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Assessment of Prevalence of Cardiac Autonomic Dysfunction by Various Cardiovascular Autonomic Function Tests Using Ewing's And Bellavarae's Criteria

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Abstract: Cardiac autonomic dysfunction is an independent risk factor for cardiovascular and cerebrovascular diseases that accelerate the mortality rate in individuals. However, complicated diagnostic tests with various criteria and a lack of relevant studies make Cardiac autonomic neuropathy (CAN) become one of the diabetic complications that is most likely to be neglected. So we undertook this study for assessment of cardiac autonomic dysfunction in 125 healthy subjects (age-20-70 years) by 3 parasympathetic tests including heart rate response to deep breathing, standing and valsalva maneuver; and 2 sympathetic tests consisting of blood pressure response to standing and sustained hand grip (SHG).Cardiac autonomic dysfunction in subject was evaluated by categorizing subjects using various scoring systems such as Ewing's criteria and Bellavere's criteria. In this study according to Ewing's and Bellavarae criteria severity of CAN increases with age & severity of CAN is more in male subjects as compare to female subjects. The present study thus can be an effective tool for screening of the cardiovascular autonomic dysfunction & its complication in subjects, thereby decreasing the morbidity and improving the quality of treatment.

Keywords: Cardiac autonomic dysfunction, Cardiac autonomic neuropathy (CAN), heart rate response to deep breathing, heart rate response to standing and valsalva maneuver, blood pressure response to standing and sustained hand grip (SHG), Ewing's criteria and Bellavarae's criteria.

INTRODUCTION

The autonomic nervous system innervates every organ in the body and is largely involuntary. One of the most ignored of all serious complications of diabetes is cardiac autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibre that innervate the heart and blood vessels intern results in the abnormalities of heart rate control and vascular dynamics.CAN occurs when peripheral autonomic fibres which include both sympathetic and parasympathetic of the cardiovascular system get affected, which leads consequential in neuro –humoral regulation disturbances. The sympathovagal balance (both tonic and phasic)modulates the function of three of the main CVS structures:the sinus node (heart rate),the ventricles (end-systolic and end-diastolic volumes) and the blood vessels ,including microcirculation (total peripheral resistance).Autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life threatening outcomes.Autonomic dysfunction occurs in primary neurologic disorders, diabetes mellitus, and chronic renal disease, as well as in cancer [3]. Autonomic neuropathy has been shown to be a risk factor for falls in older adults with dementia [4]. In diabetic patients, cardiac autonomic neuropathy is manifested as exercise intolerance, intraoperative cardiovascular liability, orthostatic hypotension, painless myocardial ischemia, and increased risk of mortality, thereby having a great impact on morbidity, mortality and quality of life.

However, cardiovascular reflex tests are being used most widely now as they are non-invasive, results are easy to reproduce and they reflect the state of ANS throughout the body. Due to these test now it is possible to identify early stage of CAN and to provide therapeutic choices that are based on symptom control and that might abrogate the underlying disorder. To our knowledge, there are very less studies investigating the prevalence of autonomic dysfunction so we decided to perform study for assessment of prevalence of cardiac autonomic dysfunction by simple bedside and objective cardiovascular reflex tests which includes 5 tests proposed by Ewing.

MATERIALS AND METHODS

A total of 125 healthy individuals of Rajasthan were included in this study with age range from 20 to 70 years. The study was conducted in the Department of Physiology at Dr. S.N. Medical college ,jodhpur .The non smoker, non alcoholic, non diabetic ,having normal pulse rate, blood pressure, normal heart sounds and having no evidence of illness and having perfect physical, mental and psychological well being were included in the study. A brief history was taken and general physical examination of all the volunteers was done with main emphasis on cardiovascular diseases, renal diseases. None of the subjects took any medication at the time of study. All the tests were carried out between 11 am to 4 pm. The procedure was explained and informed consent was obtained after the subjects had read a description of the experimental protocol, which was approved by the ethical committee of the college.

METHOD-CAN Win METHOD

Following non- invasive cardiovascular sympathetic and parasympathetic tests were carried out:-

Parasympathetic dysfunction was diagnosed by applying three tests, as follows

Heart rate (HR) response to deep breathing (HRD)

Participants lay flat. After the pulse had steadied, the pulse rate was recorded during six slow, maximal deep breaths. In normal subjects, the pulse rate should fall by at least 15 beats; borderline, 11–14 beats; and with autonomic disturbances, no more than 10 beats per minute (Ewing and Clarke)[5,6].

