CORRELATION BETWEEN EARLY MORNING SURGE IN BLOOD PRESSURE AND CARDIAC AUTONOMIC NEUROPATHY

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is among the minimal acknowledge and understood diabetes related complication, despite its sufficiently great negative impact on people ability to live and quality of life in diabetic people. It is often underestimated problem of Diabetes which is expected with surging cardiovascular morbidity and mortality. The objective of the study is to study cardiac autonomic neuropathy in subjects with diabetes mellitus and correlating with variation in early morning BP. Cross Sectional study was conducted in Chettinad Hospital and Medical College, Hospital, Kelambakkam. Hundred patients with Diabetes Mellitus who were on regular treatment with either insulin &/or oral hypoglycaemic agents were studied. Cardiac Autonomic Neuropathy Score was calculated using the clinical test variables. : Out of the 100 patients 62 had no CAN, 18 had early CAN and 20 had severe CAN. The mean CAN score increased with duration of diabetes (r0.516, p 0.000). The mean CAN score was higher in patients who had neuropathy. The mean HbA1c was 8.06 and correlated with CAN score (r0.526, p0.000).There is statistical significance with 60% of severe CAN had early morning surge in BP. The study provides evidence that patients with more severe CAN have higher blood pressure in early morning.

KEY WORDS: Cardiac autonomic neuropathy (CAN), diabetes, Cardiac and vascular disease (CVD)


INTRODUCTION

Diabetes mellitus (DM) is a worldwide illness influence not less than 0.415 billion people which is projected increase to 0.642 billion by 2040, extending throughout the world with a notable share (half of the total population) remaining undiagnosed according to International Diabetes Federation (1). It is roughly calculated that almost 16 in 100 people are contemporary with risk of being complications evolved regarding to diabetes (1). Cardiac and vascular disease (CVD) is the frontline causes for diabetes related mortality and morbidity and ultimately the utmost goal of diabetes people treatment is to sufficiently decrease the load of CVD as well as the vascular complications related to diabetes. Most of the CVD prevention plan in people with Diabetes is constructed on lowering blood pressure and Low Density Lipoprotein cholesterol levels with improving glucose level and control (2). Despite that, CVD remains very usual and an important cause of morbidity and death in people with DM. Hence, very good comprehension of, etio-pathogenesis of CVD is utmost important to develop new therapeutic ends (3).

Cardiac autonomic neuropathy (CAN) is among the minimal acknowledge and understood diabetes related complication, despite its sufficiently great negative impact on people ability to live and quality of life in diabetic people (4). It is often under estimated problem of Diabetes which is expected with surging cardiovascular morbidity and mortality(5). Little information is present regarding the rate at which CAN present in particular populations with diabetic as it fluctuate from one extreme to other extreme depending on the cohort studied & tools and methods used for evaluation. The prevalence rate varies from 1% to 90% due to significant difference in the study groups(6), particularly with related to CAN risk factors. Failure to recognize patient complain regarding autonomic neuropathy in a diabetic people may lead to lot of unnecessary investigations and sometimes to wasteful treatment. The 5-year mortality of CAN patient with diabetic is five times more than in patients who do not have diabetics (7).

Cardiac autonomic neuropathy (CAN) is one of the dreaded complications of diabetes which is defined as disturbance in the autonomic nervous system leading to cardiovascular abnormality. CAN is mostly due to injury to the autonomic nerve fibers that innervate the cardiac and vascular system and result in irregularity in heart rate control and vascular dynamics.CAN may be under the tip of iceberg for several years until the patient presents with resting tachycardia, intolerance to exercise, postural variation of blood pressure, heart dysfunction, diabetic cardiomyopathy, silent myocardial infarction and ischemia. During its sub-clinical phase, simple noninvasive cardiovascular reflex tests as proposed by Ewing can useful in evaluating CAN before the illness is symptomatic.
Aggressive treatment can retard the progression and postpone the development of abnormal autonomic function tests (8).

