A STUDY ON

"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE DIABETIC ADULTS AT A TERTIARY HOSPITAL IN CHENNAI."

Dissertation submitted to

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DEPARTMENT OF GENERAL MEDICINE GOVERNMENT

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON THE PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE DIABETIC ADULTS AT A TERTIARY HOSPITAL IN CHENNAI."** submitted by **Dr. NITIN ABHISHEK BALAJI.D** to the faculty of General Medicine,The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D Degree Branch-I (General Medicine) is a bonafide research work carried out by her under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation titled **"A STUDY ON PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE DIABETIC ADULTS AT A TERTIARY HOSPITAL IN CHENNAI"** is a bonafide work done by me at Government Stanley Hospital, Chennai between March 2022 and September 2022 under the guidance and supervision of **Prof. S.Chandrasekar M.D.** I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other university, board either in India or abroad. This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

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INTRODUCTION:

Diabetes mellitus is a significant metabolic disorder affecting almost every organ system in the human body. It is estimated that the prevalence of diabetes can go up to 57.2 million by the year 2025 in India(1). Type 2 diabetes mellitus (T2DM) is characterised by a high glucose level(hyperglycemia) in the blood, usually due to increased insulin resistance, and later by reduced insulin secretion from pancreatic beta cells. Chronic uncontrolled T2DM leads to various micro and macrovascular complications like retinopathy, nephropathy, and coronary artery disease(2,3).

Cardiovascular disease is one of the most common complications of diabetes is with significant mortality. The 3 groups of cardiovascular complications of diabetes mellitus are atherosclerotic coronary artery disease(CAD), cardiac autonomic neuropathy (CAN) and diabetic cardiomyopathy(4). These complications are defined by concurrent autonomic dysfunction, which precedes clinical symptoms of complications.

Pre-diabetes is a condition with glycemic parameters beyond normal limits, but below the levels to be diagnosed as T2DM. Pre-diabetes is a known risk factor for overt diabetes and its macrovascular complications. Each year, between 5% and 10% of people with prediabetes are progressing to diabetes. An increase in the global prevalence of prediabetes to 471 million by 2035 is predicted by the International Diabetic Federation (IDF)(5).

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ABBREVIATIONS:

DM – Diabetes Mellitus

T1DM, T2DM – Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus

BP - Blood Pressure

SBP, DPB - Systolic Blood Pressure, Diastolic Blood Pressure

FBG – Fasting Blood Glucose

PPBG – Post Prandial Blood Glucose

OGGT – Oral Glucose Tolerance Test

HbA1c – Haemoglobin A1 c – glycosylated haemoglobin

HR – Heart Rate

ECG – Electrocardiogram

QTc interval - Corrected QT interval

MI – Myocardial Infarction

OSAS - Obstructive Sleep Apnoea Syndrome

CAD – Coronary Artery Disease

DAN – Diabetic Autonomic Neuropathy

CAN – Cardiac Autonomic Neuropathy

CART – Cardiac Autonomic Reflex Tests

SGLT-2 – Sodium-Glucose cotransporter-2

IFG – Impaired Fasting Glucose

IGT – Impaired Glucose Tolerance

NGR – Normal Glucose Regulation

PCOS – Polycystic Ovarian Syndrome

HDL – High Density Lipoprotein

BMI – Body Mass Index

HRV – Heart Rate Variation

LVH – Left Ventricular Hypertrophy

bpm – beats per minute

FDA – Food and Drug Administration

DIAD - Detection of Ischemia in Asymptomatic Diabetics\

DPP – Diabetes Prevention Program

IDF – International Diabetic Federation

TCA – Tricyclic antidepressants

SSRI - Selective Serotonin Reuptake Inhibitors

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Cardiovascular disease is one of the most common complications of diabetes is with significant mortality. The 3 groups of cardiovascular complications of diabetes mellitus are atherosclerotic coronary artery disease(CAD), cardiac autonomic neuropathy (CAN) and diabetic cardiomyopathy(4). These complications are defined by concurrent autonomic dysfunction, which precedes clinical symptoms of complications.

Pre-diabetes is a condition with glycemic parameters beyond normal limits, but below the levels to be diagnosed as T2DM. Pre-diabetes is a known risk factor for overt diabetes and its macrovascular complications. Each year, between 5% and 10% of people with prediabetes are progressing to diabetes. An increase in the global prevalence of prediabetes to 471 million by 2035 is predicted by the International Diabetic Federation (IDF)(5).

Although complications and target organ disease are more common with diabetes, vascular complications, nephropathy, retinopathy, and neuropathies are more common even in people with prediabetes. Neuropathy as a complication is not well studied in patients with pre-diabetes. The major risk factors of neuropathy in pre-diabetes are found to be obesity, hypertension, and dyslipidemia.

CAN being one of the earliest manifestations of T2DM constitutes the major cause of silent cardiovascular events in patients without overt cardiac disease. CAN process in T2D start earlier than the onset of overt metabolic impairment(6). The high prevalence of CAN in patients newly diagnosed with T2D(7) suggests that its pathophysiology starts earlier in the pre-diabetes stage with the onset of metabolic derangement.

The early detection of CAN is crucial in its treatment, as it is readily reversible in people with prediabetes. Several landmark studies have reported that good glycaemic control with lifestyle modification reduces the incidence of CAN and slows its progression, particularly in the early stages.

Despite being associated with a high risk of cardiovascular morbidity and mortality, CAN remains underdiagnosed. The tests for assessing autonomic dysfunction are simple bedside, non-invasive tests that need no specialized equipment. It just requires a sphygmomanometer, a heart rate monitor, and an ECG machine.

AIM:

This study aims to estimate the prevalence of cardiac autonomic neuropathy in pre-diabetic adults in Stanley Medical College and Hospital.

OBJECTIVE :

1) To study the Prevalence of Cardiac Autonomic Neuropathy in Pre-diabetic adults in Stanley Medical College and Hospital.
2) To determine the correlation of cardiac autonomic neuropathy with QTc interval.

REVIEW OF LITERATURE:

The development of T2DM is usually heralded by prediabetes which is characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Latest studies indicate that microvascular complications of diabetes which were thought to develop in later stages of hyperglycemia are seen during prediabetes stage(8).

Definition:

Prediabetes is defined as an intermediate hyperglycemic state with glucose levels more than normal limits but less than the diabetes threshold(9).

Risk factors for T2DM:

- Less physical activity
- First-degree relative with diabetes
- High-risk race/ethnicity
- Gestational diabetes or delivery of a baby weighing >or=4kg
- LDL cholesterol 250 mg/dL
- Hypertension (>140/90 mmHg or on therapy)
- HA1C >5.7 %
- IGT or previous impaired IFG

- Conditions associated with insulin resistance: severe obesity, less physical activity, acanthosis nigricans, PCOS history, history of cardiovascular disease(10).

Diagnosis of prediabetes:

- Fasting plasma glucose of 100–125 mg/dL (IFG)
- Postprandial plasma glucose of 140–199 mg/dL (IGT)
- HbA1c level of 5.7–6.4%

Pathophysiology of pre-diabetes:

Prediabetes is associated with abnormalities in insulin sensitivity, pancreatic beta cell function, inflammatory cytokines, incretin response, and hepatic glucose production (HGP) (Figure 1)(8).

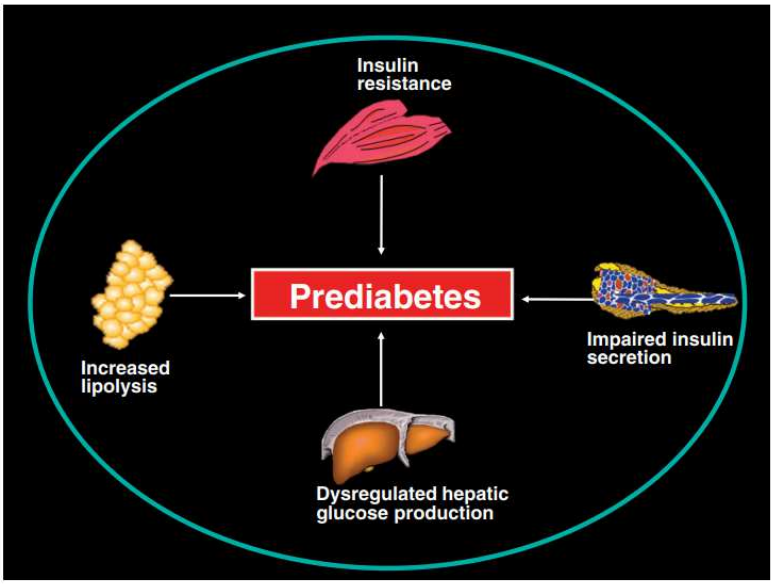


Figure 1: Pathophysiology of pre-diabetes.

The risk of development of T2DM is the most obvious sequela of prediabetes. The estimated annual conversion rate from prediabetes to diabetes is approximately 10%(11). In the China Da Qing Diabetes Prevention Study, the cumulative incidence of progression to diabetes from IGT over a 20-year period was reported to be more than 90%(12).

The associated risk factors for progression from prediabetes to T2DM are increase in body weight, reduced insulin sensitivity, reduced insulin secretion and abnormal adipocytokine profile. In addition to the risk of progression to T2DM, the prediabetes is associated with various microvascular and macrovascular complications.

Macrovascular complications:

Prediabetic dysglycemia increases the risk of myocardial infarction, stroke, or cardiovascular death. EPIC-Norfolk study suggested that 1% increase in HbA1c above normal values was associated with increased cardiovascular mortality over a period of 10 years(13). Features of the insulin resistance syndrome (metabolic syndrome) are truncal obesity, hypertension, reduced HDL levels and hypertriglyceridemia.(Figure2)(14).

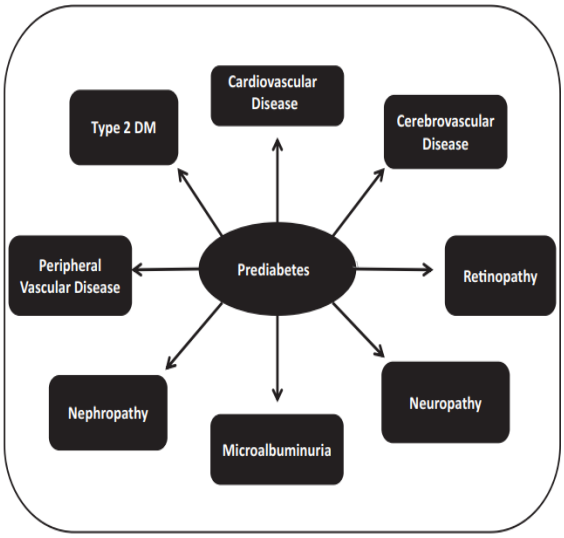


Figure 2: VARIOUS MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

<u>Microvascular complications</u>:

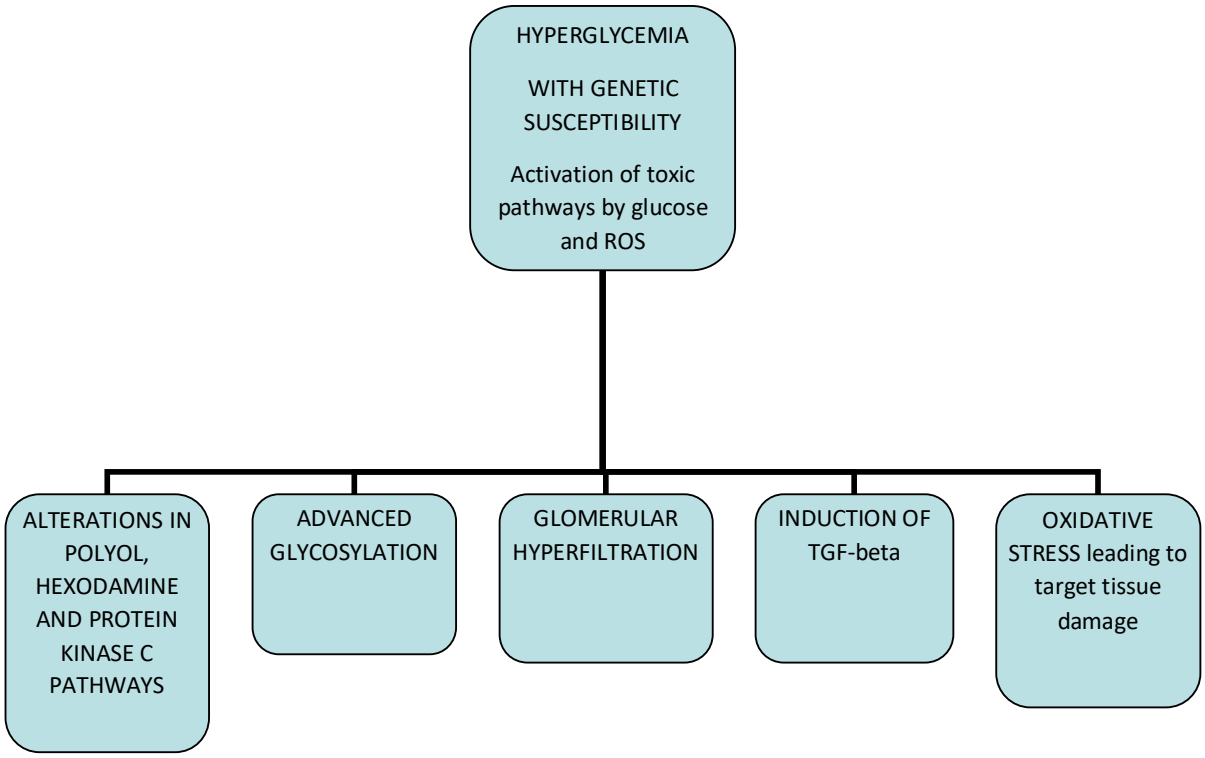
Retinopathy, neuropathy, and nephropathy are the three classical microvascular complications in pre-diabetes. In the Diabetes Prevention Program (DPP) study on patients with IGT, 8% had retinopathy(15), and the Gutenberg Health Study in Germany also showed a similar prevalence of retinopathy (8.1%) among individuals with prediabetes(16).