HR response to standing (30:15 RATIO)

The R–R interval on the ECG was recorded and used to determine the instantaneous HR at rest and then on the 15th and 30th beats after standing. The HR should normally rise after about 30 seconds as part of the response to return the blood pressure (BP) to normal. The normal 30th:15th pulse–HR ratio is at least 1.04; borderline, 1.01– 1.03; and abnormal, 1.0 or below (Ewing and Clarke)[5,6].

HR response to Valsalva (V M RATIO)

The test was performed by asking the subject to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg for 15 seconds. The ratio of the longest R–R interval shortly after the manoeuver (within about 20 beats) and the shortest R–R interval during the manoeuver is then measured. The result was expressed as the Valsalva ratio that is taken as the mean ratio from three successive Valsalva manoeuvers. In normal subjects, the Valsalva ratio is at least 1.21, and in those with autonomic disturbances, 1.20 or below (Ewing and Clarke)[5,6].

Sympathetic dysfunction was assessed with two tests, as follows

BP response to standing (BPS)

Participants were asked to stand up for 3 minutes after a 10-minute resting period in a supine position. The systolic and diastolic BP (SBP and DBP) just before standing, and 3 minutes after active standing were determined, in order to define postural change in BP and to evaluate orthostatic intolerance. A fall of SBP by: less than 10 mmHg is normal; 11–29 mmHg is borderline; and more than 30 mmHg is abnormal (Ewing and Clarke)[5,6].

BP response to sustained handgrip

Patients performed three consecutive (within 5-minute resting periods) handgrip tests for 2 minutes, while beat-to-beat BP was recorded simultaneously. The absolute difference between the highest DBP during handgrip and the basal DBP just before the handgrip was noted. A DBP that is raised by at least 16 mmHg is normal; borderline is 10–15 mmHg; and abnormal is 10 mmHg or below (Ewing and Clarke)[5,6].

Table-1: Normal, borderline, and abnormal values of cardiovascular autonomic tests

Tests	Normal (0 score)	Borderline (1 score)	Abnormal (2 score)
Heart-rate (R-R interval) variation during deep breathing. (E:I ratio)	≥ 1.21	1.20-1.110	≤ 1.10
Heart-rate response to Valsalva maneuver (Valsalva ratio)	≥ 1.21	_	< 1.21
Immediate heart-rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Blood-pressure response to sustained handgrip (increase in diastolic blood pressure)	≥16 mmHg	11-15 mmHg	<10 mmHg
Blood-pressure response to standing (fall in systolic blood pressure	≤10 mmHg	11-29 mmHg	≥30 mmHg

Categorization of subjects for CAN based on different criteria

The cardiovascular tests are classified as tests based on heart rate and tests based on blood pressure. This approach is useful clinically because it reflects the apparent sequence of abnormalities seen in diabetic subjects. Ewing *et al*. [5,6], have advised classification of the degree of autonomic involvement as early, definite or severe rather than as sympathetic and parasympathetic.

The Ewing test score is considered a standard for diagnosis of autonomic dysfunction. The Ewing score is a composite of scores from a battery of five autonomic tests, each scored as normal (0 points), borderline (1 points), or abnormal (2 point). A patient's scores on the five tests are summed to arrive at the composite Ewing score.

For this they used:-

- Deep breathing test (E:I ratio)
- Valsalva Maneuver
- 30:15 ratio
- Handgrip test
- Lying to standing test (orthostatic test)

Categorization as per Ewing's criteria

CATEGORY OF CAN	CRITERIA
NORMAL	All tests normal or one test borderline
EARLY	One of three heart rate tests abnormal or two borderline
DEFINITE	Two or more of the heart rate tests abnormal
SEVERE	Two heart rate tests abnormal plus one or both BP tests abnormal or both borderline

The scoring was added and CAN was classified according to as per Ewing Criteria as follows

Classification Category	Total Score
No CAN	0-1
Early CAN	2-3
Definite CAN	4-6
Severe CAN	Above 6

Categorization as per Bellavere's criteria[65]

Similarly, Bellavere *et al*. have given a scoring to determine the severity of CAN. According to this, score 0 to 2 is assigned for each test and the total score were obtained after addition of below three tests score:-

