

Cardiovascular Parasympathetic Changes in Type-II Diabetic Mellitus

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ABSTRACT

Objectives: To evaluate cardiovascular parasympathetic function tests in diabetes and match the data so obtained with healthy non diabetic individuals as controls.

Materials and Methods: Present prospective study was conducted in the department of physiology, Siddhartha medical college and govt.gen.hospital, Vijayawada during October 2012 to September 2014. Total 100 subjects were selected which includes 50 randomly selected population and also 50 type-II diabetics who are diagnosed based on WHO criteria. The exclusion criteria were patients taking medications other than oral hypoglycemics that could influence the autonomic functions and drugs those could affect the cardiovascular functions are excluded.

Results: The mean \pm SD of Age of group-A and group-B were found to be: group-A : 50.26 ± 5.27 , group-B cases: 49.32 ± 5.83 respectively. HR response to standing of group-A and group-B were 1.14 ± 0.13 and 1.08 ± 0.11 respectively. HR in response to deep breathing test group-A and group-B of were 25.5 ± 6.96 and 19.12 ± 9.41 respectively. HR in response to Valsalva manoeuvre of group-A and group-B were 1.39 ± 0.24 and 1.24 ± 0.13 respectively.

Conclusion: There was a statistically significant alternation in ANS functions in the test group when compared to control group. Both parasympathetic and sympathetic cardiovascular responses were altered significantly. Decreased HRV are associated with CAN in type II diabetes suggesting that impairment of autonomic function. DM affects cardiovascular autonomic function adversely through various metabolic and vascular mechanisms.

KEY WORDS: Parasympathetic, Cardiovascular, Heart rate, Diabetes.

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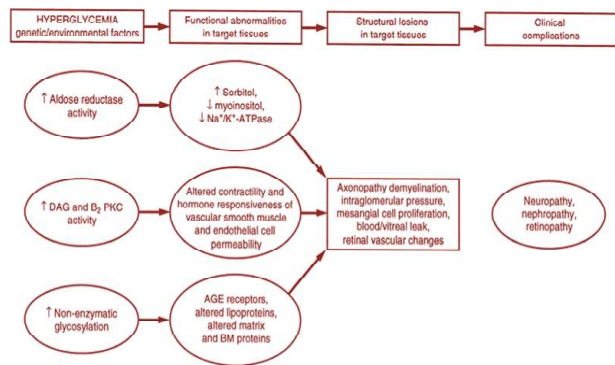
INTRODUCTION

Diabetic autonomic neuropathy is a heterogeneous condition that comprises a wide range of dysfunction and whose development might be attributed to diabetes per se or to factors associated with the disease. Both sympathetic and parasympathetic fibres may be affected with parasympathetic dysfunction preceding sympathetic dysfunction. The etiopathology of Diabetic

Autonomic Neuropathy is multi-factorial. It has been associated with round cell infiltration; hence autoimmunity may contribute to it. The polyol pathway activation in diabetes may also play a part by leading to increased sorbitol accumulation which is neurotoxic to autonomic nerves as well as other nerves. Other factor is oxidative stress. This may increase oxygen free radicals with in cells. These can react with com-

ponents of cells, including nerves, and cause damage. Nerves do have defence mechanisms against oxidative stress but they do not necessarily work to the same extent in different populations. Therefore, it is possible that autonomic nerves with a greater level of defence against oxidative stress may be able to resist the effects of diabetes while others with low levels of defense will be particularly susceptible to degenerative changes. Disturbed regulation of local blood flow may also play a role in etiopathogenesis [1-3].

Fig. 1: Patho-physiology of diabetic autonomic neuropathy.



When diabetic neuropathy affects the autonomic nervous system, it can damage the cardiovascular, gastrointestinal, genitourinary and neurovascular systems. Of these, cardiac autonomic neuropathy (CAN) encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [4].

