) i.e., the odds are males are 8.2% less likely to develop CAN than females. These findings echo similar results from a study done by Moodithaya and Avadhany (2011) in which females had a higher resting heart rate (a measure of autonomic dysfunction) than males[25]. With more than 8000 patients studied, the ACCORD trial also showed a higher occurrence of CAN in women compared to men across all definitions of CAN used within the study[2].

It is difficult to clinically diagnose CAN due to the lack of overt symptoms. However, the use of CARTs enables early detection of disease even during the sub-clinical stage.

Limitations of this study are acknowledged including: a small sample size; the inability to classify DM as Type 1 or Type 2 and the absence of a comparison group with which to (i) increase the validity of the study and (ii) control for confounding factors. Uncontrolled factors like smoking, caffeine use or antihypertensive medication (not withheld during the study due to ethical consideration) which may have affected the nervous system and, therefore, the results. Patients with conditions such as TB, HIV, peripheral vascular disease and chronic obstructive airway disease were not excluded from the study, and these may have been confounders to the presence of autonomic neuropathy. Stringent standardisation was lacking, due to the absence of a

dedicated space in which to carry out the autonomic testing such as an autonomic testing laboratory. The cross-sectional study design does not allow for the establishment of a causality relationship. The cohort of patients observed was from a single hospital so generalisation of the results to all tertiary level hospitals is difficult due to the study having been conducted in a single centre. Thus, a study designed with a comparison group and more stringent test standardisation will be beneficial in order to make more accurate inferences from the study population onto the general population. In addition, a multicentre study would need to be conducted to confirm the results to the larger population.

Despite these challenges, the study successfully demonstrated evidence of CAN within a significant proportion of the adult DM population at Levy Mwanawasa University Teaching Hospital by use of cardiac autonomic reflex tests. The results of the study demonstrate the potential for cardiovascular autonomic reflex tests to diagnose a potentially lethal complication of DM; and build on existing evidence, from previous studies, that CAN is a relatively common but undermined complication of diabetes mellitus. The study also affirms the relative ease, safety and simplicity with which these tests can be carried out in a hospital setting. The equipment needed is inexpensive and, highly likely, already available within the hospital setting, thereby, increasing the practicality of carrying out autonomic testing. Hence, with appropriate and timely intervention it may be possible to mitigate further morbidity and mortality posed by CAN.

Hence, it is recommended that screening for CAN should be implemented using cardiovascular autonomic reflex tests, to reduce disease burden and improve patient quality of life. Identifying patients with CAN allows for risk stratification amongst DM patients and hence, possible institution of appropriate and timely interventions aimed at slowing of disease progression and reducing further morbidity.

DECLARATIONS

All research procedures reported in this study was approved by the University of Zambia Biomedical Ethics Committee (UNZABREC), Ref no 111-2019.

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TABLES

Table 1: Clinical characteristics of the study participants (n=52)

Age (years)*	47.37 ± 15.07
Gender (male/female)^	23 (44.2)/ 29 (55.8)
Duration of diabetes mellitus (years)*	4.41 ± 6.16
Hypertension^	30 (57.7)
Systolic BP (mmHg)*	134.62 ± 15.91
Diastolic BP (mmHg)*	87.17 ± 11.94

BP = blood pressure
*Data are presented as means ± SD
^ Data are presented as n (%).

Table 2: Heart Rate Variation during paced deep breathing

	E/I ratio	*Frequency (n)*	*Percentage (%)*
Normal	≥ 1.21	13	25.0
Borderline	1.11 – 1.20	14	26.9
Abnormal	≤ 1.10	25	48.1
Total		52	100.0

Table 3: Valsalva Ratio (Heart rate variation following Valsalva manoeuvre)

	Valsalva ratio	*Frequency (n)*	*Percentage (%)*
Normal	≥ 1.21	13	25.0
Borderline	1.11 – 1.20	11	21.2
Abnormal	≤ 1.10	28	53.8
Total		52	100.0

Table 4: Normal and abnormal variation in heart rate following postural change from supine to standing upright.

	Change in heart rate	Frequency (n)	Percentage (%)
Normal	≥ 15	21	40.4
Borderline	11 – 14	10	19.2
Abnormal	≤ 10	21	40.4
Total		52	100.0

Table 5: Systolic blood pressure change following postural change from supine to standing upright

	Systolic BP change (mmHg)	*Frequency (n)*	*Percentage (%)*
Normal	≤ 10	36	69.2
Borderline	11 – 14	12	23.1
Abnormal	≥ 30	4	7.7
Total		52	100.0

BP: Blood pressure

Table 6: Ewing`s criteria for the categorisation of CAN

Category of CAN	Criteria
Normal	All tests normal or one test borderline
Early	One of three HR tests abnormal or two borderlines
Definite	Two HR tests abnormal
Severe	Two HR tests abnormal + one or two BP tests abnormal

BP: Blood pressure, HR: Heart rate

Table 7: Prevalence of CAN

	Frequency (n)	*Percentage (%)*
No CAN	9	17.3
Possible CAN	18	34.6
Definite CAN	22	42.3
Severe CAN	3	5.8
Total	52	100.0

Table 8: Demographic and clinical variables between the patients with and without CAN (combined, n=34)

Variable	CAN (n=25)	No CAN (n=9)	P value
Age (years)	54.44 ± 10.90 SD	37.67 ± 16.39 SD	0.002
Sex (male/female)	7(28.0%)/ 18(72.0%)	7(77.8%)/ 2(22.2%)	
Duration of diabetes mellitus (years)	5.36 ± 6.78 SD	2.78 ± 2.28 SD	0.106
Hypertension	19 (55.9%)	1 (2.94%)	

BP = blood pressure

*Data are presented as means ± SD.

^ Data are presented as n (%).

Table 9: Fishers' Exact Test for association between hypertension and CAN

Hypertension * CAN					
absent present			CAN		Total
Hypertension	non-hypertensive	Count	8	6	14
		Expected Count	3.7	10.3	14.0
		% Within Hypertension	57.1%	42.9%	100.0%
		% of Total	23.5%	17.6%	41.2%
	hypertensive	Count	1	19	20
		Expected Count	5.3	14.7	20.0
		% within Hypertension	5.0%	95.0%	100.0%
		% of Total	2.9%	55.9%	58.8%
Total		Count	9	25	34
Expected Count		9.0	25.0	34.0	
% within Hypertension		26.5%	73.5%	100.0%	
% of Total		26.5%	73.5%	100.0%	

Table 10: Odds ratios (95% CI) of predictors of CAN among participants (n=34)

Independent variables	Odds ratios (95% CI)	P Value (α = 0.05)
Sex	0.082 (.009 -.735)	.025
Age	1.096 (1.013 - 1.186)	.023
Duration of DM	1.054 (.831-1.337)	.663

FIGURES

Figure 1: Prevalence of CAN in Adult Diabetic Mellitus Patients at Levy Mwanawasa University Teaching Hospital