- Deep breathing test
- Valsalva maneuver
- Lying to standing

Categorization as per Bellavere's criteria

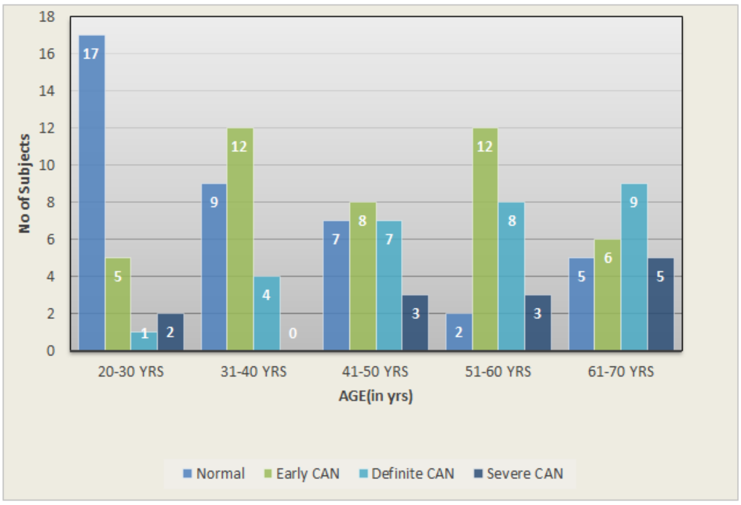
Classification Category	Total Score
No CAN	0-1
Early CAN	2-3
Definite CAN	4-6

RESULTS

Table-1: Association between age groups and prevalence of can (cardiac autonomic neuropathy) according to ewing's criteria

Age group in years	Total Number (%)	Normal No.(%)	Early CAN No.(%)	Definite CAN No.(%)	Severe CAN No.(%)	p value from chi square test
20-30	25(20)	17(68)	5 (20)	1 (4)	2 (8)	<0.001
31-40	25(20)	9 (36)	12 (48)	4 (16)	0 (0)	
41-50	25(20)	7 (28)	8 (32)	7 (28)	3 (12)	
51-60	25(20)	2 (8)	12 (48)	8 (32)	3 (12)	
61-70	25(20)	5 (20)	6 (24)	9 (36)	5(20)	
Total	125	40(32)	43(34.4)	29(23.2)	13(10.4)	

Table no.1 shows association between different age groups & prevalence of cardiac autonomic neuropathy in subjects. On statistical analysis with Chi-Square test we found highly significant results (p-value <0.001).

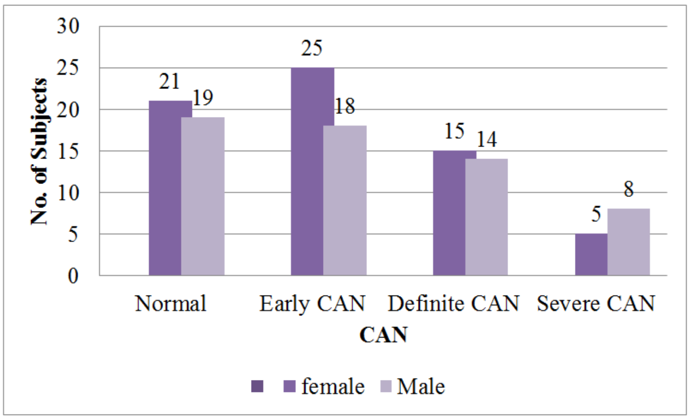


Graph-1: Association between age group & prevalence of can

Table-2: Association between gender and prevalence of can according to ewing's criteria

Gender	Total No.(%)	Normal (%)	Early CAN (%)	Definite CAN (%)	Severe CAN (%)	p value from chi square test
Female	66(52.8)	21(31.81)	25(37.87)	15(22.72)	5(7.57)	0.6641
Male	59(47.2)	19(32.20)	18(30.50)	14(23.72)	8(14.28)	
Total no.	125	40(32)	43(34.4)	29(23.2)	13(10.4)	

Table No. 2 shows association between gender and prevalence of cardiac autonomic neuropathy according to Ewing's criteria. On statistical analysis the result was found to be non-significant (p-value 0.67).