In Cardiovascular autonomic neuropathy, a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. Individuals with parasympathetic dysfunction have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Persons with a combined parasympathetic and sympathetic dysfunction have slower heart rates. With advanced nerve dysfunction, heart rate is fixed. Thus, it is apparent that the determination of heart rate itself is not a reliable diagnostic sign of CAN [5,6].

Clinical Manifestations of Cardiovascular Autonomic Dysfunction:

Resting Tachycardia: An increased resting heart rate is observed frequently in diabetic patients most likely due to the vagal cardiac neuropathy that results in an unopposed cardiac sympathetic activity. Heart rate variability is considered the earliest indicator and most frequent finding in symptomatic cardiovascular autonomic dysfunction.

Exercise Intolerance: In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic/sympathetic responses that would normally enhance cardiac output and result in directing peripheral blood flow to skeletal muscles. Reduced ejection fraction, systolic dysfunction, and decreased diastolic filling, potentially as a result of CAN, also limit exercise tolerance.

Intraoperative Cardiovascular Liability: There is a 2- to 3-fold increase in cardiovascular morbidity and mortality intraoperatively for patients with diabetes.

Orthostatic Hypotension (OH): A change from lying to standing normally results in activation of a baroreceptor-initiated, centrally mediated sympathetic reflex, resulting in an increase in peripheral vascular resistance and cardiac acceleration. OH is characterized by a defect in this reflex arc, resulting in signs and symptoms such as weakness, faintness, dizziness, visual impairment, and syncope. Although the absolute fall in blood pressure is arbitrary, OH is usually defined as a fall in blood pressure [i.e. 20-30 mmHg for systolic or 10 mmHg for diastolic] in response to postural change from supine to standing.

Painless Myocardial Ischemia: Inability to detect ischemic pain can impair the recognition of myocardial ischemia or MI. The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, sub-threshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms.

Increased Risk of Mortality: Impaired autonomic control of heart rate is linked to increased risk of mortality. Reduced parasympathetic function or increased sympathetic activity may provide the propensity

for lethal arrhythmias [7].

The functional characteristics of the autonomic nervous system can be assessed by certain physiologic tests. These tests are non-invasive, easy to use, and provide quantitative or regional information about autonomic function. Today, sensitivity and early assessment of cardiovascular autonomic neuropathy is possible by means of noninvasive autonomic function tests, including time domain (statistical analysis), indices of heart rate variability, aiming at prevention of advanced stages. Standard tests of cardiac autonomic function were initially used to classify subjects according to the presence or absence of neuropathy; however, more recent studies attempted to grade the severity of neuropathy.

Assessing Cardiovascular Autonomic Function Tests by Sympathetic function tests Blood Pressure Response to Standing, Sustained Handgrip, Cold Pressor Test and parasympathetic Heart Rate Response to Standing, Deep Breathing, Valsalva Maneuver.

Normal: All tests normal, or one borderline results.

Mildly abnormal: One of the three heart rate tests abnormal or 2 borderline

Definitely abnormal: Two or more of the heart rate tests abnormal.

Severely abnormal: Two or more of the heart rate tests abnormal, plus one or both of the BP tests abnormal, or both borderline.

The traditional cardiovascular risk factors are related to increase with the age and diabetes duration correlates of diabetic autonomic neuropathy. CAN is a common complication in type 2 diabetes [8]. The loss of parasympathetic activity being commoner than loss of sympathetic activity which leads to abnormal responses to autonomic function tests [9]. HRV is inversely associated with glycemic variability in patients with T2D, which might be a sign of causation between GV and autonomic dysfunction [10]. Autonomic dysfunction predicts short-term cardiovascular events among CAD patients with T2D [11]. Cardiovascular reflex tests were performed to determine the cardiovascular autonomic function. There was a statistically significant decrease in HRV in type-II diabetes

with microalbuminuria [12]. Against this background, the present study was undertaken to evaluate cardiovascular parasympathetic function tests in diabetes and match the data so obtained with healthy non diabetic individuals as controls.