In another study, the estimated prevalence of microalbuminuria among prediabetic subjects at 15.5%(17).

Signs and symptoms of classical diabetic peripheral polyneuropathy can be observed in prediabetes. Peripheral neuropathy was seen in 11-25% of people with prediabetes(18).

Pre-diabetes is associated with autonomic dysfunction, manifesting as reduced HRV and increased prevalence of erectile dysfunction(9).

Mechanisms of prediabetic complications(19):



Management of pre-diabetes:

The primary goal for intervention in people with prediabetes is the reversal of prediabetes and restoration of NGR. There is no FDA-approved drug for the treatment of pre-diabetes.

The efficacy of lifestyle modifications in pre-diabetes was studies in several landmark clinical trials. Diabetes reduction by 16% with 1kg decrease in body weight was observed in the Finnish Diabetes Prevention Study(20).

A 42% decrease in the diabetes incidence over a 6 year-follow-up period and a reduction in cardiovascular mortality and other diabetes complications over a period of 20-year follow-up was observed in the group with lifestyle intervention(21).

Characteristics of an ideal drug for pre-diabetes(8):

- It should have an efficacy more than or equal to lifestyle modifications, i.e., more than 60% reduction in diabetes risk.
- It should address the pathophysiological defects behind pre-diabetes.
- It should normalize metabolism of glucose.
- It should be affordable with less toxicity and adverse effects.

Many studies evaluated and concluded that drugs approved for treatment of obesity like orlistat and pharmacological agents used for the treatment of T2DM such as metformin, alpha-glucosidase inhibitors and thiazolidinediones delay and prevent the transition of prediabetes to T2DM. These drugs have proven adverse effects and they are prone to mask the symptoms instead of reducing the progression.

Metformin and pioglitazone showed no effect on diabetes prevention when combined with lifestyle modification in the Indian Diabetes Prevention Program (IDPP)(22).

Definition of Cardiac Autonomic Neuropathy:

The definition of Diabetic Autonomic Neuropathy(DAN) as per Toronto Consensus is "a disorder of the autonomic nervous system in the setting of diabetes or metabolic derangements of pre-diabetes after the exclusion of other causes" and CAN is defined as "the impairment of autonomic control of the cardiovascular system." The Toronto Consensus emphasized the possible presence of an autonomic dysfunction already in pre-diabetes(23,24,25).

Clinical correlates or risk markers for CAN are age, obesity, duration of diabetes, glycaemic control, microvascular complications (peripheral polyneuropathy, retinopathy, and nephropathy), hypertension, dyslipidaemia, smoking, waist circumference, insulin levels in T2DM, coronary artery disease, and anti-hypertensive drugs use(24,26,27,28).

The prevalence of diagnosed cases of CAN is 20%, and it increases with age and diabetes duration up to 65%.CAN is usually documented using several cardiovascular autonomic reflex tests (CARTs). About 7% of DM patients had abnormalities in CART results at the time of diagnosis(26).

The following abnormalities are associated with CAN in cardiovascular system and peripheral vascular function.

Cardiovascular system:

- Perioperative instability
- Tachycardia at rest
- Reflex Heart Rate Variations(HRV) loss
- Systemic hypertension
- Intolerance to exercise
- Orthostatic and post prandial hypotension
- Silent myocardial ischaemia
- Left ventricular dysfunction and Left Ventricular Hypertrophy (LVH)
- QT prolongation
- Baroreflex sensitivity impairment
- Non-dipping and reverse dipping
- Sympathovagal imbalance
- Cerebral circulation dysregulation
- Decreased sympathetically mediated vasodilation of coronary vessels
- Increased arterial stiffness

Peripheral vascular function:

- Warm skin due to increased peripheral vascular blood flow
- Swollen veins and increased arteriovenous shunting
- Foot edema due to increased venous pressure
- Protective cutaneous vasomotor reflexes loss
- Microvascular damage due to loss of venoarterial reflex
- Increased leakage of macromolecules through capillaries
- Calcification of medial artery

Association between pre-diabetes and CAN:

The reduced HRV observed in IGT and IFG indicates decreased parasympathetic activity.

In subjects with IFG and IGT compared to control subjects , some studies suggested sympathovagal imbalance with an abnormal predominance of sympathetic activity in pre-diabetes(29).

The various risk factors of autonomic changes in pre-diabetes:

- Increase in age, increased Body Mass Index (BMI), truncal obesity and other presentations of metabolic syndrome
- Hypertension and antihypertensive intake

- Fasting and 2-hour post load glucose levels

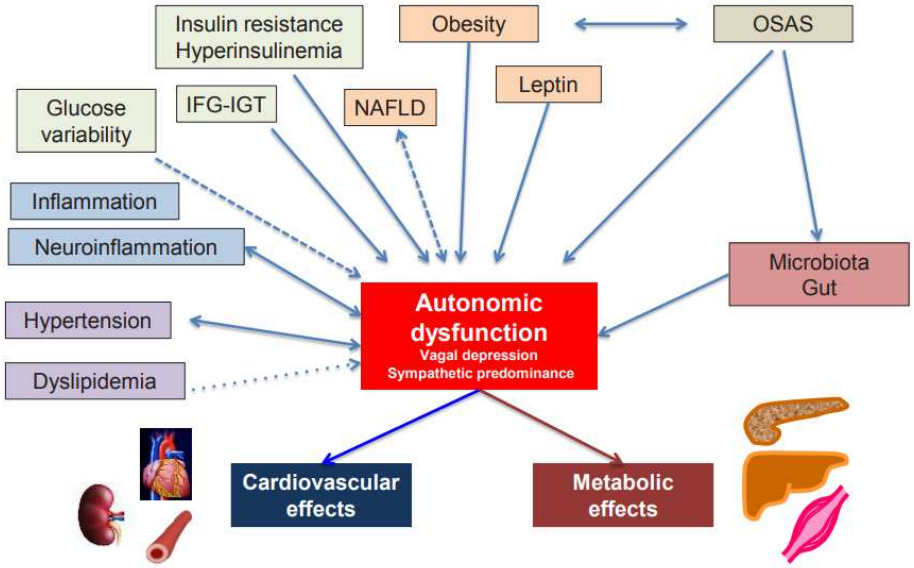


Figure 3: MULTIPLE FACTORS IN THE RELATIONSHIP BETWEEN METABOLIC SYNDROME AND AUTONOMIC DYSFUNCTION

(OSAS- Obstructive Sleep Apnoea Syndrome)

<u>Criteria for diagnosis and staging of CAN:</u>

(1) one abnormal cardiovascular autonomic reflex tests (CARTs) to identify early CAN

(2) at least 2 abnormal CARTs results to confirm CAN

(3) orthostatic hypotension and heart rate tests to identify severe or advanced CAN.

Progression in stages of CAN indicates poor prognosis.

CAN assessment is used to

(1) diagnose CAN clinically,

(2) detection and appropriate treatment of various presentations of CAN like orthostatic hypotension, tachycardia, QT interval prolongation and non-dipping.

(3) risk categorisation of complications of diabetes

(4) modulation of targets in diabetes therapy

(5) risk assessment of cardiovascular morbidity and mortality

CLINICAL MANIFESTATIONS OF CAN:

1. Exercise Intolerance

Kahn et al, in their study of persons with CAN and without CAN, found a decreased response in blood pressure and heart rate in individuals with CAN(30).

Various studies have established decreased cardiac output with exercise in persons with CAN(31).

CAN is associated with a lesser rise in heart rate on exertion. The heart rate increase after exercise and the maximum heart rate increase achieved with

exercise is inversely related to the severity of CAN. Cardiac autonomic dysreflexia produces,

- reduced exercise tolerance
- decreased cardiac ejection fraction
- reduced systolic and diastolic dysfunction

2. Cardiovascular Liability During Intraoperative Period

Burgos et al described need for increased vasopressor support in diabetics with autonomic dysreflexia(32).

Kitamura et al has shown increased hypothermia during intra operative period in patients with CAN(33). Intraoperative reduction of core temperature causes decrease in metabolism of drugs and impairs healing of wounds.

Sobotka et al has demonstrated decreased hypoxia related ventilatory drive in individuals with CAN. (34).

In patients with CAN, anaesthesia related vaso dilatation is not compensated by autonomic response like vaso constriction and increase in heart rate.

3. Orthostatic Hypotension

A reduction in systolic BP of >20mmHg and diastolic BP of >10mmHg from lying down in supine position to standing posture is called as orthostatic hypotension.

- Normally, there is a sympathetic nervous system stimulation by activation of baroreceptor reflex and release of norepinephrine in response to change in posture. This causes splanchnic vasoconstriction and a raise in blood pressure. This mechanism is impaired in diabetics as the efferent sympathetics are damaged. This along with a generalised decrease in total vascular resistance produces a postural fall in blood pressure
- Extravascular fluid retention due to cardiac and renal failure produces a reduction of blood volume
- Insulin itself has hypotensive action
- Splanchnic vasodilation in post prandial state
- Decreased cardiac stimulation and decrease in cardiac output has a role

Symptomatology

- light headedness , black outs, presyncope
- dizziness, easy fatigue, blurring of vision , neck pain

4. Silent Myocardial Infarction(MI)

Uma Chandran et al had studied the perception of angina pain threshold in persons with and without diabetes. Assessment of the autonomic function tests in those individuals was also done in this study. There was a documented

decreased angina pain perception in persons with diabetes and there is a corelation of associated autonomic neuropathy in these individuals(35).

The study by Vinick et al has also documented a definitive relation between CAN and silent MI(26).

In Detection of Ischemia in Asymptomatic Diabetics (DIAD), 1123 patients were studied. CAN was found to be a strong predisposing factor of silent MI and cardiovascular deaths in diabetic individuals in that study(36). Earlier detection of CAN is very important in diabetics as they develop myocardial ischemia with poor pain perception.

CLINICAL SIGNS OF CAN:

1) HRV Impairment:

a. It is an earliest sign of CAN

b. Beat to beat HRV shows functional integrity of sympathetic, parasympathetic function

c. due to dysfunction of autonomic nervous system, HRV in accordance with normal respiration producing sinus arrhythmias disappears

2) Tachycardia at rest:

a. An increased sympathetic tone with increase in resting heart rate of >100 bpm due to dysfunction of parasympathetic function.

b. Other causes of resting tachycardia such as stress, exercise, anaemia, thyrotoxicosis and heart failure should be ruled out.

c. Persistence of fixed heart rate, even in the presence of stress or after exercise indicates CAN.

3) Testing of cardiac stress:

Stress test is used to assess poor tolerance to exercise. Decrease in heart rate, blood pressure, and cardiac output after exercise are noted in individuals with CAN.

4) Non-Dipping blood pressure with sleep at night:

In normal individuals fall in BP and heart rate are noted with sleep at night due to predominance of parasympathetic activity.

But in individuals with autonomic dysfunction, nondipping of blood pressure is noted due to predominance of sympathetic tone. Development of concentric hypertrophy of the left ventricle is noted in these individuals.

5) Orthostatic Hypotension:

a. It is a late manifestation of CAN

b. It occurs due to the impairment of sympathetic vasomotor function. Easy fatiguability, light headedness, dizziness, blurred vision, presyncope and neck pain are the various clinical symptoms.

DIAGNOSIS OF CARDIOVASCULAR AUTONOMIC DYSFUNCTUION:

To evaluate sympathovagal response, five non-invasive tests were recommended by Ewing et al in 1970(37).