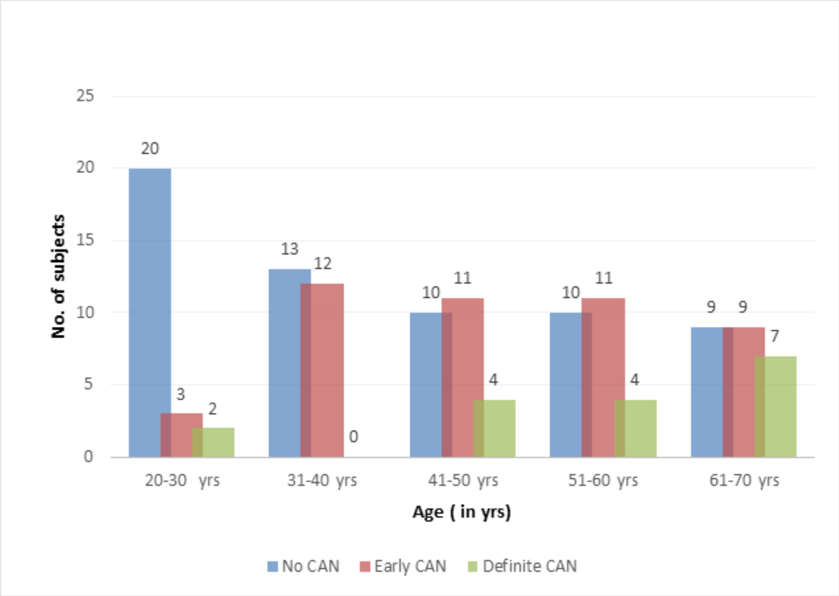


Graph-13: Prevalence of can with gender ewing's criteria

Table-3: Association between age groups and prevalence of can (cardiac autonomic neuropathy) according to bellavarae's criteria

Age (in yrs)	Total Number (Per.)	No CAN	Early CAN	Definite CAN	p value
20-30	25(20)	20(8)	3(12)	2(8)	0.009301
31-40	25(20)	13(52)	12(48)	0(0)	
41-50	25(20)	10(40)	11(44)	4(16)	
51-60	25(20)	10(40)	11(44)	4(16)	
61-70	25(20)	9(36)	9(36)	7(28)	
	125	62(49.6)	46(36.8)	17(13.6)	

Table no.3 shows association between different age groups & prevalence of cardiac autonomic neuropathy in subjects. On statistical analysis with Chi-Square test we found highly significant results (p-value <0.001).

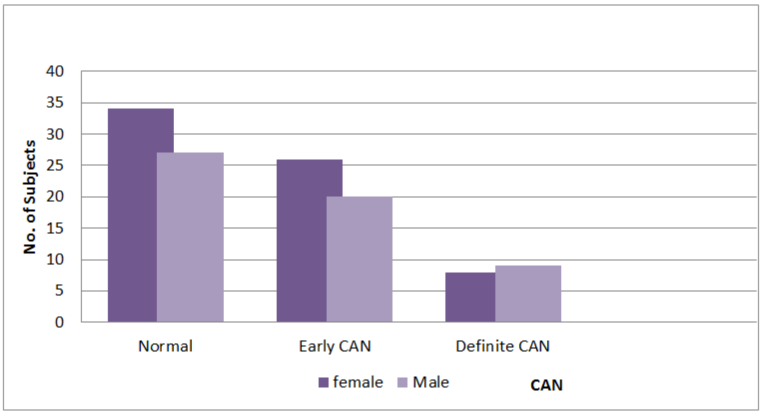


Graph-3: Prevalence of can with age-bellavarae criteria

Table-4: Association between gender and prevalence of cardiac autonomic neuropathy (can) according to bellavarae's criteria

Gender	Total Number (%)	No CAN	Early CAN	Definite CAN	p value from chi square test
Female	66(52.8)	34(51.51)	26(39.39)	8(12.12)	0.7835
Male	59(47.2)	27(45.76)	20(33.89)	9(15.25)	
total number	125	62(49.6)	46(36.8)	17(13.6)	