The pathophysiological mechanisms linking cardiovascular dysautonomy to mortality are not understood, but are probably various factors involved. Little of the augmented risk can be attributed to sympathetic-vagal imbalance (9) causing life-threatening ventricular arrhythmias. The variance of 24-hr blood pressure seen in patients with CAN may be involved for increased risk associated with mortality (10, 11). Previous studies clearly show the existence of the night-time fall in blood pressure and early morning blood pressure rise, have their role in the prognosis of cardiovascular events (12). It may be seen that blood pressure fluctuating patterns between day and night may cause various type and extent of organ damage and cardiovascular events.

Considering the varied frequency of CAN in representative diabetic populations, impact of presence of CAN and variability patterns of blood pressure levels on cardiovascular morbidity and mortality in diabetic patients, we in the study, aim to investigate CAN in diabetic patients and correlation between cardiac autonomic neuropathy and early morning blood pressure surge.

**MATERIAL AND METHODS** The authors have adopted a Cross sectional study in Chettinad Hospital and Research Institute, Kelambakkam–Chennai. Convenient sampling was adopted.

**STATISTICAL METHODS**

The subjects were clinically examined. The examination consists of complete, clinical history, examination which included ankle reflex and vibration sense using 128 Hz tuning fork.

**Data Analysis:** The total CAN score was calculated. The diabetics were divided in three groups as mentioned in table no.6. Mean and Standard deviation of various parameters were calculated. Confidence interval of 95% & p value <0.05 was considered significant. Chi square, Kruskal Wallis and Mann Whitney test was applied to calculate p value. Pearson’s coefficient was used for correlation of CAN with individual variables in the Ewings battery of tests. Analysis was done using Statistical Package for Social Sciences (SPSS) version 13.

**DISCUSSION**

Cardiac autonomic neuropathy (CAN) is a stealthy complication of diabetes, developing slowly over the years and quietly robbing diabetic patients of their ability to sense when they are becoming hypoglycaemic or having a heart attack.
This cross sectional study was carried out in Chettinad Hospital and Research Institute, Kelambakkam OCT 2018 to AUG 2019. One hundred subjects fulfilling the inclusion criteria were included in the study. They were subjected to standard tests to determine cardiac autonomic neuropathy (CAN) and also relationship between CAN and early morning BP surge was assessed.

The mean age of subjects in the study was 46.29 years. Noronha JL et al\(^{(13)}\) studied Indian diabetics and found the mean age of 57.8 years and Roy TM et al\(^{(14)}\) in a study on autonomic influence of cardiovascular performance in diabetic subjects, found the mean age to be 48.9 years. In another study by Lakhota et al\(^{(15)}\) mean age was reported as 45 years and Vinik AI et al\(^{(3)}\) reported mean age of 47.68 years. In all the above studies, maximum number of subjects was between the age group of 40-60 years, similar to the study.

In the study, 27\% of subjects were females and 73\% were males. Noronha JL\(^{(13)}\) et al in his study had 32\% females and 68\% males. Roy TM et al\(^{(14)}\) studied the prevalence of autonomic neuropathy with 40\% females and 60\% males.

In the study, the majority 45\% of subjects had diabetes of 5-10 years with mean duration of 6.84 ± 4.29 years. In a study done by Keen H\(^{(16)}\), the mean duration of diabetes was 8.2 ± 2.6 years. In the study done by Noronha JL et al\(^{(13)}\) the mean duration of diabetes was 7.2 ± 2 years while for Bathwal et al\(^{(17)}\) was 6.5 years. Vinik AI et al\(^{(3)}\) reported mean diabetes duration of 10.4 ± 2.2 years.

