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THE PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY (CAN) IN DIABETIC AND NON-DIABETIC ADULTS WITH NORMAL LV SYSTOLIC FUNCTION ASSESSED BY TIME-DOMAIN HEART RATE VARIABILITY.

Cardiology

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ABSTRACT

Reported prevalence of Cardiac autonomic Neuropathy (CAN) among Diabetic patients in India show high levels of variability, from 34% to 98% (1,2). The available studies have limitations such as comparison groups with unmatched data or a lack of description of confounding factors, such as age, sex, hypertension, body mass index (BMI), coronary artery disease, and cardiac function. We conducted a comparative study among matched Diabetic and non-diabetic populations, using time-domain heart rate variability as the criterion for diagnosis. In our study, people with diabetes had a prevalence of 35.1%, compared to 9.1 % in non-diabetic control group. Meticulous inclusion criteria, matching of confounding parameters in both groups, the purity of data requiring less than 1% editing, and analysis based on age-specific cutoff values are significant advantages of this study.

KEYWORDS

CAN-Cardiac Autonomic Neuropathy. TD-HRV-Time Domain Heart Rate Variability. SDNN - standard deviation of 'NN' intervals, expressed in milliseconds. RMSSD - root mean square of successive 'NN' interval differences, expressed in milliseconds. pNN50 - percentage of successive 'NN' intervals that differ by more than 50 milliseconds.

INTRODUCTION.

Comparative studies of Cardiac autonomic Neuropathy (CAN) among Diabetic patients are rare in India. Available studies show high levels of variability. The prevalence in the diabetic population varied from 34% to 98% [1,2] and from 0% to 33.77 [3,4] among controls. Studies are also limited by the comparison groups with unmatched data or a lack of description of confounding factors, such as age, sex, hypertension, body mass index (BMI), coronary artery disease, and cardiac function. We aimed to conduct a comparative study among matched Diabetic and non-diabetic populations, using time-domain heart rate variability as the criterion for diagnosis.

Heart Rate Variability.

The time interval measured between corresponding points of two successive ECG complexes, such as two successive 'p' waves (pp interval) or two 'R' waves (RR interval), is the 'Inter-beat interval' (IBI). IBI of Normal Sinus Beats are referred to as 'NN' intervals. Beat-to-beat variation in 'NN' intervals (HRV) is under the control of the Autonomic Nervous System, and the level of this variation serves as an index for cardiac autonomic neuropathy testing.

An optimum level of HRV indicates a healthy state. Lower HRV values are abnormal. Non-sinus beats with fluctuating heart rates, as in Atrial Fibrillation, frequent ectopic beats, and conduction blocks, result in erroneously high HRV values. Proper editing to remove these non-"NN" intervals from the analysis is mandatory in clinical studies [5].

Different methods of HRV assessment, including time–domain indices, frequency-domain indices, and nonlinear measurements, have been described. The duration of ECG recordings, varying from one minute to 24 hours, has been studied for HRV analysis. In this study, we have adopted three-time domain parameters (TD-HRV), SDNN (standard deviation of "NN" intervals, expressed in milliseconds), RMSSD (root mean square of successive NN" interval differences, expressed in milliseconds) and pNN50 (percentage of successive "NN" intervals that differ by more than 50 milliseconds), to assess CAN prevalence and an ECG recording duration of two to three minutes. In short-term recordings, SDNN is an indicator of parasympathetic function, while in long-term recordings, it is also influenced by sympathetic function [5]. In this study, recordings last two to three minutes, and all three parameters primarily assess parasympathetic function.

MATERIALS AND METHODS.

Study Population.

The inclusion criteria were Diabetic and non-diabetic adults with no structural heart disease and normal cardiac function, as determined by echocardiography and coronary angiographic evidence of absent obstructive coronary artery disease. Arrhythmia (either tachyarrhythmias or conduction blocks), h/o an acute coronary disease, cerebrovascular events, neurodegenerative or neuropsychiatric disorder, those with poor general conditions, and those with an eGFR <30 mL/mt/1.73 m2 were excluded.

Data Collection.

After obtaining written, informed consent, resting ECG (lead II) data were collected for two to three minutes using the Medicollector software (MediCollector Inc., Boston, MA, United States). This software has proven credentials [6] and was manually verified again by comparing it with data obtained from the monitor. The software enables the visualization of ECG, and if the data quality was inadequate, a repeat sampling was performed. The ECG voltages were captured at 2- or 4-millisecond intervals and were converted to an Excel data sheet. A dedicated software tool was developed for detecting peak values of ECG voltages. The maximum positive value in R-dominant ECG complexes, such as in rsR or Rs patterns, and the minimum negative value in S-dominant complexes, such as in rS or Qs complexes, were used as reference points for calculating 'NN' intervals. The 'NN' intervals thus obtained were verified with manually collected 'NN' intervals from the monitor during an initial trial run period. After confirming the validity of this specially developed software tool, it was used for detecting the 'NN' interval.