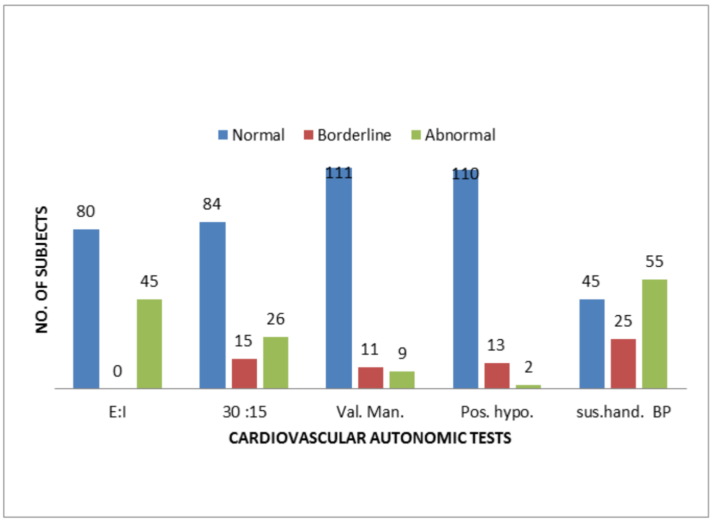
Table No. 4 shows association between gender and prevalence of cardiac autonomic neuropathy according to Bellavarae's criteria. On statistical analysis the result was found to be non-significant (p-value 0.78).



Graph-4: Association between gender and prevalence of can-bellavarae criteria

Table-5: Distribution of Subjectss by Various Cardiovascular Reflex Tests N (125)

Test Type	Cardiovascular reflex Test	Normal	Borderline	Abnormal
Parasympathetic Tests	Effect of deep breathing on heart rate	80(64)	0(0)	45(36)
	Effect of standing 30 :15 ratio on heart rate	84(67.20)	15(12)	26(20.80)
	Effect of Valsalva maneuver on heart rate	111(88.80)	11(8.8)	9(7.2)
Sympathetic Tests	Postural hypotension	110(88)	13(10.4)	2(1.6)
	Effect of Sustained Handgrip on Blood Pressure	45(36)	25(20)	55(44)



Graph-5: Distribution of subjects according to cardiovascular autonomic tests

DISCUSSION

The present study was carried out in 125 healthy subjects in the age range of 21-70 years, to assess the prevalence of cardiac autonomic dysfunction by various cardiovascular reflex test using Ewing's and Bellavarae's criteria. The subjects were distributed into five age groups. Total 25 subjects (20%) were included in each group. Out of the total 125 subjects, 66(52.8%) were females and 59 (47.2%) were males. In the present study, the mean age of Group A,Group B ,Group C ,Group D and Group E was 25.32,36.36,45.8,57.36 and 67.44 respectively ,with significant p value (<0.01).

Association between various factors and prevalence of CAN- Very few studies have been done for assessment of CAN in population and many of them used only one criterion for assessment of CAN in population. In this study, we use two criteria for assessment of Prevalence of CAN in subjects. The Bellavere's criteria use the tests that only represent the parasympathetic component while Ewing's criteria use the tests for parasympathetic as well as sympathetic component.

EWING'S tests criteria

Table no.1 shows association between different age groups & prevalence of cardiac autonomic neuropathy in subjects .Out of 125 subjects,32% were Normal, 34.4% were Early CAN, 23.2% were with Definite CAN and 10.4 % subjects shows Severe CAN .According to Ewing's Criteria severity of CAN increases with age as number of Severe CAN (Two heart rate tests abnormal plus one or both BP tests abnormal or both borderline) in 20-30 yrs age group was 2 (8%) which increases up to 5(20%) in 60-70 yrs age group. So according to this study elderly subjects are severely affected by autonomic dysfunction, as both the parasympathetic and sympathetic pathways are affected. On statistical analysis with Chi-Square test we found highly significant results (p-value <0.001) .With increase in age there is changes in neurons such as pigment accumulation, Schwann cell demyelination, neuronal loss axonal degeneration progressive reduction in pre-ganglionic sympathetic neurons of intermediolateral column of spinal cord , which causes increase incidence of autonomic dysfunction in elderly.