CARTs (cardiovascular autonomic reflex testing) should be done after ruling out confounding factors. Age, exercise(avoided 24 hours before testing), caffeine, tobacco and alcohol use(there should be a caffeine, smoking and alcohol-free period of 2 hours before testing), intake of drugs like aspirin, insulin, antidepressants, sympatholytics, vasodilators and diuretics (withdraw the drug or exclude those patients) should be considered when performing these tests.

Tests are done in fasting state or 2 hours after a light meal. Interpretation of the test results must be done cautiously in patients having chronic respiratory diseases, obstructive sleep apnoea syndrome(OSAS) and cardiac diseases, especially heart failure.

Parasympathetic function testing:

HRV to Valsalva manoeuvre(38):

There will be decrease in BP and increase in HR during strain phase of Valsalva.

Followed by increase in BP above the values at rest and HR reduction after the release phase. This response is mediated by Vagus nerve, as the HR was abolished with atropine and no change noted with Propranolol(39).

In patients who have autonomic damage, a slow decrease in BP during strain phase and slow return to normal values after release is noted. There was no overshoot in BP and no variation in HR.

"The Valsalva manoeuvre has four phases in healthy people"(30).

• Phase I: There will be a transient increase in BP and a reduction in heart rate because of the aortic compression and blood propulsion into peripheral circulatory system. These hemodynamic variations occur in response to mechanical factors

• Phase II: There will be an early reduction in BP with subsequent normalization. This is associated with increase in heart rate. As there is an impairment in venous return, there will be a decreased cardiac output. This results in increased resistance in the periphery and there will be an increase in sympathetic response.

•Phase III: When stopping the expiration, there will be a fall in BP and increase in heart rate.

• Phase IV: In this phase, an overshoot in BP levels from normal occurs. This is because of the venous return and hence cardiac output is restored to normal due to residual vasoconstriction.

Procedure: The patient blows into a mouthpiece which is connected with a modified sphygmomanometer. The breath should be held at a pressure of 40 mmHg for 15 seconds There will be a continuous ECG is recording during the test. This test should be performed three times. There should be a gap of one minute between each test.

$$\text{Test result (41)} = \frac{\text{longest R-R interval after the manoeuvre (bradycardia)}}{\text{longest R-R interval during the manoeuvre (tachycardia)}}$$

The R-R interval is measured with a ruler from the electrocardiogram tracing. The mean value from the three test results is taken as the final Valsalva ratio.

HRV with breathing (40)

In normal individuals with an intact parasympathetic activity the heart rate varies continuously with breathing (39,40). This variation is noted obviously in individuals with slow HR, deep respiration and in children and adolescents.

There will be a total abolition of HRV or considerable decrease in this response in diabetic patients with cardiac dysautonomia.

HRV is assessed in different types of breathing like quiet breathing, deep inspiration and expiration 6 times in a minute. This test is a simple bedside objective test. The patient should sit comfortably and take deep breaths at a rate of six times per minute .There should be 5 seconds of deep inspiration followed by 5 seconds of deep expiration. ECG is recorded all along the manoeuvre throughout the period of deep breathing, and beginning of inhalation and exhalation tracings are marked". The longest and shortest R-R intervals during each respiratory cycle is measured with a scale and mean value is taken.

HRV(39,40) = HR at expiration/HR at inspiration, which is the E:I ratio.

Heart-rate response to standing(26):

During change from lying in supine posture to standing posture, there will be an immediate rapid rise in heart rate which is maximum at around the 15th beat after standing position. There will be an overshoot in bradycardia at around 30th beat. This response is mediated by Vagus nerve.

In diabetic patients with CAN, this change in heart rate is not appreciated. There will be a minimal or no response at all to the standing posture.

There will be a continuous ECG recording with patient lying at ease in supine position. Then the patient is asked to stand up without help. There will be a note of the point in ECG once he stands up. Using a ruler, the shortest R-R

interval at the 15th beat and the longest R-R interval at the 30th beat post standing is noted.

The typical HR response to standing is represented as the 30:15 ratio. This is a simple to perform and easily reproducible test and is not dependent on other confounding factors(26).

Sympathetic Autonomic Function Test:

BP response to standing position:

Normally there will be stagnation of blood in the lower limbs during standing and thereby a drop in BP, which is then rectified by peripheral vasoconstriction.

In diabetic patients who have autonomic dysfunction the drop in BP continues to persist and will be at a lower level, below the values of lying position.

This test is performed by recording patient's blood pressure using a sphygmomanometer, with the patient lying comfortably and then two minutes after standing position.

Postural drop in BP = systolic BP in supine position – systolic BP in standing position.

Orthostatic hypotension by definition as a reduction of systolic BP ≥20 mmHg or diastolic BP of ≥10 mmHg in less than 3 minutes of standing (41,42) and a fall in systolic BP of 30 mmHg.

Blood pressure variation to sustained handgrip:

Isometric exercises are usually associated with increase in BP. Hand grip is one of the isometric exercises, which causes increase in BP due to HR dependent increase in cardiac output with no change in peripheral vascular resistance.

The normal autonomic reflex pathways are altered in patients with CAN and this results in various sympathetic abnormalities. Because of this dysfunction, there will be a reduction in rise of BP significantly during sustained hand grip.

Initial maximum voluntary contraction is estimated using a hand grip dynamometer. Hand grip is sustained at 30% of initial maximum contraction for long as possible up to 5minutes. BP is recorded 3 times before and after hand grip and the mean of the three diastolic BPs before and after hand grip is calculated. Result is expressed as a difference between highest DBP recorded during sustained hand grip and the mean diastolic BP before the hand grip. Normally, the result should be more than 15 mm Hg. A rise of 11-15 mm Hg is borderline. This test is relatively independent of age as proposed by Ewing et al(43).

Summary of cardiovascular autonomic tests:

Test	Posture	Appropriate test time	Apparatus required
Heart rate response to valsalva	Sitting	5 min	Sphygmomanometer,ECG
Heart rate variation to deep breathing	Sitting	2 min	ECG
BP to sustained hand grip	Sitting	5 min	Sphygmomanometer
Heart rate response standing	Lying to standing	3 min	ECG
BP response to standing	Lying to standing	3 min	sphygmomanometer

BATTERY OF AUTONOMIC TESTS-EWING AND CLARKE

The following five simple, non invasive CARTs based on works of Ewing et al (43) are used to assess autonomic function.

1.Postural fall in systolic blood pressure (BP)

Systolic BP is measured with the patient in supine position and 2 minutes after standing.

A fall of systolic BP ≥ 30 mm Hg considered 'abnormal' - Score 2

11-29mm Hg fall is BP is considered as 'borderline' - Score 1

≤ 10 mm Hg is taken as 'normal' - Score 0

2. Increase in diastolic pressure during hand grip

Hand grip is sustained at 30% of the maximum for 5 minutes. The diastolic BP(DBP) is measured in the opposite upper limb.

Rise in DBP ≥16mmHg considered 'Normal' - Score 0

11-15mmHg considered 'borderline' – Score 1

Less than 10 mm Hg considered 'abnormal' – Score 2

3. HR response to Valsalva manoeuvre:

The patient is made to exhale forcefully by closing the nostrils into the manometer for 15 seconds to increase the pressure to 40 mmHg.

Ratio of longest RR interval to the shortest RR interval is measured and is expressed as Valsalva ratio.

Ratio of ≥1.21 is considered as 'Normal' - score – 0

Value of 1.11-1.20 is considered 'Borderline' - score - 1

Value of ≤1.10 considered 'Abnormal' - score - 2

4. HR response to deep breathing

The patient should be at rest and take deep breaths at a rate of six times per minute .There should be 5 seconds of deep inspiration followed by 5 seconds of deep expiration. The HR at expiration/HR at inspiration, which is the E:I ratio is calculated accurately.

≥15 beats per minute considered 'Normal' - Score 0

11-14 beats per minute considered 'Borderline' - Score 1

≤10 beats per minute considered 'Abnormal' - Score 2

5. HR response to standing

The RR interval is measured at 15th and 30th beat after standing from supine position. A ratio of 30th beat to15th beat is being precisely measured and a

Value of ≥1.04 is considered as 'Normal' - Score 0

Value of 1.01-1.03 is considered 'Borderline' - Score 1

Value of ≤1.00 is considered 'Abnormal' - Score 2

Score	Deep breathing	Heart rate ratio during Valsalva	Heart rate variability to standing	BP variabilty to hand grip	BP change to standing
0	≥15	≥1.21	≥1.04	≥16	≤10
1	11- 14	1.11 -1.20	1.01 -1.03	11-15	11- 29
2	≤10	<1.20	≤1	≤10	≥30 mm

CAN SCORING

Total score out of 10 is calculated.

1. An overall score of '0' or '1' is considered 'normal'

2. A score of 2,3,4 = 'borderline'

3. A score of ≥5 = 'abnormal' autonomic function

QTc INTERVAL AND CAN:

The time interval between the beginning of the Q wave and the end of the T wave in the ECG is known as the QT interval. It represents the total duration of the ventricular activity which is the electrical depolarisation and repolarisation of ventricles. QT interval is varied in different parts of the ventricles.

1. The QT decreases with tachycardia. Here there will be reduction in R-R interval.

2. The QT interval increased with bradycardia.

For accurate evaluation, the QT interval should not be viewed in absolute terms and must be corrected for the associated heart rate effectively.

QT interval measurement:

Measurement of QT interval has some difficulty sometimes, because of the difficulty to determine the exact beginning and end of the interval .

1) The beginning of QRS complex is best appreciated in leads with an initial q wave(32). It is measured in any of the lead I,II or V5 ,V6.

2) The T wave's end is sometimes obscured by the superimposition of U wave. Larger U waves are taken into consideration for measurement.

3) The maximum slope intercept method is used to determine the end of T wave(32).

Corrected QT interval:

QTc interval is corrected for a theoretical HR of 60 beats per minute(bpm) by the Bazett's formula.

Bazett's formula:

$QTc = QT \text{ (in seconds)} / \sqrt{RR \text{(in seconds)}}$

- Bazett's formula is the simplest and most commonly used.
- For HR < 60 bpm there will be an under-correction
- It over corrects at HR >100
- Adequate correction is provided for HR between 60-100 bpm.

Causes of a prolonged QTc: (>440ms)

1) Sleep- QTc prolongs during sleep
2) Acute myocarditis from any cause, particularly rheumatic carditis
3) Low potassium levels - Hypokalemia
4) Low serum calcium – Hypocalcemia - due to prolonged ST segment
5) Hypothermia
6) Myocardial ischemia which has chances to develop complex arrhythmias
7) Post-cardiac arrest
8) Increased intracranial pressure
9) Drug intake - quinidine, procainamide, TCA
10) Congenital long QT syndrome

An association between cardiac autonomic neuropathy and prolongation of QT interval has been demonstrated by various studies and there is a predisposition to sudden death in diabetes. QT interval prolongation is suggested as a marker of diabetic autonomic neuropathy.

MANAGEMENT OF CARDIAC AUTONOMIC DYSREFLEXIA:

- Weight control and physical activity,
- Cessation of smoking,
- Healthy dietary modifications,
- Control of glycemic levels, control of cardiovascular risk factors like BP and dyslipidemia,
- And a behavioural approach for stress control, and education are the basic main strategies for the CAN management.

The conclusion of Toronto Consensus includes lifestyle modifications which proved to improve HRV in pre-diabetes and diabetes and this was recommended as the primary preventive measure by the study (24).

1. Strict glycemic control:

Poor blood sugar control is the primary risk factor increasing the incidence and progression of CAN.

DCCT has showed that patients with T1DM with intensive blood sugar control, had less incidence in the development of abnormal HRV. Intensive insulin therapy is shown to be effective in preventing the complications inT1DM and T2DM patients.

Worsening of the autonomic neuropathy is noted with delay in the treatment of diabetes. Strict control of blood sugar caused stabilization and this prevents further worsening of CAN. But chances of reversal of CAN is less.

Hypoglycemic unawareness is common among the individuals with CAN. Hence vigilant monitoring of glucose levels is recommended.

2. Treatment options for CAN:

Early identification of CAN helps in early initiation of

a. Pharmacological and non-pharmacological treatment for BP and dyslipidemia

b. Angiotensin Converting Enzyme inhibitors and aspirin prophylaxis

c. Stopping smoking and alcohol intake

d. Good nutrition intake

e. Alpha lipoic acid which is an antioxidant has shown good promising results in slowing the progression of CAN in some studies. Further studies are needed to support the beneficial effects of vitamins.

f. Cardio selective beta blockers such as metaprolol has shown to improve parasympathetic tone by antagonizing sympathetic activity.

Aldose redutase inhibitors such as sorbinil and eparlestat have demonstrated good results in patients with mild CAN. They have no role in advanced CAN disease.

3. Strict Diet and Exercise Regimen

Preventive measures in individuals with Pre-diabetes such as lifestyle modifications, regular exercise are shown to have a promising role in the prevention of micro and macro vascular complications.