Data Cleaning And Editing.

The electronic data in Excel format were converted to ECG complexes and were visually inspected. Non-sinus beats or artifacts were edited by appropriate methods as described, either by deletions or interpolations [7,8]. Interpolation was the method used for editing premature complexes, both atrial and ventricular complexes. A short segment of irregular, uninterpretable tracing, if collected, was deleted. The visualization of complexes and manual editing were feasible, as the duration of data collection was short. The total number of complexes requiring editing was less than 1%, which is significantly lower than the standard recommendation of 20% or less [9].

RESULTS.

The Participants were adults and seniors whose ages ranged from 34 years to 75 years, with a mean age of 57.23 ± 8.90 years. A total of 81 adults, including 37 individuals with diabetes and 44 without, were included in the study. Table 1 presents the prevalence of confounding factors for estimating Cardiac Autonomic Neuropathy.

Table 1: Distribution Of Confounding Variables.

Variable	Category	Frequency (%)
Sex	Female	59 (72.8%)
	Male	22 (27.2%)
Diabetes	Yes	37 (45.7%)
	No	44 (54.3%)

Hypertension	Yes	31 (38.3%)
	No	50 (61.7%)
Thyroid Disorder	Yes	16 (19.8%)
	No	65 (80.2%)
COVID History	Yes	13 (16.0%)
	No	68 (84.0%)
BMI Category [10]	Underweight	3 (3.7%)
	Normal	36 (44.4%)
	Overweight	31 (38.3%)
	Obese	3 (3.7%)
	Missing	8 (9.9%)
RAAS Inhibitor	Yes	21 (25.9%)
	No	60 (74.1%)
Beta Blocker	Yes	29 (35.8%)
	No	52 (64.2%)

The majority were females (72.8%), hypertension was present in 38.3%, thyroid disorders in 19.8%, and 16% gave a history of COVID-19. Nearly 1/3 of hypertensives were using medications influencing CAN testing (25.9% were on drugs acting at the Renin-angiotensin axis and 35.8% on beta blockers).

Both groups matched for other confounding factors (Table 2).

Table 2: Comparison Of Confounding Variables - Diabetic And Non-diabetic Groups

Variable	Response	Diabetic (n = 37)	Non-Diabetic (n = 44)	p-value
Age (years)	Range	39 – 75	34 – 75	0.28[a]
	Mean ± SD	58.41 ± 8.31	56.25 ± 9.35	
Sex	Female	27 (73.0%)	32 (72.7%)	0.98[b]
	Male	10 (27.0%)	12 (27.3%)	
BMI (kg/m²)	Range	20.34 – 33.33	16.61 – 36.79	0.362[a]
	Mean ± SD	25.32 ± 3.03	24.54 ± 4.06	
Hypertension	Yes	17 (45.9%)	14 (31.8%)	0.193[b]
	No	20 (54.1%)	30 (68.2%)	
Thyroid Disorder	Yes	9 (24.3%)	7 (15.9%)	0.343[b]
	No	28 (75.7%)	37 (84.1%)	
COVID History	Yes	4 (10.8%)	9 (20.5%)	0.239[c]
	No	33 (89.2%)	35 (79.5%)	
RAAS Inhibitor	Yes	10 (27.0%)	11 (25.0%)	0.836[b]
	No	27 (73.0%)	33 (75.0%)	
Beta Blocker	Yes	15 (40.5%)	14 (31.8%)	0.415[b]
	No	22 (59.5%)	30 (68.2%)	

a: Independent T-test, b: Chi-square test, c: Fisher's Exact test.
p<0.05 indicates statistical significance.
Prevalence of CAN.

The Time domain Heart Rate Variability (TD-HRV) parameters, SDNN (standard deviation of "NN" intervals, expressed in milliseconds), RMSSD (root mean square of successive NN" interval differences, expressed in milliseconds), and pNN50 (percentage of successive "NN" intervals that differ by more than 50 milliseconds), were studied to assess CAN prevalence. Analysis was performed using age-specific normative values of TD-HRV [11]. Abnormal CAN was defined as the presence of at least one abnormal TD-HRV parameter. SDNN was the most sensitive parameter (21%); both SDNN and RMSSD showed statistically significant differences between the groups. The pNN50 was the least sensitive parameter and did not show a significant difference between groups (Table 3). Twenty-one percent of participants had at least one TD-HRV parameter abnormality; thus, the overall prevalence of CAN is 21%.