In a study Kunachgi Preeti Nagkumar *et al.* [8] had observed that autonomic nervous system dysfunction was more prominent in males above the age of 60 rather than females of the same age group. This gender related difference in parasympathetic regulation which diminishes after 50 years of age was also observed by Kuo *et al*.[9] in a similar study in Taiwan . Liao D Barnes et al [10], found that HRV spectral indices were associated with age and sex and as age increases, the sympathetic and parasympathetic activity decreases. In yet another study by Zhang *et al*. [11], it was concluded that age had a greater impact on HRV than gender where though males were more prone to ANS dysfunction than females, it was seen only in the age above 50 years than in the young.Guatschy *et al.* [12], found that each of the functional parameters depending on cardiac parasympathetic integrity, i.e. the beat to beat variation, orthostatic 30/15 R-R ratio and Valsalva ratio, decreased progressively with increase in age. The indices based in the heart rate differences are more suitable for assessment of autonomic disturbances in the elderly than BP response tests.Our study was also in agreement with study done by Rachna Parashar *et al.* [13], Dr. Mohit Malage *et al.* [14] and Vita G *et al.* [15].

Table No. 2 shows association between gender and prevalence of cardiac autonomic neuropathy according to Ewing's criteria. Out of 125 subjects 66(52.8 %) was female and 59 (47.2 %) was male. according to Ewing's criteria more number 13(14.28%) of male shows severe CAN as compared to female 5 (7.57 %).On statistical analysis the result was found to be non significant (p-value 0.67). Our results are in accordance with the results of earlier studies done by Kunachgi Preeti Nagkumar [8], Kuo *et al*. [9], Zhang *et al*. [10] and our results are not in accordance with Philip A *et al*. [16] and Yukishita *et al.* [17] . Yukishita *et al*. [17] in his study assessed that there is significant more decline in autonomic function in women in old age then men.

Bellaverae criteria

Table no.3 shows association between different age groups & prevalence of cardiac autonomic neuropathy in subjects .Out of 125 subjects, 49.6% were No CAN,36.8% were Early CAN and 13.6 % were with Definite CAN. According to Bellavarae's Criteria severity of CAN increases with age as number of Definite CAN in 20-30 yrs age group was 2 (8%) which increases up to 7(28%) in 60-70 yrs age group. On statistical analysis with Chi-Square test we found highly significant results (p-value <0.001). Our study is not accordance with Snyder dl *et al*. [18] and Vaz M et al [19] concluded that sympathetic function remains unchanged with increasing age but on other side Romero-Vecchione *et al*. [20] found atypical pattern among changes in sympathetic functions with age i.e. increase from young to middle age and then decline towards group older age .In a study, Qi Fu *et al*. [21] concluded that there is varied response among change in sympathetic parameters with age (Increase, decrease or unchanged).

Table No. 4 shows association between gender and prevalence of cardiac autonomic neuropathy according to Bellavarae's criteria.Out of 125 subjects 66(52.8 %) was female and 59 (47.2 %) was male. According to Bellavarae's criteria more number 9(15.25%) of male shows Definite CAN as compared to female 8 (12.12 %).On statistical analysis the result was found to be non significant (p-value 0.78).Our results are in accordance with the results of earlier studies done by Kunachgi Preeti Nagkumar [8], Kuo *et al.* [9], Zhang *et al*. [10] and our results are not in accordance with Philip A *et al.* [16] and Yukishita *et al.* [17].

Hence from our study we find that according to Ewing's and Bellavarae'scriteria severity of CAN increases with age & severity of CAN is more in male subjects as compare to female subjects.

Distribution of subjects according to cardiovascular autonomic tests

According to Table no 5, Out of all cardiovascular autonomic function tests 36 % subjects shows abnormal result in effect of Deep Breathing on Heart Rate ,20.80% subjects shows abnormal result in effect of orthostatic test on HR,7.2% subjects shows abnormal valsalva maneuver,1.6% subjects shows abnormal postural hypotention and 44% subjects shows abnormal effect of sustained .handgrip test on BP. So according to our study sympathetic system is affected more than parasympathetic system.

CONCLUSIONS

So from our study it may concluded that severity of cardiac autonomic dysfunction increases with age and severity of cardiac autonomic dysfunction is more in male subjects as compared to female subjects. So findings of our study suggest that screening for cardiac autonomic dysfunction should be done to prevent further complications as above mentioned tests are reliable, reproducible, simple, non invasive and quick to carry out. The simple bedside tests described above can provide an objective guide to whether or not autonomic damage is present, and to what degree. Some of the troublesome symptoms in the later stages can now be more successfully treated than before. Also such early screening can significantly reduce the mortality and morbidity in diabetic patients and thereby decrease the global burden of cardiac autonomic neuropathy arising due to diabetes mellitus. The longer-term aim of management should, however, be the prevention or reversal of autonomic damage, particularly in its early stage.

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