4. Anaesthetic Implications of CAN Testing

Preoperative CAN testing in diabetics helps the anaesthesiologist to fore see the expected intra operative complications such as fall in HR and BP during induction of anaesthesia especially during general anaesthesia. Reduced ventilatory drive is expected in these patients in the immediate post operative period. The need for vasopressors is more in these patients with significant CAN.

5. Treatment for Orthostatic hypotension:

A. Non-Pharmacological Measures:

1. Increasing the water intake

2. Use of elastic stockings for lower extremities

3. To prevent post prandial hypotension, intake of frequent small feeds is recommended.

4. Straining is avoided as increase in intra-abdominal and intra-thoracic pressures impedes venous return

5. Physical manoeuvres such as squatting and leg crossing increase cardiac filling and thereby stroke volume

6. Drugs that aggravate hypotension such as TCAs, phenothiazides should be avoided if possible

B. Pharmacological Measures:

1. Midodrine

- It is a selective peripheral alpha 1 receptor agonist

- It is the only FDA approved agent for the treating orthostatic hypotension

- Dose 2.5 – 10 mg TDS

- It does not cross the blood brain barrier and has fewer CNS side effects.

- Side effects- pruritis, paraesthesia, urinary retention, piloerection, supine hypertension

2. Fludrocortisone acetate

- It is a synthetic mineralocorticoid with a longer plasma half life

- lncreases the sensitivity of the blood vessels to circulating catecholamines

- Increases plasma expansion

- Dose 0.05 mg @ bed time titrate slowly to a maximum dose of 0.2 mg/day

- Adverse effects –supine hypertension , hypokalaemia, hypomagnesemia, fluid retention, congestive cardiac failure

3. Erythropoietin

- Increases RBC levels and blood volume

- It also mediates neuro humoral effects on blood vessel wall and regulates the vascular tone by mediating interaction of haemoglobin and nitric oxide

- Dose 25- 75 units/kg body weight, three times a week SC/IV until patient

achieves normal haematocrit. It is followed by a low maintenance dose of 25 units/kg thrice a week

4. Non-selective β blockers

- These drugs cause vasodilatation by blocking the beta 2 receptors in the blood vessels. Hence there will be an unopposed alpha receptor action causing vasoconstriction.

- They are found to have only a limited role

5. Clonidine

- Alpha 2 blocker having a central sympatholytic activity

- The central sympathetic efferent activation is blunted in patients with CAN. Clonidine produces increase in venous return without affecting peripheral vascular resistance in these cases

- It is studied to have only a limited use due to serious adverse effects

6. Somatostatin analogues

- These drugs inhibit vasoactive peptides released from GIT. Hence increases splanchnic vasoconstriction , venous return and cardiac output

- Dose 25-200 mcg /day

- Use of this drug is avoided dueto the development of severe hypertension

7. Pyridostigmine bromide

- Cholinesterase inhibitor

- It increases ganglionic transmission without affecting supine hypertension

8. Fluoxetine

- Selective Serotonin Reuptake Inhibitors(SSRI) has shown improvement in symptoms in patients with Parkinson disease

Other drugs with beneficial effects include,

(1) Desmopressin acetate which is a vasopressin analogue is used in correcting nocturnal polyuria and morning orthostatic hypotension

(3) Drugs such as Caffeine and Acarbose are shown to attenuate postprandial hypotension in patients with autonomic dysfunction.

METHODOLOGY :

STUDY DESIGN: Cross-Sectional Observational Study.

STUDY POPULATION: Pre- Diabetic individuals aged ≥18 years.

INCLUSION CRITERIA:

Confirmed cases of pre-diabetes as evidenced by:

1. Fasting Blood Glucose - (110-125 mg/dl)
2. Post-Prandial Blood Glucose - (140-200 mg/dl)
3. HbA1C level - (5.7 % - 6.4 %)

EXCLUSION CRITERIA:

1. Anaemia
2. Alcohol consumption
3. Chronic kidney disease
4. Use of beta blockers or drugs that affect autonomic nervous system
5. Serum electrolyte abnormalities
6. Bronchial asthma or Chronic obstructive pulmonary disease

7. Use of drugs that prolong QTc interval like Azithromycin, Chloroquine, Nelfinavir, Ketoconazole, etc.,

8.Non complying patients who do not consent to participate in the study

SELECTION OF CASES:

Patients in the outpatient department and general medical ward meeting the inclusion and exclusion criteria were selected for the study.

PLACE OF STUDY : Department of General Medicine, Government Stanley Medical College and Hospital.

DURATION OF STUDY : 12 months

SAMPLING METHOD : Convenient sampling.

SAMPLE SIZE : Based on the reference study (KORA S4 Survey) done by Ziegler et al., the prevalence of Cardiac Autonomic Neuropathy Among Pre-Diabetics is 11%.

Sample Size is calculated using the formula- $n = (z)^2 p (1 – p) / d^2$

Where- Z-1.96 , d-0.05 , p-0.11

Sample Size (n) is 150

STUDY TOOLS :

1. Complete Hemogram
2. Fasting blood glucose (FBG)
3. Post Prandial Blood Glucose (PPBG)
4. Oral Glucose Tolerance Test (OGTT)
5. Glycosylated hemoglobin (HbA1c)
6. Electrocardiography
7. Bed-side BP Measurement
8. Modified BP Apparatus for Performing Valsalva Manoeuvre

DATA COLLECTION :

After getting permission from Institutional Ethical Committee information regarding the study was explained to the patients; written and informed consent were obtained from them.

All the patients are evaluated by detailed history including history and treatment details of systemic illnesses and symptoms of autonomic neuropathy and relevant basic blood Investigation is done.

Battery of five autonomic function tests done in all participants (as described by Ewing and Clarke et al). Autonomic neuropathy testing using simple bed side tests was done in op department and medical ward with the use of 12 lead ECG monitor,

pulse-oximeter and BP apparatus .The same 150 patients were tested after obtaining proper informed consent, with 10 minutes interval after each manoeuvre.

The following 5 tests for detecting Cardiac Autonomic Neuropathy will be :

1) BLOOD PRESSURE FOR POSTURAL OR ORTHOSTATIC HYPOTENSION

Blood pressure recording is done with the subject in supine position and again 2 minutes after standing up. The difference in systolic pressure from lying to standing is recorded as a measure of orthostatic hypotension

2) CHANGE IN HEART RATE TO VALSALVA MANOEUVRE:

This test was performed using a modified BP apparatus. Patient blows in to the rubber tubing to raise the pressure to 40 mmHg. A long strip ECG in lead II is taken. Ratio of longest to shortest R-R interval is measured and mean ratio is obtained.

3) DEEP BREATHING ASSOCIATED CHANGES IN HEART RATE:

ECG is recorded continuously when the patient is taking breath at a regular rate of 6 breaths/min. A difference in heart rate <15 bpm between expiration and inspiration is taken as abnormal.

4)BLOOD PRESSURE CHANGES DURING SUSTAINED HAND GRIP:

The subject is given a ball and is asked to press the ball in his or her left hand for about 5 minutes. Failure to rise the diastolic BP >15 mmHg is considered as an abnormal finding and graded accordingly.

4) HEART RATE RESPONSE TO STANDING:

R-R interval is measured at beats 15 and 30th minute after standing.A 30:15 ratio is calculated.

EWING'S AUTONOMIC FUNCTION TESTS AND SCORING

Score	Deep breathing	Heart rate response to Valsalva ratio	Heart rate variability to standing	BP variability to hand grip	BP change during standing
0	≥15	≥1.21	≥1.04	≥16	≤10
1	11- 14	1.11 -1.20	1.01 -1.03	11-15	10- 29
2	≤10	<1..20	≤1	≤10	≥30 mm

The test is graded as

· Score 0 – normal

· Score 1- borderline

· Score 2 – abnormal

1. An overall score of '0' or '1' is considered 'normal'

2. Score 2,3,4 are considered 'borderline'

3. Score ≥5 is considered as 'abnormal autonomic function'

QTc INTERVAL: QT interval is determined on a 12 lead ECG taken at rest and correction for cardiac cycle, the QTc is determined by using Bazett's formula : QTc = QT/√RR interval

QTc >440 ms is taken as abnormal

Apart from these CARTs, symptoms suggestive of autonomic dysfunction such as light headedness, vertigo, palpitations, sweating abnormalities, etc. were asked.

BENEFIT TO THE PATIENTS

If a diagnosis of pre-diabetes with CAN is made, they will be explained about the hazardous effects of progression to diabetes, diabetic autonomic neuropathy and chances of dreadful cardiac diseases. They will be explained about the relationship of sugar levels causing damage to nerves throughout body and CAN interfering body's ability to adjust blood pressure and heart rate. Chances of preventing further progression with exercises and lifestyle modifications and other treatment options are explained. Exercises are encouraged with gradual prolonged warm up and cool down periods. Avoiding sudden changes in postures, isometric exercises and straining are explained. They are advised to avoid large, high carbohydrate meals, as it may cause sudden fall in BP and encouraged to take frequent small meals.

ANALYSIS :

Data were entered in Microsoft Excel spread sheet and analyzed using the SPSS software. Results were analysed using Chi square test with p-value as a measure of significance.

RESULTS

Age Distribution

The mean age of the study participants was 47.88 years ± 8.562 with a minimum age being 28 years and maximum age of the study participant being 65 years