CAN score was calculated for all subjects and they were classified into no autonomic neuropathy, early autonomic neuropathy and severe autonomic neuropathy. In the study, we found autonomic neuropathy in 38\% subjects with 18\% having early autonomic neuropathy and 20\% having severe autonomic neuropathy. Keen H et al\(^{(16)}\) in his study found autonomic neuropathy in 32\% of the subjects, Noronha et al\(^{(13)}\) found the CAN in 38.5\% with 11\% of subjects having severe autonomic neuropathy. In studies done by Toyry et al\(^{(18)}\) and Vinik AI et al\(^{(3)}\) CAN was present among 22\% and 41\% of their patients respectively.

Mean CAN score of our subjects was 1.93, with males having CAN score of 1.81 and females 2.26 but there was no significant association (p value 0.47). Noronha JL et al\(^{(13)}\) in his study, found the mean CAN score was 2.23. Vinik AI et al\(^{(3)}\) in his study found the mean CAN score as 2.23 with mean CAN score of 2.60 in males and 2.10 in females. Similar to the current study both studies did not show association of CAN with gender.

When we analyzed the mean CAN score with the duration of diabetes, we found the mean CAN score was higher in diabetics of more than 10 years duration and the observation was statistically significant. Vinik AI et al\(^{(3)}\), Toyry et al\(^{(18)}\) and Cardoso et al\(^{(19)}\) also had similar observation in their studies. Noronha JL et al\(^{(13)}\) also found increasing
mean CAN score with duration of diabetes but the observation was not statistically significant; in contrast to the study. Lakhotia et al (15) also showed a greater incidence of dysautonomia with increasing duration. The above studies and our present study indicate the correlation between increasing duration of diabetes and the occurrence of autonomic neuropathy.

In the study, peripheral neuropathy was present in 39% of the subjects. The mean CAN score in patients with peripheral neuropathy was 4.00 and without was 0.61; highly significant correlation was found with peripheral neuropathy and CAN. In the study by Vinik AI et al (1), the mean CAN score with peripheral neuropathy was 3.26 and the correlation was statistically significant. Noronha JL et al (13) and Cardoso et al (19) also observed similar correlation in their studies.

The glycaemic control in the study was assessed using HbA1C, the mean value of HbA1C in the study was 8.05 and we found a highly significant correlation between HbA1C and CAN score. Pappachan et al (20) also showed that incidence of diabetic autonomic neuropathy increased with increasing duration and poor glycaemic control.

Resting tachycardia which is regarded as the characteristic feature of cardiac denervation was present in subjects with severe CAN, who had an average heart rate of 99.50 ± 17.31 beats/min which was significantly higher than the heart rate of subjects without CAN (76.31 ± 9.81). Similar finding have been described by Vinik AI et al (3).

Heart rate variability with respiration- 24% subjects had abnormal response in the study. In Ewing et al (21) study it was 42%, Bathwal et al (17) it was 38.3% and in Lakhotia et al (15) the abnormal response was 42% with 20% borderline cases. Subjects with severe CAN had a heart rate variability of 6.76 ± 2.49/min and those with early CAN had a heart rate variability of 11.73 ± 4.47. Similar observations were shown by Toyry et al (18).

Heart rate variability in response to valsalvamanoeuvre -24% of subjects had abnormal response (i.e. <10). Previous studies by Ewing et al (18), Bathwal et al (17) and Lakhota et al (15) had abnormal response of 26%, 22.3 % and 20 % respectively. We found that the patients with early and severe CAN had a valsalva ratio of 1.26 ± 0.21 and 1.15 ± 0.12 respectively. Similar finding was observed by Vinik AI et al (3). 30:15 Ratio - The study had 7% subjects with abnormal response. In Ewing et al (21) study 38% cases had abnormal response, Bathwal et al (17) had 17% cases and in Lakhota et al (15) the abnormal response was seen in 42%. In the study subjects with severe CAN had little variation of the RR intervals during the manoeuvre with an average 30:15 ratio of 1.06 ± 0.12. The ratio was 1.13 ± 0.09 in patients with early CAN.
BP Response to Standing - The study had 1% subjects with abnormal response. In Ewing et al (70) it was 16% cases and in Bathwal et al (17) study it was 4.4% cases and in Lakhotia et al (15) study it was 16% abnormal. We found that postural hypotension was a late feature of CAN. The patients with severe CAN had an average fall of systolic BP of 15.50 ± 9.20mmHg. This was also noted by Toyry et al (18) in their study.