MATERIALS AND METHODS

The Present prospective study was conducted in the department of physiology, Siddhartha medical college and Govt. Gen. Hospital, Vijayawada during October 2012 to September 2014. The study was undertaken to analyse the differences in cardiovascular parasympathetic function tests in normal individuals and type-II diabetics in the age group 40-60 years.

Selection of Subjects: In the present study total 100 subjects were selected which includes group-A (controls) 50 normal individuals and also group-B (cases) 50 type-II diabetics who are diagnosed based on WHO criteria. They were selected from the general population of Vijayawada City randomly and patients who were attending government general hospital, Vijayawada.

Inclusion Criteria:

- The protocol was explained to the subjects and patients, who volunteered for the present study and informed consent was obtained from each of the participant.
- Includes 50 healthy, non-diabetics, non - smokers within the age group of 40-60 years.
- Cases of already diagnosed type-II diabetes mellitus who are full filling who criteria's
- Who are attending medicine out patient at Govt. General Hospital, Vijayawada with in the age group of 40 – 60 years are selected.

Exclusion Criteria:

- Diagnosed diabetic patients are excluded.
- Subjects who are suffering from cardiac disorders are excluded as control groups.
- Non-diabetic patients are excluded from the study
- Patients taking medications other than oral hypoglycemics that could influence the autonomic functions and drugs those could affect the cardiovascular functions are excluded.
- Patients suffering from cardiac disorders are

excluded.

Materials used for the study: Electro cardiograph (Version-CARDIART 108T MK/VII), Mercury Sphygmomanometer, Stethoscope, Cold water.

Method of Collection of Data:

The following parameters were recorded:

Physiological Parameters: The subjects were instructed not to have coffee, tea cola 12 hours before the tests and were asked to have light breakfast two hours before the tests. The subject was asked to relax in supine position for 30 minutes. The resting heart rate was recorded on a standard ECG from lead II, at a paper speed of 25 mm/sec. B.P was measured with sphygmomanometer. The cardiovascular tests performed are detailed below in the order of execution. These tests were demonstrated to the subjects.

Resting pulse rate: The subjects / patients were asked to take rest for 10 minutes and radial pulse rate was recorded in supine position and expressed as beats / min.

Resting Blood Pressure: The resting blood pressure was recorded in supine position using mercury sphygmomanometer by the standard auscultatory Riva-Rocci method and expressed in mm of Hg.

Body Temperature: The body temperature (oral) was recorded in °F, using clinical thermometer.

Autonomic Function Tests: The following autonomic function tests were performed, that are HR response to standing, response to deep breathing test, valsalva mamouvere for testing parasympathetic nervous system.

Heart Rate Response to Standing: The subjects were asked to lie on the examination table, the ECG limb leads were attached and ECG was recorded in lead II. Subject/patient stands from supine position as quickly as possible. The 30: 15 ratios i.e. Ratio of longest R-R interval around 30th beat after standing to shortest R-R interval about 15th beat after standing were considered. Normal: ≥ 1.04 . Borderline: 1.01-1.04. Abnormal: ≤ 1.00 .

Heart Rate Response to Deep Breathing: With subject /patient sitting, ECG was recorded in lead II throughout the period of deep breathing.

Subject/ patient breaths deeply and evenly at 6 breaths per minute (5 sec. In, 5 sec. Out) for 3 cycles (30 sec.). The onset of inspiration and expiration were marked on ECG paper. The maximum and minimum R-R intervals were measured during expiration and inspiration respectively in each cycle. The heart rate difference during each cycle was measured and average of the 3 differences was considered.

Normal: ≥ 15 beats / min. Borderline: 11 – 14 beats / min. Abnormal: ≤ 10 beats / min.

Heart Rate Response to Valsalva Manoeuvre:

The subject was seated comfortably and was asked to blow into a mouthpiece connected to a mercury sphygmomanometer and holding it at a pressure of 40 mm of mercury for 15 seconds, while a continuous ECG was being recorded. The ECG was continued to be recorded after release of pressure at the end of 15 seconds for 30 seconds. The heart rate changes induced by the valsalva manoeuvre were expressed as the ratio of the maximal tachycardia during the manoeuvre to the maximal bradycardia after the manoeuvre. This ratio was defined as the valsalva ratio and was calculated as the ratio of maximum R-R interval after the manoeuvre to minimum R-R interval during the maneuver.