Table: Age Distribution of the study participants

Age (in years)	Mean	Standard Deviation
	47.88	8.562

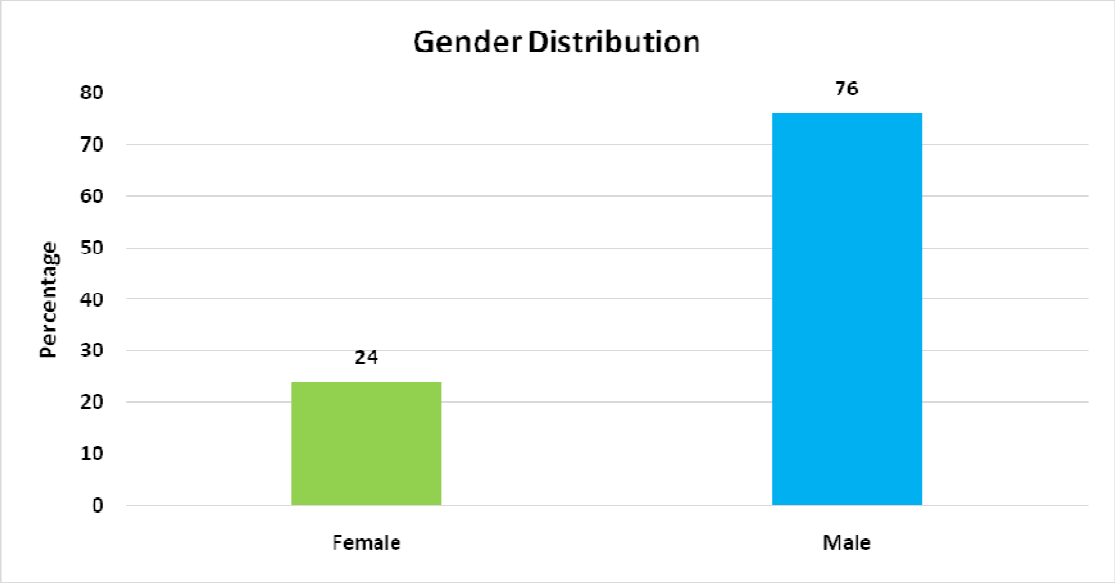
Gender Distribution

In our study population, 76% of them were males and 24% of them were females

Table: Gender Distribution of the study participants

Gender	Frequency (N)	Percentage (%)
Female	36	24
Male	114	76

Figure: Gender Distribution of the study participants



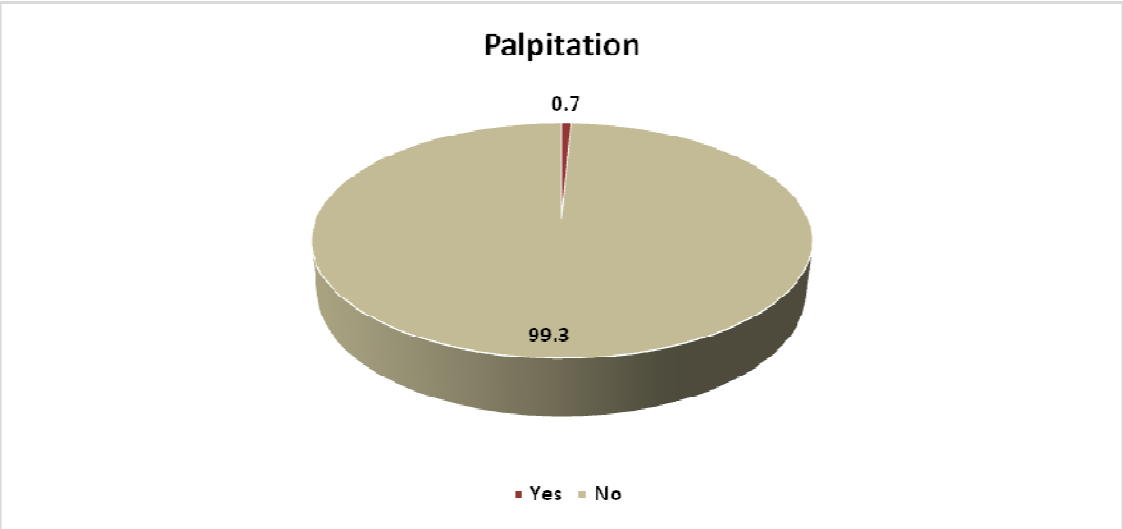
Palpitation

Only one study participant among the 150 had palpitation complaint

Table: Palpitation complaints of the study participants

Palpitation	Frequency (N)	Percentage (%)
Yes	1	0.7
No	149	99.3

Figure: Palpitation complaints of the study participants



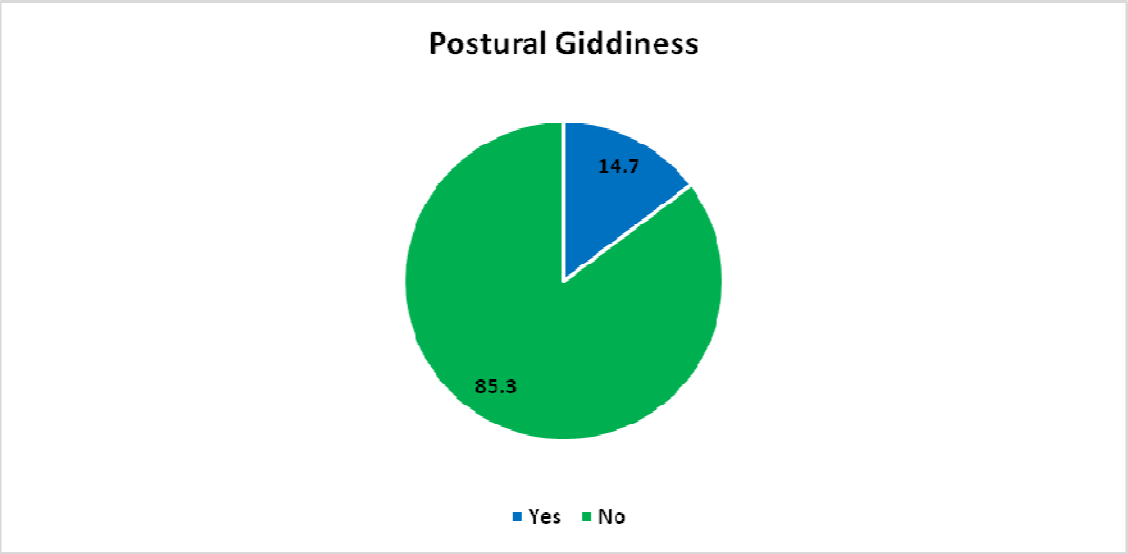
Postural Giddiness

14.7% of the study population had postural giddiness

Table: Postural Giddiness of the study participants

Postural Giddiness	Frequency (N)	Percentage (%)
Yes	22	14.7
No	128	85.3

Figure: Postural Giddiness of the study participants



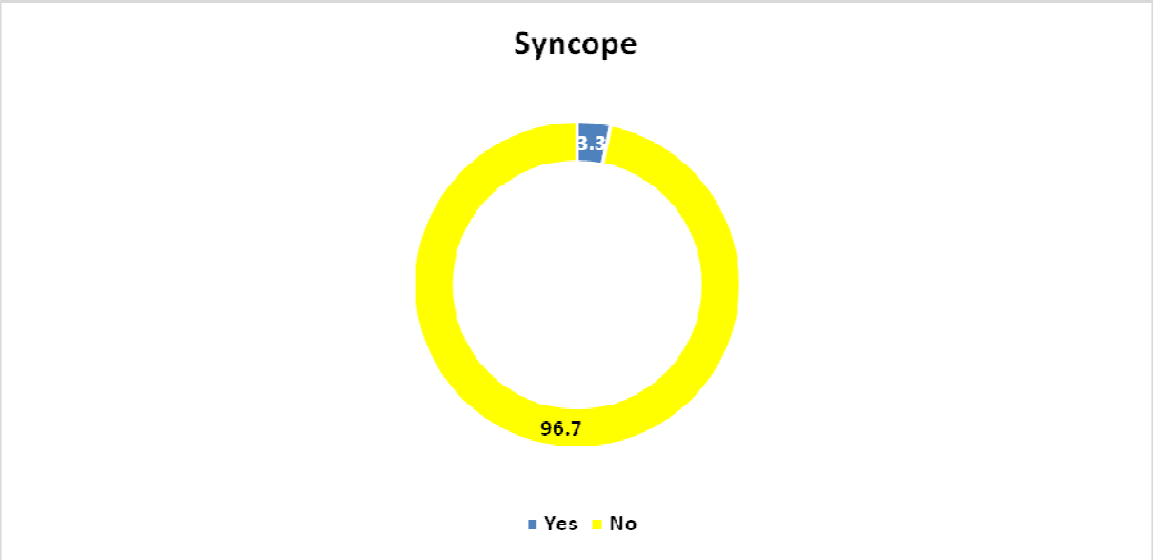
Syncope

Syncope was associated with 3.3% of the study population

Table: Syncope Complaints of the study participants

Syncope	Frequency (N)	Percentage (%)
Yes	5	3.3
No	145	96.7

Figure: Syncope Complaints of the study participants



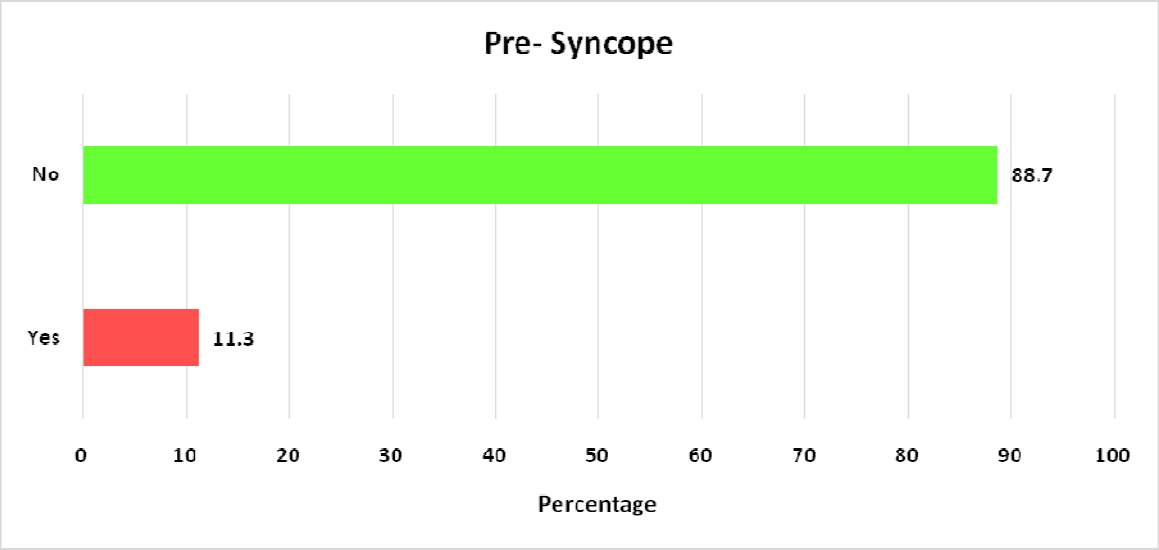
Pre -Syncope

Pre- Syncope complaint was seen in 11.3% of the study participants

Table: Pre-Syncope Complaints of the study participants

Pre-Syncope	Frequency (N)	Percentage (%)
Yes	17	11.3
No	133	88.7

Figure: Pre-Syncope Complaints of the study participants



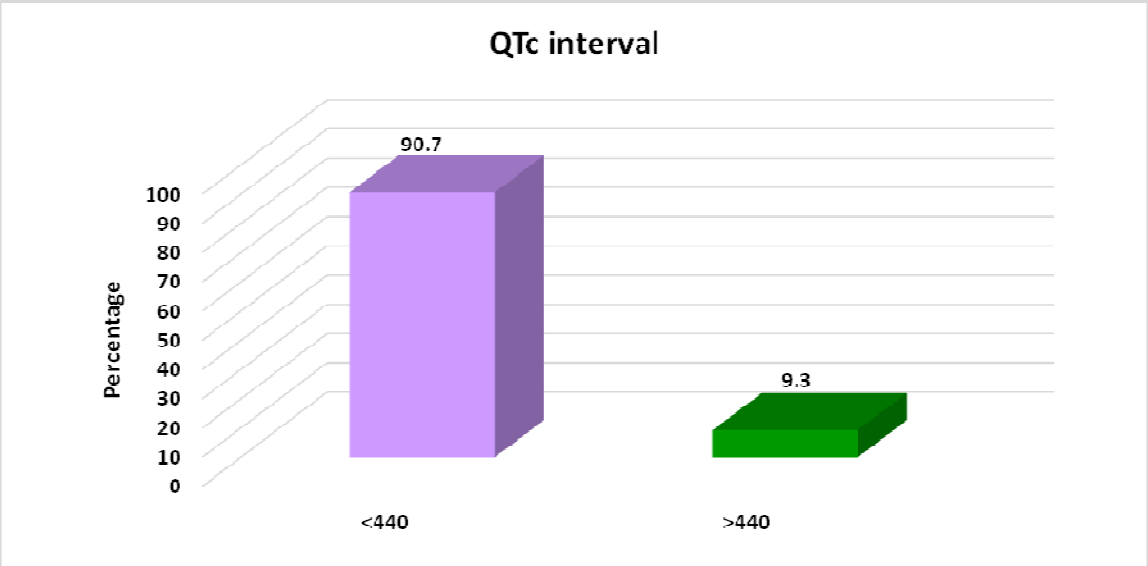
QTc interval of the study participants

The QTc interval was <440 ms in 90.7% of the study population and >440 ms in 9.3% of the study population

Table: QTc interval of the study participants

QTc interval (in ms)	Frequency (N)	Percentage (%)
<440	136	90.7
>440	14	9.3

Figure: QTc interval of the study participants



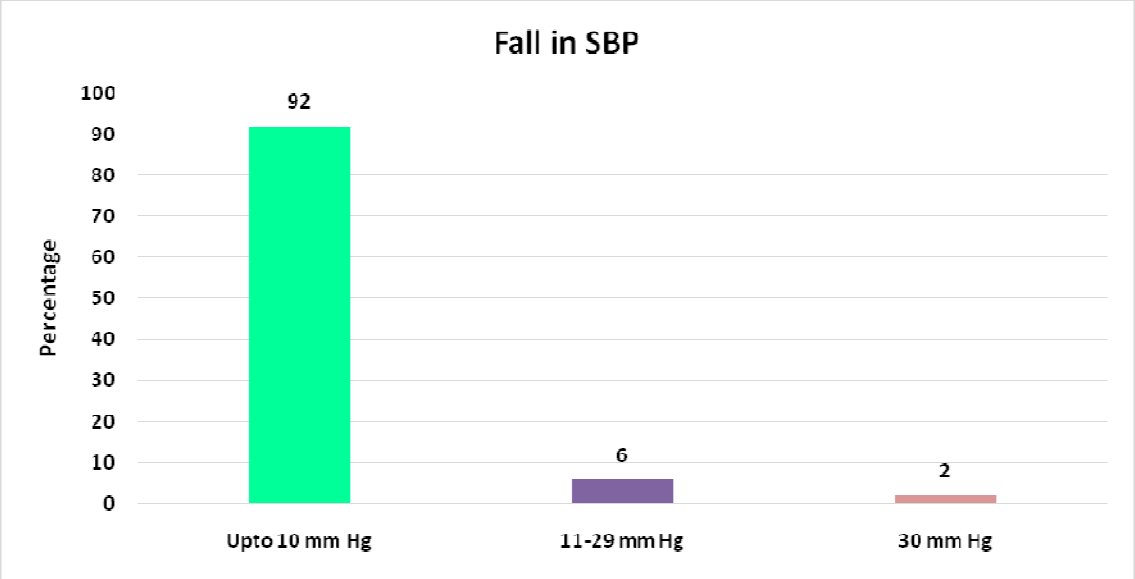
Fall in Systolic Blood Pressure on Standing

92% of the study population had fall in blood pressure on standing by 10 mm Hg, 6 % of them had a fall of 11-29 mm Hg and 2% had a fall of 30 mm Hg

Table: Fall in Systolic Blood Pressure on Standing of the study participants

Fall in SBP on standing	Frequency (N)	Percentage (%)
Upto 10 mm Hg	138	92
11-29 mm Hg	9	6
30 mm Hg	3	2