BP response to sustained handgrip - 12% subjects had an abnormal response in the study. In Ewing et al (21) study it was 14% abnormal cases and in Bathwal et al (17) study it was 14.9% and in Lakhotia et al (15) study it was 26% abnormal cases. The patients with severe CAN showed a rise of 10.60 ± 3.25 mmHg in the diastolic BP in response to sustained handgrip. Patients with early CAN showed a rise of 14.33 ± 3.96 mmHg. Similar observations were also noted by Toyry et al (18) in their study.

In the study the percentage abnormal result for HRV with respiration was highest among other CARTs, which also corroborated with the previous studies. HRV to Valsalva stood second and postural hypotension was least affected. This clearly demonstrates that autonomic neuropathy typically involves parasympathetic fibers before the sympathetic nerve fibers (22).

The present study also shows that diabetic subjects with more severe CAN have higher systemic BP particularly nighttime BP and early morning which is statistically significant compared to who do not have CAN. Similar results were observed in a study done in 2007 by Cardoso et al (19).

In the present study, although early morning blood pressure was significantly higher in patients with CAN, since these subjects also presented greater nighttime BP levels, no statistical significant difference in the morning BP surge was observed between the subgroups, when evaluated as the absolute difference between early morning and nighttime BP values. Similar results were observed with study done by Cardoso et al (19). Also, the absence of a standard definition of morning BP surge precludes comparisons between different studies and groups of subjects.

The study shows that diabetic subjects with more severe CAN have higher systemic BP particularly during nighttime and early morning. This adverse profile may contribute to cardiovascular morbidity and mortality in diabetics.

It is of considerable importance that HRV and BP variability should be taken into consideration during the assessment and management of diabetes mellitus with autonomic dysfunction. Assessment should be clearly made not only at resting state but also on dynamic manoeuvres. In the study the authors analyzed autonomic dysfunction
by using CAN score and also analyzed the individual parameters of the entire battery. It was observed that each of the individual parameters were significantly associated with the degree of autonomic neuropathy.

Thus in the wake of these observation, it becomes imperative to evaluate autonomic function tests in every diabetic for early detection of any evidence of autonomic involvement, so that we can encourage both the patient and physician to improve metabolic control. We can consider for BP profile in patients with autonomic neuropathy, as it may also contribute to the increased cardiovascular morbidity and mortality.

CONCLUSION

In the study the prevalence of cardiac autonomic neuropathy in DM is 38%. The CAN score has significant positive correlation with duration of DM and HbA1c. Occurrence of CAN correlates with surge in BP. Thus this study provides evidence that patients with more severe CAN have higher blood pressure in early morning. This adverse profile may increase the cardiovascular morbidity and mortality of diabetic patients with dysautonomy.

1. In the study cardiac autonomic neuropathy in diabetes mellitus as assessed by CAN score was 38%.
2. Cardiac autonomic neuropathy correlates with duration and glycaemic control of diabetes and has no correlation with age, sex of patients.
3. In the current study, occurrence of cardiac autonomic neuropathy correlated with the presence of peripheral neuropathy.
4. All individual tests in the battery of cardiac autonomic neuropathy score were significantly showing the presence of autonomic neuropathy, where heart rate variation with respiration is a better tool for identifying autonomic neuropathy.
5. This study shows evidence that more severe cardiac autonomic neuropathy have higher nighttime and early morning blood pressure than those without cardiac autonomic neuropathy.
6. In the study there is no correlation of cardiac autonomic neuropathy with early morning blood pressure surge.

REFERENCES