Valsalva ratio = longest R-R interval after manoeuvre / shortest R-R interval during manoeuvre.

i.e. maximal tachycardia/maximum bradycardia= maximum R-R interval / minimum R-R interval. A value of 1.10 or less is defined as an abnormal response, 1.11-1.20 as borderline, and 1.21 or more as a normal response.

Statistical analysis: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean and S.D.(standard deviation) of all the cardiovascular parameters Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure were worked out, before and after evaluation of autonomic function tests for both groups. Students – t test was applied Microsoft Excel 2007 with P value less than 0.05 ($P < 0.05$) was considered statistically significant to test the significance of changes in cardiovascular parameters stated above and all p-values

reported are two tailed. Data represented as appropriate tables, bar diagrams, for discussion under different headings.

RESULTS

Table 1: Mean, SD of age in both study groups.

		Age (yrs)	t-value	P value	Inference
Group	Mean	S.D	0.82	>0.05	Non-significant
Group-A	50.26	5.27			
Group-B	49.32	5.83			

Table 2: Mean, SD of FBS, PGBS, and HbA1C in both study groups.

	Group - A		Group - B		p-value
	MEAN	SD	MEAN	SD	
FBS	163.1	24.68	92.08	12.27	0
PGBS	287.24	29.52	127.24	9.27	0
HbA1C	8.39	1.32	4.53	0.3	0

Table 3: Mean, SD of resting pulse rate in both study groups.

		RPR	t-value	P value	Inference
Group	Mean	S.D	2.92	0.004	Significant
Group-A	78.52	4.36			
Group-B	81.4	5.07			

Table 4: Mean, SD of resting blood pressure in both study groups.

		Resting Blood Pressure (SBP & DBP)	t-value	P value	Inference
Group	Mean	SD	SBP: 5.96 DBP: 2.29	SBP: <0.0001 DBP: 0.02	Significant Significant
Group-A	122.8 and 78	9.91 and 12.4			
Group-B	136.2 and 82.2	8.81 and 9.54			

Table 5: Mean, SD of body temperature in both study groups.

		Resting Body	t-value	P-value	Inference
Group	Mean	S.D	2.66	0.009	Significant
Group-A	97.24	0.53			
Group-B	97.15	0.46			

Table 6: Comparison of HR response to standing in group-A and group-B and results of t-test: values mentioned are mean and SD in each group.

Group	Mean ± SD	t-value	P value	Inference
Group-A	1.14 ± 0.13	2.51	0.01	Significant
Group-B	1.08 ± 0.11			

Fig. 2: The graphical representation of Mean of HR response to standing of both groups.

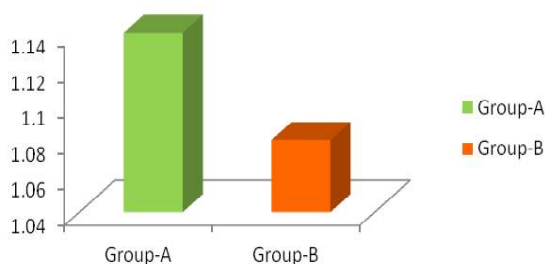


Table 7: Comparison of HR response to DBT in group-A and group-B and results of t-test: values mentioned are mean and SD in each group.

Group	Mean ± S.D	t-value	P value	Inference
Group-A	25.5 ± 6.96	3.86	0.0002	Significant
Group-B	19.12 ± 9.41			

Fig. 3: The graphical representation of Mean of HR response to deep breathing test of both groups.