Figure: Fall in Systolic Blood Pressure on Standing of the study participants



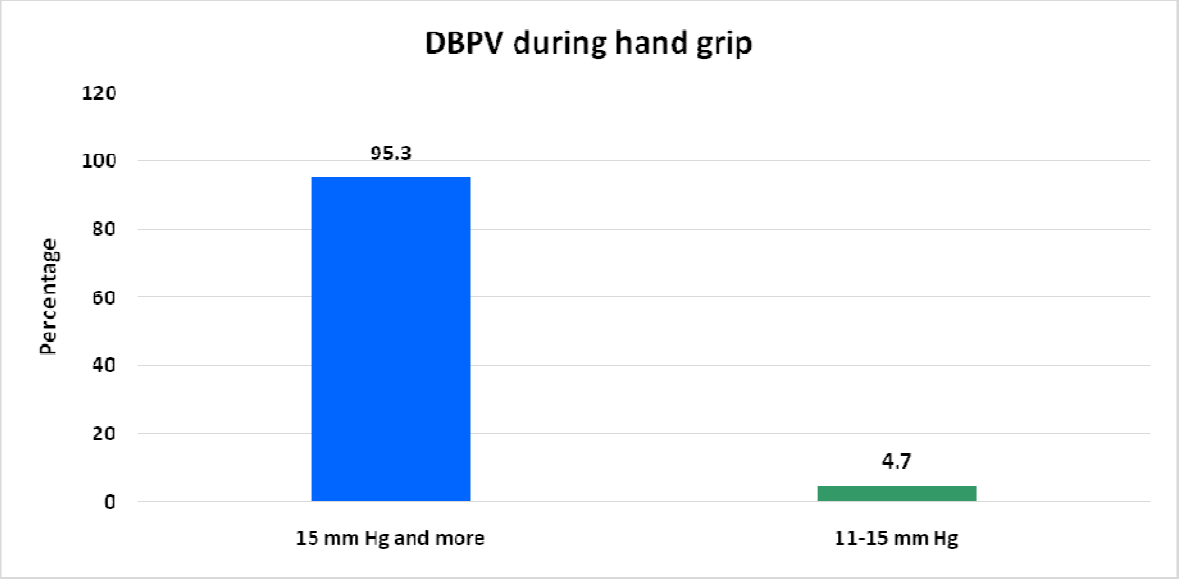
Diastolic Blood Pressure Variation During Hand Grip

95.3% of the population in our study had a diastolic variation of 15 mm Hg and more and 4.7% of them had a variation during hand grip to be 11-15 mm Hg

Table: Diastolic Blood Pressure Variation during hand grip of the study participants

DBPV	Frequency (N)	Percentage (%)
15 mm Hg and more	143	95.3
11-15 mm Hg	7	4.7

Figure: Diastolic Blood Pressure Variation during hand grip of the study participants



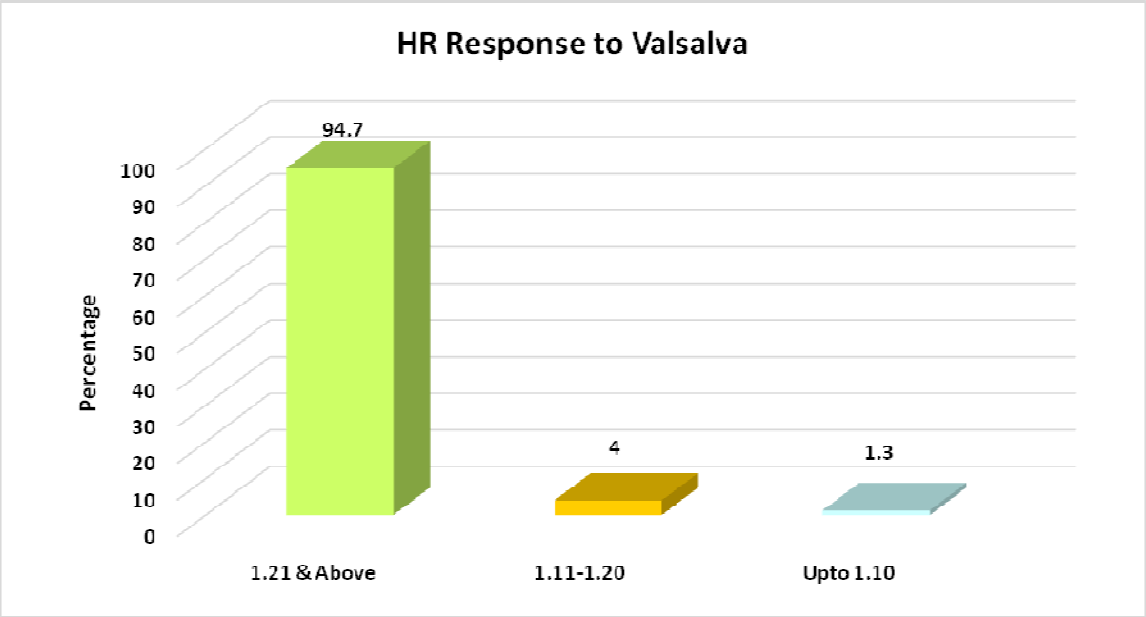
Heart Rate Response to Valsalva

The heart rate response to Valsalva was 1.21 & above in 94.7% of the study population

Table: HR Response to Valsalva of the study participants

HR Response to Valsalva	Frequency (N)	Percentage (%)
1.21 &Above	142	94.7
1.11-1.20	6	4
Upto 1.10	2	1.3

Figure: HR Response to Valsalva of the study participants



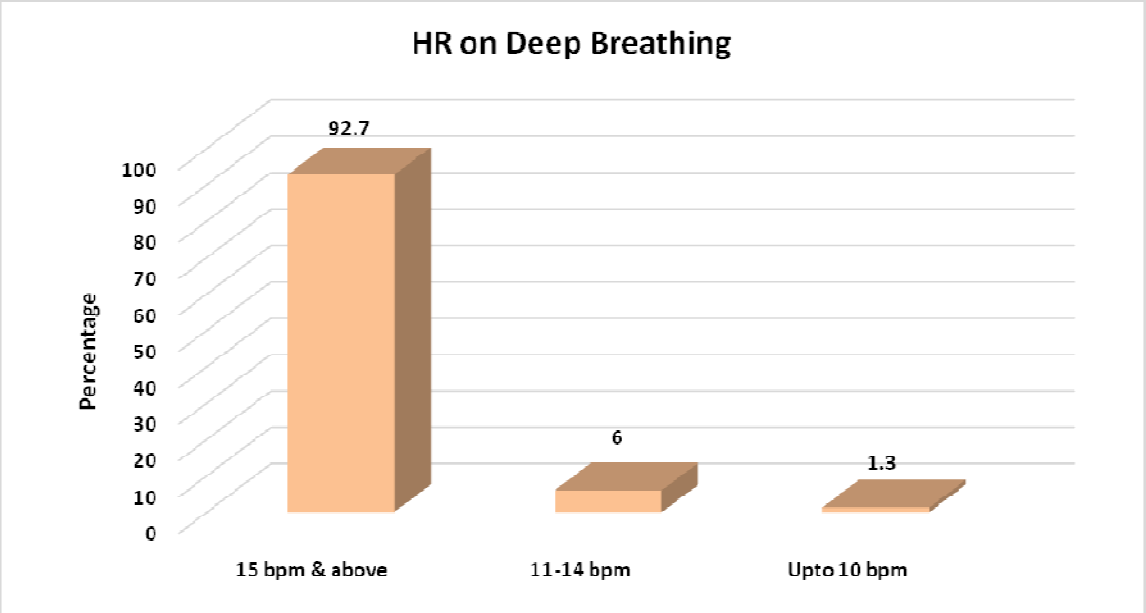
HR on Deep breathing

HR on deep breathing had a variation of 15 beats per minute in 92.7% of the study population and 11-14 beats per minute variation in 6% of the study population

Table: HR on deep breathing of the study participants

HR on Deep Breathing	Frequency (N)	Percentage (%)
15 bpm & above	139	92.7
11-14 bpm	9	6
Upto 10 bpm	2	1.3

Figure: HR on deep breathing of the study participants



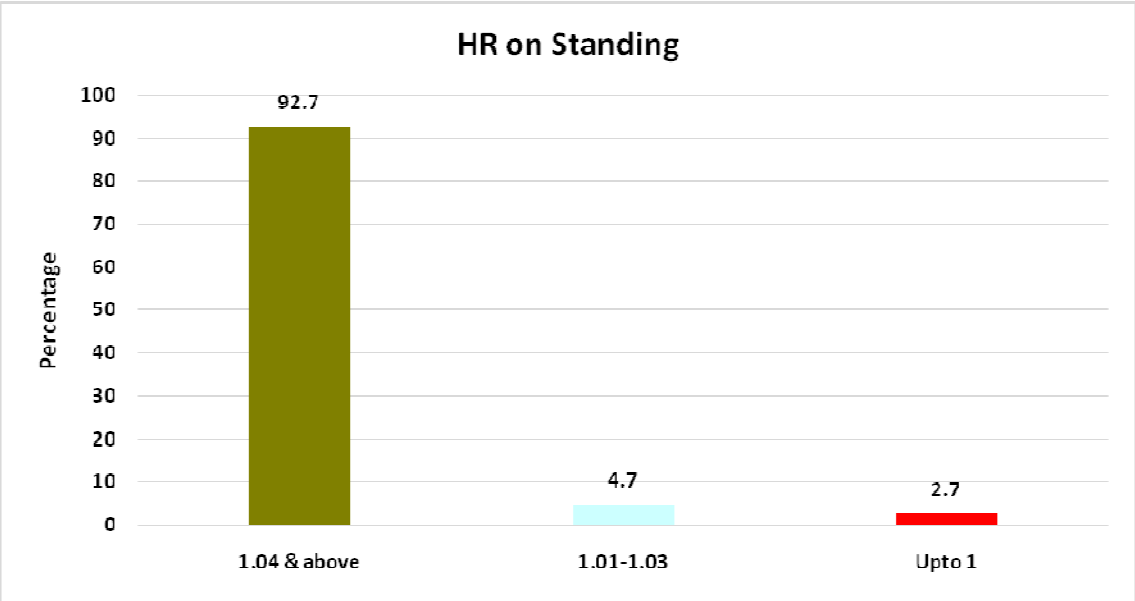
HR on Standing

HR on standing was 1.04 & above in 92.7% of the study participants and it was 4.7% in 1.01-1.03 of the study participants

Table: HR on Standing of the study participants

HR on Standing	Frequency (N)	Percentage (%)
1.04 & above	139	92.7
1.01-1.03	7	4.7
Upto 1	4	2.7

Figure: HR on Standing of the study participants



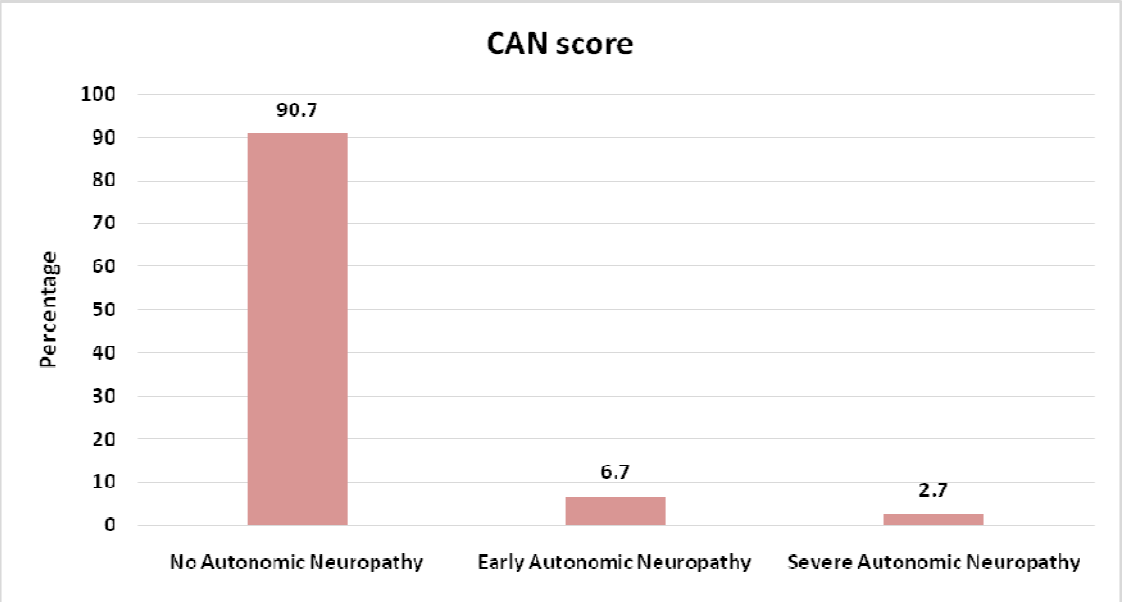
CAN Score

There was no autonomic neuropathy in 90.7% of the study population. 6.7% of them had early autonomic neuropathy and 2.7% had severe autonomic neuropathy