Table 3: HRV Parameters And Overall CAN

Parameter	SDNN	RMSSD	pNN50	Overall CAN Prevalence
Abnormal (%)	17 (21.0%)	8 (9.9%)	3 (3.7%)	17 (21.0%)
Normal (%)	64 (79.0%)	73 (90.1%)	78 (96.3%)	64 (79.0%)

Table -4. Distribution of abnormal TD-HRV parameters in the overall study population.

All three	SDNN+ RMSSD	SDNN+ pNN50	RMSSD+ pNN50	Only SDNN	Only RMSSD	Only pNN50
2	6	1	0	8	0	0

This table shows that RMSSD and pNN50 are abnormal only in patients with abnormal SDNN. SDNN has the maximum discriminative power, and the addition of RMSSD or pNN50 does not enhance the sensitivity of TD-HRV for CAN diagnosis.

Table-5. Prevalence of abnormal HRV parameters (Diabetics compared to non-diabetics).

	SDNN	RMSSD	pNN50	Overall CAN prevalence*
Diabetics	13	7	3	13 (35.1%)
Non-Diabetics	4	1	0	4 (9.1%)

*P=0.004.

The Prevalence of CAN is significantly higher in people with diabetes (35.1%) compared to non-diabetics (9.1%) with p = 0.004.

DISCUSSION.

The development of Autonomic neuropathy in diabetes is considered to be multifactorial. The factors include hyperglycemia-glucotoxicity, inflammation, and genetic polymorphism. [12,13,14] CAN in diabetes is studied using varying criteria, and therefore, the prevalence varies between studies.

Most of the Indian studies followed Ewing's battery of Cardiovascular Autonomic Reflex Tests (CARTs). Studies were primarily done in the Diabetic population alone, and comparative studies between Diabetics and non-diabetics are rare in India. A very high prevalence of CAN in Diabetes was reported in studies by Paneerselvam et al. (80.39%), Karthikeyan et al. (85.7%), PP Sethy et al. (98%) [2,15,16] while it was only 58% in the study by Birajdar et al. [17]

A similar disparity is also observed in comparative studies. A very high prevalence of CAN is noticed by Viswanathan et al. [3]in diabetes (56 % in diabetes and 96% in Diabetic Nephropathy) and Jyotsna et al. [4], who reported 71.32 % with CAN and 20.93% with borderline CAN (a total of 93.25%) while Mahesh et al. [1] reported a prevalence of 34 % only. The CAN prevalence in the control group also showed similar variation; Jyotsna et al. [4] reported 33.7% each of definite and borderline CAN, whereas Mahesh et al. [1] found only 2%. In contrast, none of the control group participants had CAN in a study by Viswanathan et al. [3].

In a comparative study from Raipur, Chhattisgarh, by M. S. Siddiqui et al. [18], HRV and cold pressor tests were criteria in addition to Ewing's battery of CARTs. In his study, 88.66% of people with diabetes had abnormal HRV compared to 17 % in controls.

All the mentioned studies were based on Ewing's battery of CARTs as the primary criterion [19]. Mahesh et al. considered QTc dispersion [1], and Jyotsana et al. Cold pressor tests [4] in addition to Ewing's battery of CARTs.

The wide variation in CAN prevalence despite using similar diagnostic criteria is intriguing. Variations in selection criteria, influence of confounding variables, and inadequate data editing may be possible causes. The high prevalence in the above studies can be attributed to the use of a single cutoff value rather than age-specific cutoff values.

The HRV values vary with the length of the recording period and sampling frequency. A constant recording period and a sampling frequency of 250 -500 Hz are preferable [5]. Our recording speed was optimal according to the recommendation.

The conventional short-term recording period is 5 min. However, multiple studies have compared varying durations of recordings and found that 2- to 3-minute recordings are equally effective as longer-duration recordings [5]. An analysis of 3,387 data by Munoz et al. reports that 120 seconds of recording correlated well with 240-300 seconds of data for determining SDNN and RMSSD [20]. Moreover, short-duration recordings allow meticulous data cleaning.

CONCLUSION

1. People with diabetes have a higher prevalence of Cardiac Autonomic Neuropathy (35.1%) compared to non-diabetics (9.1%).
2. SDNN is the most sensitive Time-Domain HRV parameter for the diagnosis of CAN. The addition of RMSSD or pNN50 does not enhance the sensitivity of TD-HRV for CAN diagnosis.

Study Highlights And Limitations.

The small sample size and single-centre study are limitations of the study. However, meticulous inclusion criteria, matching of confounding parameters in both groups, the purity of data requiring less than 1% editing, and analysis based on age-specific cutoff values are significant advantages.

Acknowledgement- This study is a sub-analysis of CAN-HF (Cardiac Autonomic Dysfunction in Diabetic Heart Failure Patients compared to Non-Diabetic Heart Failure Patients) study.

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