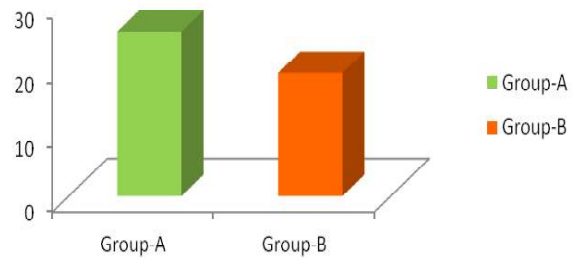
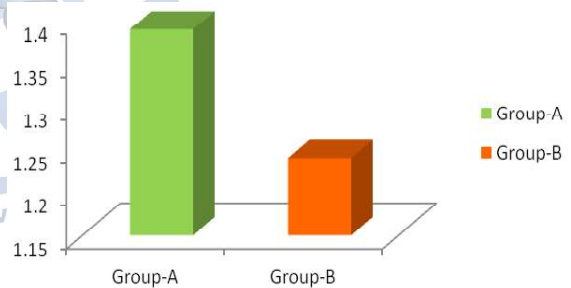


Table 8: Comparison of HR response VR in group-A and group-B and results of t-test: values mentioned are mean and SD in each group.

Group	Mean± S.D	t-value	P-value	Inference
Group-A	1.39 ± 0.24	3.87	0.0001	Significant
Group-B	1.24 ± 0.13			

Fig. 4: The graphical representation of Mean of HR response to Valsalva maneuver of both groups.



DISCUSSION

Cardiovascular autonomic neuropathy has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular liability, and increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction. The activity of the autonomic nervous system is of crucial importance in the moment to moment regulation of heart rate and blood vessels resistance, thereby controlling arterial pressure, cardiac output and tissue perfusion. Assessment of cardiovascular autonomic nerve damage can be made from the combined results of simple non-invasive cardio-autonomic tests [13] The present study was designed to assess the cardiovascular autonomic

function in type II diabetics and normal subjects by cardiovascular reflex tests. These include blood pressure response and heart rate response to deep breathing, valsalva manoeuver and standing to evaluate the parasympathetic function.

Physiological Parameters: The mean \pm SD of Age of both groups were found to be group-A: 50.26 ± 5.57 , group-B: 49.3 ± 5.8 respectively. There will be no significant association between age of both groups with $P > 0.05$. The mean \pm SD of resting pulse rate of both groups were found to be: group-A: 78.52 ± 4.36 , group-B: 81.4 ± 5.07 respectively with statistically significant association between both groups with $P < 0.05$. The mean \pm SD of resting blood pressure, systolic and diastolic, of both groups were found to be in group-A : 122.8 ± 9.91 and 78 ± 8.8 , group-B: 136.2 ± 12.4 and 82.2 ± 9.5 , respectively with statistically significant association between both groups with $P < 0.001$ and $P < 0.05$ respectively. The mean \pm SD of body temperature of both groups were, group-A: 97.2 ± 0.53 °F, group-B: 97.1 ± 0.46 °F respectively with statistically significant association between both groups with statistically significant association between both groups with $P < 0.005$. Parasympathetic function tests were studied in both groups.

Heart Rate Response to Standing: The ECG limb leads were attached and ECG was recorded in Lead II. Subject / Patient stands from supine position as quickly as possible. The 30:15 ratio i.e. the ratio of longest R-R interval around 30th beat after standing to shortest R-R interval about 15th beat after standing were considered. The values of mean \pm SD of the shortest R- R interval, longest R-R intervals and 30: 15 ratio of group-A and group-B are given in the master chart. The mean and standard deviation of HR response to standing of group-A and group-B were 1.14 ± 0.13 and 1.08 ± 0.11 respectively. The mean and standard deviation of HR response to standing of group-A and group-B and results of t-test are shown in Table 6. The graphical representation of Mean of HR response to standing of both groups are shown in Figure – 4. Heart rate response to standing were analysed between the two groups. The HR response to standing was a significantly reduced in group-B when

compared to group-A ($P < 0.05$). It can thus be concluded from Table-8 and Figure – 2 that the heart rate response to standing, a measure of cardiac parasympathetic function is reduced in group-B (test group).