Table: CAN score of the study participants

CAN Score	Frequency (N)	Percentage (%)
No Autonomic Neuropathy	136	90.7
Early Autonomic Neuropathy	10	6.7
Severe Autonomic Neuropathy	4	2.7

Figure: CAN score of the study participants



CHI SQUARE TEST

There was no significant difference between gender and CAN score as the p value was >0.05

Table: Association of Gender with CAN score

Variable	Sub category	CAN Score N (%)			p value
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
Gender	Female	35 (97.2%)	0	1 (2.8%)	0.184
	Male	101 (88.6%)	10 (8.8%)	3 (2.6%)	

Association of symptoms with CAN score

Variables like palpitation, postural giddiness, Syncope and pre syncope were subjected to univariate analysis with CAN score and it was found that palpitation and pre syncope had a statistically significant association with CAN score as the p value was <0.05

Table: Association of symptoms with CAN score

Variable	Sub category	CAN Score N (%)			p value
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
Palpitation	Yes	1 (100%)	0	0	0.950
	No	135 (90.6%)	10 (6.7%)	4 (2.7%)	
Postural Giddiness	Yes	8 (36.4%)	10 (45.5%)	4 (18.2%)	**<0.001**
	No	128 (100%)	0	0	
Syncope	Yes	5 (100%)	0	0	0.766
	No	131 (90.3%)	10 (6.9%)	4 (2.8%)	
Pre Syncope	Yes	10 (59.8%)	4 (23.5%)	3 (17.6%)	**<0.001**
	No	126 (94.7%)	6 (4.5%)	1 (0.8%)	

QTc Interval & CAN score

There was a significant association between QTc interval and CAN score as the p value was less than 0.001

Table: Association of QTc interval with CAN score

Variable	Sub category	CAN Score N (%)			p value
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
QTc	<440 ms	136 (100%)	0	0	**<0.001**
	>440 ms	0	10 (71.4%)	4 (28.6%)	

Bedside tests and CAN score

Fall in SBP on standing, DBPV during hand grip, HR response to Valsalva, HR on deep breathing and HR on standing were found to have a statistically significant association with a p value of <0.05

Table: Association of Bedside tests with CAN score

Variable	Sub category	CAN Score N (%)			P value
		No Autonomic Neuropathy	Early Autonomic Neuropathy	Severe Autonomic Neuropathy	
Fall in SBP on standing	Upto 10 mm Hg	136 (98.6%)	2 (1.4%)	0	**<0.001**
	11 – 29 mm Hg	0	8 (88.9%)	1 (11.1%)	
	30 mm Hg & above	0	0	3 9100%)	
DBPV during hand grip	15 mm Hg & more	136 (95.1%)	7 (4.9%)	0	**<0.001**
	11- 15 mm Hg	0	3 (42.9%)	4 (57.1%)	
HR response to Valsalva	1.21 & above	136 (95.8%)	5 (3.5%)	1 (0.7%)	**<0.001**
	1.11- 1.20	0	5 (83.3%)	1 (16.7%)	
	Upto 1.10	0	0	2 (100%)	
HR on deep breathing	15 bpm & above	136 (97.8%)	3 (2.2%)	0	**<0.001**
	11 – 14 bpm	0	7 (77.8%)	2 (22.2%)	
	Upto 10 bpm	0	0	2 (100%)	
HR on standing	1.04 & above	136 (97.8%)	3 (2.2%)	0	**<0.001**
	1.01-1.03	0	7 (100%)	0	
	Upto 1	0	0	4 (100%)	

ANOVA- Bonferroni Tests

For the association of continuous variables like Age, SBP, DBP, PR, FBS, PPBS and HbA1c with CAN score, they were subjected to one way ANOVA- Bonferroni tests and it was found that they were significant with Age with significant mean difference occurring between no autonomic neuropathy and early autonomic neuropathy and between no autonomic neuropathy and severe autonomic neuropathy with a p value of <0.001

Variable	CAN score sub category	Mean	Standard Deviation	p value
Age (in years)	No Autonomic Neuropathy	46.76	7.922	**<0.001**
	Early Autonomic Neuropathy	56.90	7.505	
	Severe Autonomic Neuropathy	63.25	2.363	
SBP (mm Hg)	No Autonomic Neuropathy	114.04	8.976	0.435
	Early Autonomic Neuropathy	114.00	6.992	
	Severe Autonomic Neuropathy	107.50	5	
DBP (mm Hg)	No Autonomic Neuropathy	70.83	7.669	0.895
	Early Autonomic Neuropathy	71	5.676	
	Severe Autonomic Neuropathy	67.50	9.574	
PR (per min)	No Autonomic Neuropathy	78.55	7.812	0.916
	Early Autonomic	78.70	6.499	

	Neuropathy			
	Severe Autonomic Neuropathy	77	7.394	
FBS (mg/dl)	No Autonomic Neuropathy	119.18	3.539	0.712
	Early Autonomic Neuropathy	119	2.981	
	Severe Autonomic Neuropathy	119.25	2.062	
PPBS (mg/dl)	No Autonomic Neuropathy	169.78	16.057	1.000
	Early Autonomic Neuropathy	169	21.458	
	Severe Autonomic Neuropathy	171.50	16.763	
HbA1c (g%)	No Autonomic Neuropathy	5.985	0.188	0.676
	Early Autonomic Neuropathy	6.080	0.175	
	Severe Autonomic Neuropathy	6.100	0.081	

DISCUSSION

The results of this study illustrate the fact that cardiac autonomic dysfunction is not so uncommon in pre-diabetic patients and its prevalence increases with the duration . Similar results have been reported in previous studies conducted in India and other countries.

Jayaprasad Narayana Pillai et al reported in their study the association between cardiac autonomic neuropathy and QTc interval. They found that prolongation of QTc interval correlated with the severity of CAN.

In our study, among the study population, 76% were males and 24% were females. Among the participants, 14.7% had Postural Giddiness and 11.3% had Pre-Syncope. QTc interval was prolonged in 9.3% of the participants. 8.8% had early autonomic neuropathy and 24% had early autonomic neuropathy. Mean heart rate was significantly more in patients with autonomic neuropathy than those without neuropathy.

Ziegler et al studied the prevalence the CAN among prediabetics, in Europe assessed by the five autonomic function tests by Ewing's methodology. The prevalence of CAN was 11% which is comparable to the results obtained in this study 9.4%.

The association between prolonged QT interval and sudden cardiac death was reported by Ninkovic VM et al in their study

CONCLUSION

Cardiac autonomic neuropathy is a dreaded complication of diabetes mellitus predisposing to sudden cardiac death and myocardial infarction.

In this study, following were concluded;

1. The presence of cardiac autonomic neuropathy is independent of gender. It was found that the prevalence of CAN increases with increase in age.

2. Postural giddiness and Pre-syncope were the most common symptom of CAN in our patients. Palpitation was the least common.

3. Patients with poor glycemic control had higher incidence of CAN. There was a positive correlation between the FBS, PPBS and the Hba1c levels.

4. In 14 cases of CAN, all 14 had QT prolongation. In 4 cases of severe CAN, all 4 had QT prolongation. QT prolongation is 82.7% sensitive and 62.1% specific in detecting severity of CAN.

LIMITATIONS

1. Newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be done because of limitations in resources and cost.

2. Serum Magnesium and Serum Calcium which may alter QT interval could not be done as they would add to the cost factor.

3. Patients could not be followed up to assess the incidence of adverse cardiac events.

4. The study was done in a single centre in a single geographic area

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ANNEXURES

INFORMATION SHEET

We are conducting a study on **"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE-DIABETIC ADULTS"** among patients attending Government Stanley General Hospital, Chennai and for that your specimen may be valuable to us. The purpose of this study is to look for autonomic dysfunction by using five non-invasive bedside tests and corrected QT-Interval using Electrocardiogram in pre-diabetic adults.

We are selecting certain cases and if you are found eligible, we may beusing your blood samples to do certain tests which in any way do not affectyour final report or management.

The privacy of the patients in the research will be maintained throughoutthe study. In the event of any publication or presentation resulting from theresearch, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether toparticipate in this study or to withdraw at any time; your decision will not resultin any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of thestudy period or during the study if anything is found abnormal which may aid inthe management or treatment.

Signature of Investigator Signature of Participant

Date:

Place:

ஆராய்ச்சிதகவல்தாள்

சென்னைஅரசுஸ்டான்லி பொதுமருத்துவமனையின்பொது மருத்துவத்துறையில்"நீரிழிவுநோய்வரும்முன்நிலையில்உள்ளவயதுவந்தநபர்களிடம்இருதயதன்னியக்கசெயலிழப்புஇருக்கும்நிலையின்பரவல்"பற்றியஆய்வுநடைபெறுகிறது.இந்த ஆய்வின் நோக்கம், ஐந்து உடலில்ஊடுருவாதபடுக்கைஅருகில்செய்யும்பரிசோதனைகள் மற்றும் எலக்ட்ரோ கார்டியோகிராம் பயன்படுத்தி சரிசெய்யப்பட்டQT-இடைவெளிகண்டறிந்துபயன்படுத்துவதன் மூலம்இருதய தன்னியக்க செயலிழப்பை கண்டறிவது.

நீங்களும்இந்தஆராய்ச்சியில்பங்கேற்கநாங்கள்விரும்புகிறோம். இதனால்தங்களதுசிகிச்சையில்பாதிப்புஏற்படாதுஎன்பதையும்தெரிவித்துக்கொள்கிறோம்.

முடிவுகளைஅல்லதுகருத்துக்களைவெளியிடும்போதோஅல்லதுஆராய்ச்சியின்போதோதங்களதுபெயரையோஅல்லதுஅடையாளங்களையோவெளியிடமாட்டோம்என்பதைதெரிவித்துக்கொள்கிறோம்.

இந்தஆராய்ச்சியில்பங்கேற்பதுதங்களுடையவிருப்பத்தின்பேரில்தான்இருக்கிறது.

மேலும்நீங்கள்எந்தநேரமும்இந்தஆராய்ச்சியிலிருந்துபின்வாங்கலாம்என்பதையும்தெரிவித்துக்கொள்கிறோம்.

இந்தசிறப்புபரிசோதனைகளின்முடிவுகளையும்நோயின்தன்மைபற்றியும்ஆராய்ச்சியின்போதுஅல்லதுஆராய்ச்சியின்முடிவின்போதுதங்களுக்குஅறிவிப்போம்என்பதையும்தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர்கையொப்பம் பங்கேற்பாளர்கையொப்பம்

நாள் :

இடம் :

CONSENT FORM

Study Detail :**"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE- DIABETIC ADULTS"**
Study Centre : Government Stanley Medical College and Hospital, Chennai.
Patient's Name :
Patient's Age :
Identification Number :

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access, However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

Patient's signature/left thumb impression Signature of Investigator

Patient's Name and Address:

Study Investigator's Name
Dr.Nitin Abhishek Balaji.D

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு:
"நீரிழிவுநோய்வரும்முன்நிலையில்உள்ளவயதுவந்தநபர்களிடம்இருதயதன்னியக்க செயலிழப்புநிலையின்பரவல்"
ஆய்வு நிலையம்: பொது மருத்துவத்துறை,அரசுஸ்டான்லி மருத்துவக் கல்லூரி
சென்னை - 1.
பங்கு பெறுபவரின் பெயர் :
உள்நோயாளி எண் :

பங்குபெறுபவர் இதனை (√) குறிக்கவும்

- மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்தவிளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. □
- நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்தகாரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான்இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.□
- இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைபார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில்இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். □
- இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனைமுடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர்மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழுமனதுடன் சம்மதிக்கின்றேன்.
  □
- இந்தஆய்வுதொடர்பாகநான்எதற்கும்பணம்செலவழிக்கவேண்டியதில்லைஎன்பதை நான்புரிந்துகொள்கிறேன் □
- இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்டஅறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும்மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். □
- இந்தஆய்விற்குதேவையானஅனைத்துஉடல்மற்றும்இரத்தபரிசோதனைகளஒப்புக் கொள்ளப்பட்டமுறைகள்என்பதையும் இதனால் உடலுக்குஎந்தவிதமான உபாதைகளும் இருக்காதுஎன்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழுமனதுடன்சம்மதிக்கிறேன்□

பங்கேற்பவரின் கையொப்பம்/ இடது கை பெருவிரல் ரேகை

ஆய்வாளரின்கையொப்பம்

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்:

ஆய்வாளரின்பெயர்
மரு.நிதின்அபிஷேக் பாலாஜி.த

இடம்:

PROFORMA

Name: Age/Sex:
Address: Occupation:

SYMPTOMS:

Easy fatiguability	
Palpitation	
Chest discomfort	
Light Headedness	
Syncope	
Blurring of Vision	
Dizziness	

PAST HISTORY:

CAD	
CKD	
CLD	

PERSONAL HISTORY:

SMOKING	
ALCOHOL	

FAMILY HISTORY OF DIABETES:

GENERAL EXAMINATION:
Pallor
Icterus
Cyanosis
Clubbing
Pedal edema
Lymphadenopathy

BMI:

VITAL SIGNS:
PR BP
RR JVP
Temp-

SYSTEMIC EXAMINATION:
CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATIONS:

1. COMPLETE HEMOGRAM:
   Hemoglobin:
   MCV:
   MCH:
   MCHC:
   Hematocrit:
   ESR:

2. ELECTROCARDIOGRAM:

3. FASTING BLOOD GLUCOSE (FBG):

4. POST PRANDIAL BLOOD GLUCOSE (PPBG)

5. HbA1c:

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI_-01
INSTITUTIONAL ETHICS COMMITTEE
EC Registration No.ECR/131/Inst/TN/2013/RR-19
DHR Registration Number : EC/NEW/INST/2020/461

TITLE OF THE WORK	: "TO STUDY THE PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN PRE DIABETIC ADULTS AT A TERTIARY CARE HOSPITAL IN CHENNAI"
PRINCIPAL INVESTIGATOR	: DR. NITIN ABHISHEK BALAJI. D,
DESIGNATION	: PG IN GENERAL MEDICINE,
DEPARTMENT	: DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held 29.06.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 11 am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

6/7/21.