Parasympathetic fibers being the longest fibers are affected first due to atherosclerotic changes of vasa nervosum. In diabetes, changes in metabolic and hemodynamic abnormalities, including a disadvantageous lipid profile, altered diurnal blood pressure rhythm. PTI was significantly reduced in test group when compared to It can thus be concluded from Table-6 and Figure-2 that the heart rate response to standing, a measure of cardiac parasympathetic function is reduced in group-B (test group). The finding of the present study is in conformity with earlier studies.

Cardiac autonomic neuropathy was assessed heart rate response to standing 30:15. They found that HR response to standing, a measure of parasympathetic function test was abnormal in 38% of cases [14]. Ewing D.J, et.al. found that a characteristic and consistent response to standing, with tachycardia (measured as a shortened R-R interval) maximum at about 10 sec.- i.e. between beats 10 and 20 and relative bradycardia (lengthened R-R interval) maximum at about 20 sec. – i.e. between beats 25 and 35. The diabetics with no evidence of autonomic neuropathy had responses similar to those of controls in contrast the diabetic with autonomic neuropathy showed a flat response with only small increase in heart rate and no relative bradycardia [15]. Sudhavana Set al. They studied HR response to standing, a measure of autonomic parasympathetic function in diabetics without microalbuminuria, diabetics with microalbuminuria and in controls. HR response to standing was found to be statistically significant decrease in both groups of type-2 diabetics than controls [16] Murray A et al. found diabetics showed a significantly smaller mean R – R interval and less R – R interval variation and whereas only four of the diabetic subjects had shorter mean R – R interval, 22 of diabetic had R-R interval variation that were less than any of the normal subjects [17] Fisher B.M et.al. in a study seven subjects out 115 asymptomatic diabetic patients showed

an abnormal response to 30:15 ratio and in among 9 symptomatic diabetic patients 8 patients have shown abnormal response [18]. Reduction HR response to standing in diabetics and cardiovascular autonomic function was decreased in type-II diabetics because of that severe damage to large myelinated nerve fibers in addition to the widespread neurological degeneration which usually affects the small nerve fibers of the autonomic nervous system was responsible for profound parasympathetic neuropathy in patients with type-2 DM [19].

Heart rate response to deep breathing: With subject/ patient sitting and strip ECG recording, subject breaths deeply and evenly at 6 breaths / min (5 sec in, 5 sec. out) for three cycles for 30 sec. Then the greatest heart rate difference was measured in each cycle and average of this difference of three cycles was calculated. The mean and standard deviation of HR in response to deep breathing test group-A and group-B of were 25.5 ± 6.96 and 19.12 ± 9.41 respectively. The mean and standard deviation of HR response to deep breathing test of group-A and group-B and results of t-test are shown in Table-7. The graphical representations of Mean of HR response to deep breathing test of both groups are shown in Figure -3. Heart rate response to deep breathing were analysed between the two groups. The HR response to deep breathing was significantly reduced in group-B when compared to group-A ($P < 0.05$). It can thus be concluded from Table 7 and Figure - 3 that the heart rate response to deep breathing, a measure of cardiac parasympathetic function is reduced in group-B (test group).

HR response to breathing is a normal phenomenon and is due primarily to fluctuations in parasympathetic output to heart. Respiration is most important stimulus for sinus arrhythmia, thoracic stretch receptors being responsible for this phenomenon. Beat-to-beat variation of heart rate is under the parasympathetic control. Reduced beat-to-beat variation is considered a reliable sign of cardiac vagal neuropathy. HR response to breathing is a normal phenomenon and is due primarily to fluctuations in parasympathetic output to heart. During inspiration impulses in vagi from stretch receptors in lungs inhibit the cardio-inhibitory

area in medulla oblongata. The tonic vagal discharge that keeps heart rate slow decreases and heart rate rises. In diabetes, loss of vagal tone (vagal denervation) is responsible for reduced heart rate response to deep breathing in diabetes.

This shows that there is progressive parasympathetic dysfunction in diabetics but it is more in diabetics. The basis of this finding is multi-factorial and may be at multiple levels of neuraxis including peripheral and central mechanism as reviewed earlier under effect of glycemic control over cardiac autonomic dysfunction. Parasympathetic fibers being the longest fibers are affected first due to atherosclerotic changes of vasa nervosum. In diabetes, there is a cluster of metabolic and hemodynamic abnormalities, including a disadvantageous lipid profile and altered diurnal blood pressure rhythm.

DBD was significantly reduced in group-B when compared to group-A ($P < 0.05$). It was thus concluded that from Table 7, and Figure -3 that the heart rate response to deep breathing, a measure of cardiac parasympathetic function is reduced in group-B (test group). The finding of the present study is in conformity with earlier studies.

The Deep breathing difference was found to be the most sensitive index for the autonomic neuropathy [20] HRV DBT represents a very sensitive measure of cardiovagal or parasympathetic cardiac function and thus is an important component of the battery of cardiovascular autonomic function tests used in clinical autonomic laboratories. In most autonomic disorders, parasympathetic function is affected before sympathetic function, so HRV DBT provides a sensitive screening measure for parasympathetic dysfunction in many autonomic disorders [21]. Lakhotia M, et.al. They observed that 19 diabetics giving normal response (> 1.21) to 'heart rate response to deep breathing' test, 10 diabetics showed border line response (1.11 to 1.20) and 21 patients gave abnormal response (< 1.10). So HR response to deep breathing test, a measure of parasympathetic function was found to be decreased in type-II diabetes mellitus [22]. HR response to deep breathing test, a measure of parasympathetic function was

found to be significantly decreased in type 2 diabetes with microalbuminuria [12].

Heart rate response to Valsalva Manoeuvre:

The quantitative Valsalva manoeuvre was performed by blowing with open glottis into a mouthpiece connected to a mercury column of sphygmomanometer. A pressure of 40 – 50 mmHg was asked to maintain for 15 sec. The ECG was recorded 15 sec. during and 30 sec. after the manoeuvre. Valsalva Ratio was calculated. The mean and standard deviation of HR in response to Valsalva manoeuvre of group-A and group-B were 1.39 ± 0.24 and 1.24 ± 0.13 respectively. The mean and standard deviation of HR response to Valsalva manoeuvre test of group-A and group-B and results of t-test are shown in Table-8. The graphical representations of Mean of HR response to Valsalva of both groups are shown in Figure – 6. Heart rate response to Valsalva manoeuvre were analysed between the two groups. The HR response to Valsalva manoeuvre was significantly reduced in group-B when compared to group-A ($P < 0.05$). It can thus be concluded from Table 8 and Figure – 4 that the heart rate response to Valsalva manoeuvre, a measure of cardiac parasympathetic function is reduced in group-B (test group).

Phases: There are four phases during the Valsalva maneuver.

Phase 1: Is the onset of straining with increased intrathoracic pressure. The heart rate does not change but blood pressure rises.

Phase 2: Is marked by the decreased venous return and consequent reduction of stroke volume and pulse pressure as straining continues. The heart rate increases and blood pressure drops.

Phase 3: Is the release of straining with decreased intra-thoracic pressure and normalization of pulmonary blood flow.

Phase 4: Marks the blood pressure overshoot (in the normal heart) with return of the heart rate to baseline.

This increased intra-thoracic pressure prevents venous return to the right atrium, which leads to progressive decrease in the cardiac output, accompanied by a fall in arterial pressure. This results in increased sympathetic activity,

manifested by tachycardia and peripheral vasoconstriction. Upon release of the strain, there is an abrupt increase in venous return as well as in the capacity of the pulmonary vascular bed. Thus, following the release, for a few beats, there may be a further fall in arterial pressure, due to pooling of blood in pulmonary vasculature. However, eventually, there is increase in the cardiac output ejected into the constricted systemic vasculature. This results in sudden overshoot of arterial pressure. The rise in blood pressure results in increased vagal activity, which manifests as bradycardia.

The Valsalva maneuver is a well-known and widely accepted test of cardiac parasympathetic function. The heart rate changes provoked during the maneuver and expressed as the Valsalva ratio are mostly dependent on cardio-vagal integrity. The mechanisms responsible for the abnormal heart rate changes during the Valsalva maneuver are due to progressive ventricular dilatation may diminish the normal inhibitory action of cardiac vagal afferents on the brainstem vasomotor center which in turn may decrease the efferent parasympathetic traffic to the sinus node and partially explain the abnormal heart rate changes observed during the Valsalva maneuver.

The abnormal Valsalva response in diabetics may be due to early damage of parasympathetic nervous system involving vagus nerve. The heart rate response to Valsalva maneuver relies to some extent on the integrity of sympathetic as well as parasympathetic pathways.

There was a significant decline in VR in group-B compared to that of group-A ($P < 0.05$). It can thus be concluded that from Table-8 and Figure -4 that the heart rate response to Valsalva manoeuvre, a measure of cardiac parasympathetic function is reduced in group-A (test group). The finding of the present study is in conformity with earlier studies.

Clarke B.F et al. were found decreased Valsalva ratio found in diabetics this was attributed early damage of parasympathetic due to axonal degeneration of longer vagal fibers [23] Wael Refaie was found from his study CAN was detected in 70% of the studied cases and Valsalva ratio was abnormal in 22% patients, Parasympathetic neuropathy 52% cases while

sympathetic 20% cases [24]. Naliboff BD, et.al. Found that the non-insulin dependent diabetic subjects without hypertension showed altered cardiovascular responses in response to heart rate variability during Valsalva maneuver [25] In another study HR response to VR was found to be statistically decreased in in type-II diabetics [26].

Diabetic autonomic neuropathy is a heterogeneous condition that comprises a wide range of dysfunction and whose development might be attributed to diabetes per se or to factors associated with the disease. Both sympathetic and parasympathetic fibres may be affected with parasympathetic dysfunction preceding sympathetic dysfunction. The etiopathology of Diabetic Autonomic Neuropathy is multifactorial. It has been associated with round cell infiltration, hence auto immunity may contribute to it. The polyol pathway activation in diabetes may also play a part by leading to increased sorbitol accumulation which is neurotoxic to autonomic nerves as well as other nerves. It has been postulated that metabolic consequences of hyperglycemia rather than the type of diabetes may lead to autonomic damage. One factor of particular interest is oxidative stress. This occurs when there is an increase within cells of certain reactive molecules containing oxygen. These can react with components of cells, including nerves, and cause damage. Alternatively, the metabolic and vascular changes associated with diabetes may adversely affect almost all the organs of the body, particularly the cardiovascular system.

There was a statistically significant alternation in ANS functions in the group-A when compared to group-B. Both parasympathetic and sympathetic cardiovascular responses were altered significantly. Decreased HRV and blunted BP responses are associated with CAN in type II diabetes suggesting that impairment of autonomic function. DM affects cardiovascular autonomic function adversely through various metabolic and vascular mechanisms.

The main finding of this study is that, decreased Heart rate variability as measured by cardiovascular testing is associated with type II diabetes patients. Hence, it is suggested that cardiovascular autonomic functions declining in

type II DM patients as the disease progresses.

CONCLUSION

Parasympathetic cardiovascular responses were altered significantly. Decreased HRV responses are associated with CAN in type II diabetes suggesting that impairment of autonomic function. DM affects cardiovascular autonomic function adversely through various

1. Metabolic and vascular mechanisms. As the clinical importance of diabetic autonomic neuropathy is increasingly recognized, this study elucidates that simple bedside tests, as employed in this study, based on cardiovascular reflexes, can provide an objective and useful guide to know the presence and degree of damage to autonomic nervous system in diabetics.

2. Proper treatment regimens, and stricter dietary and exercise modifications help in controlling the glycemic status. This not only helps prevent early onset of autonomic neuropathy in diabetics, but will also eventually help in reducing the symptoms in those that have diabetic autonomic neuropathy.

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