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

S.NO	AGE	SEX	PALPITATION	POSTURAL GIDDINESS	SYNCOPE	PRESYNCOPE	BP	PR	FBS	PPBS	HBA1C	QTc	FALL IN SBP ON STANDING	DBPV DURING HAND GRIP	HR RESPONSE TO VALSALVA	HR ON DEEP BREATHING	HR ON STANDING	CAN SCORE
1	42	M	2	2	2	2	100/64	82	117	147	5.9	1	1	1	1	1	1	A
2	47	M	2	2	2	2	120/80	76	120	185	5.8	1	1	1	1	1	1	A
3	50	M	2	2	2	1	110/70	74	114	180	5.7	1	1	1	1	1	1	A
4	50	M	2	2	2	2	110/60	76	120	188	5.9	1	1	1	1	1	1	A
5	33	F	2	2	2	2	100/60	68	124	177	6	1	1	1	1	1	1	A
6	38	M	2	2	2	2	130/80	76	123	172	6.2	1	1	1	1	1	1	A
7	50	M	2	2	2	2	110/80	68	120	148	6.1	1	1	1	1	1	1	A
8	36	M	2	2	2	2	110/60	80	119	166	5.7	1	1	1	1	1	1	A
9	44	M	2	2	2	2	120/70	68	123	192	6.2	1	1	1	1	1	1	A
10	48	M	2	2	2	2	130/80	74	121	149	6	1	1	1	1	1	1	A
11	37	M	2	2	2	2	130/90	68	118	193	5.9	1	1	1	1	1	1	A
12	45	M	2	2	2	2	100/60	88	110	151	6	1	1	1	1	1	1	A
13	46	F	2	2	2	2	100/60	76	122	157	6.2	1	1	1	1	1	1	A
14	50	M	2	2	2	2	110/70	70	119	183	6.1	1	1	1	1	1	1	A
15	45	M	2	2	2	2	120/70	84	120	150	6.3	1	1	1	1	1	1	A
16	45	M	2	2	2	2	110/60	86	117	154	5.9	1	1	1	1	1	1	A
17	53	M	2	2	2	1	100/60	76	120	167	5.7	1	1	1	1	1	1	A
18	52	M	2	2	2	2	120/70	72	114	162	6.2	1	1	1	1	1	1	A
19	54	M	2	1	2	1	120/70	82	120	179	6	2	2	1	2	2	1	B
20	40	M	2	2	2	2	110/60	94	124	156	5.8	1	1	1	1	1	1	A
21	46	M	2	2	2	2	130/90	86	123	198	5.7	1	1	1	1	1	1	A
22	51	M	2	2	2	2	110/60	68	120	179	5.9	1	1	1	1	1	1	A
23	45	M	2	2	2	2	120/70	94	119	165	6	1	1	1	1	1	1	A
24	44	M	2	2	2	2	110/60	68	111	145	6.2	1	1	1	1	1	1	A
25	45	M	2	2	2	2	100/60	88	121	178	6.1	1	1	1	1	1	1	A
26	50	M	2	2	2	1	110/80	88	118	168	6.3	1	1	1	1	1	1	A
27	31	M	2	2	2	2	120/70	74	110	155	5.9	1	1	1	1	1	1	A
28	47	M	2	2	2	2	110/70	86	122	147	5.7	1	1	1	1	1	1	A
29	45	M	2	2	2	2	100/60	80	119	185	6.2	1	1	1	1	1	1	A
30	46	M	2	2	2	2	110/70	76	120	180	6	1	1	1	1	1	1	A
31	40	M	2	2	2	2	130/90	86	118	188	5.9	1	1	1	1	1	1	A
32	48	F	2	2	2	2	110/70	82	122	177	6	1	1	1	1	1	1	A
33	50	M	2	2	2	2	130/90	65	119	172	6.2	1	1	1	1	1	1	A
34	53	F	2	2	2	1	100/60	74	120	148	6.1	1	1	1	1	1	1	A
35	50	M	2	2	2	2	120/70	82	117	166	6.3	1	1	1	1	1	1	A
36	52	M	2	2	2	2	100/60	92	120	192	5.9	1	1	1	1	1	1	A
37	42	M	2	1	2	2	110/70	86	114	149	5.7	2	2	1	2	1	2	B
38	52	M	2	2	2	2	110/70	88	120	147	6.2	1	1	1	1	1	1	A
39	54	M	2	2	2	1	110/80	82	124	185	6	1	1	1	1	1	1	A
40	60	M	2	2	2	1	110/60	78	123	180	5.7	1	1	1	1	1	1	A
41	63	M	2	2	2	2	100/60	72	120	188	6.2	1	1	1	1	1	1	A
42	65	M	2	1	2	1	110/70	68	119	177	6	2	3	2	3	3	3	C
43	53	M	2	2	2	2	110/60	72	111	172	5.9	1	1	1	1	1	1	A
44	54	M	2	2	2	2	120/70	72	124	148	6	1	1	1	1	1	1	A
45	65	M	2	1	2	1	110/60	86	122	147	6.2	2	3	2	2	2	3	C
46	60	M	2	1	2	2	100/60	76	119	185	6.1	2	3	2	3	2	3	C
47	61	M	2	2	2	1	110/70	88	120	180	6.3	1	1	1	1	1	1	A
48	60	M	2	2	2	1	120/70	68	117	188	5.9	1	1	1	1	1	1	A

49	45	F	2	2	2	2	110/70	80	120	177	5.7	1	1	1	1	1	1	A
50	28	M	2	2	2	2	100/60	90	122	172	6.2	1	1	1	1	1	1	A
51	65	M	2	1	2	2	120/80	74	119	148	6	2	2	2	2	1	1	B
52	47	M	2	2	2	2	110/70	82	120	147	5.8	1	1	1	1	1	1	A
53	46	M	2	2	2	2	110/70	84	117	185	5.7	1	1	1	1	1	1	A
54	63	M	2	1	2	1	100/70	78	120	180	5.9	1	1	1	1	1	1	A
55	60	M	2	2	1	2	110/70	68	114	188	5.9	1	1	1	1	1	1	A
56	44	M	2	2	2	2	110/60	68	120	177	5.8	1	1	1	1	1	1	A
57	42	M	2	2	2	2	130/80	74	124	172	5.7	1	1	1	1	1	1	A
58	33	M	2	2	2	2	110/60	88	122	148	5.9	1	1	1	1	1	1	A
59	35	M	1	2	2	2	120/70	68	119	166	6	1	1	1	1	1	1	A
60	38	M	2	2	2	2	110/70	80	120	192	6.2	1	1	1	1	1	1	A
61	33	M	2	2	2	2	130/70	68	117	147	5.9	1	1	1	1	1	1	A
62	47	M	2	2	2	2	120/70	82	120	185	5.9	1	1	1	1	1	1	A
63	40	M	2	2	2	2	110/80	86	114	180	5.8	1	1	1	1	1	1	A
64	45	M	2	2	2	2	130/70	74	120	188	5.7	1	1	1	1	1	1	A
65	44	M	2	2	2	2	120/70	88	124	177	5.9	1	1	1	1	1	1	A
66	42	M	2	2	2	2	110/80	72	123	172	6	1	1	1	1	1	1	A
67	47	F	2	2	2	2	120/80	64	122	148	6.2	1	1	1	1	1	1	A
68	41	M	2	2	2	2	110/70	78	119	166	5.9	1	1	1	1	1	1	A
69	57	M	2	1	2	2	110/80	84	120	192	6.2	2	2	2	1	2	1	B
70	61	M	2	1	2	2	100/60	84	117	149	5.9	1	1	1	1	1	1	A
71	52	M	2	2	2	2	110/70	82	120	193	5.8	1	1	1	1	1	1	A
72	45	M	2	2	2	2	130/80	90	114	151	5.7	1	1	1	1	1	1	A
73	43	M	2	2	2	2	110/60	82	120	157	5.9	1	1	1	1	1	1	A
74	46	M	2	2	2	2	120/70	82	124	183	6	1	1	1	1	1	1	A
75	65	M	2	1	2	1	110/70	76	123	150	6.2	2	2	2	2	1	2	B
76	42	F	2	2	1	2	130/70	82	123	148	5.7	1	1	1	1	1	1	A
77	47	F	2	2	2	2	120/70	76	120	147	6.2	1	1	1	1	1	1	A
78	50	M	2	1	2	1	110/80	74	119	185	6	1	1	1	1	1	1	A
79	50	M	2	2	2	2	130/70	76	123	180	5.9	1	1	1	1	1	1	A
80	33	M	2	2	2	2	120/70	68	121	188	6	1	1	1	1	1	1	A
81	38	F	2	2	1	2	110/80	76	118	177	6.2	1	1	1	1	1	1	A
82	50	F	2	1	2	2	120/80	68	110	172	6.1	1	1	1	1	1	1	A
83	36	F	2	2	2	2	110/70	80	122	148	6.3	1	1	1	1	1	1	A
84	44	F	2	2	2	2	110/80	68	119	147	5.9	1	1	1	1	1	1	A
85	48	M	2	2	2	2	100/60	74	120	185	5.7	1	1	1	1	1	1	A
86	37	F	2	2	2	2	110/70	68	117	180	6.2	1	1	1	1	1	1	A
87	45	F	2	2	2	2	110/70	88	120	188	6	1	1	1	1	1	1	A
88	46	M	2	2	2	2	120/70	76	114	177	5.8	1	1	1	1	1	1	A
89	50	F	2	2	2	2	110/70	70	120	172	5.7	1	1	1	1	1	1	A
90	45	M	2	2	2	2	120/70	84	124	148	5.9	1	1	1	1	1	1	A
91	45	M	2	2	2	2	110/80	86	123	166	6	1	1	1	1	1	1	A
92	53	M	2	1	2	1	100/60	76	120	192	6.2	2	2	1	1	2	2	B
93	52	M	2	1	2	2	110/70	72	119	147	6.1	1	1	1	1	1	1	A
94	54	M	2	2	2	2	110/70	82	111	185	6.3	1	1	1	1	1	1	A
95	40	F	2	2	2	2	130/80	94	121	180	5.9	1	1	1	1	1	1	A
96	46	M	2	2	2	2	110/60	86	118	188	5.7	1	1	1	1	1	1	A
97	51	F	2	2	2	2	120/70	68	110	177	6.2	1	1	1	1	1	1	A
98	45	M	2	2	2	2	110/70	94	122	172	6	1	1	1	1	1	1	A
99	44	M	2	2	2	2	130/70	68	119	148	5.9	1	1	1	1	1	1	A
100	45	F	2	2	2	2	120/70	88	120	166	6	1	1	1	1	1	1	A
101	50	M	2	2	2	2	110/80	88	118	192	6.2	1	1	1	1	1	1	A
102	31	M	2	2	2	2	130/70	74	122	149	6.1	1	1	1	1	1	1	A
103	47	M	2	2	2	2	120/70	86	119	193	6.3	1	1	1	1	1	1	A
104	45	F	2	2	2	2	110/80	80	120	151	5.7	1	1	1	1	1	1	A

105	46	F	2	2	1	2	120/80	76	117	157	6.2	1	1	1	1	1	1	A
106	40	F	2	2	2	2	110/70	86	120	183	6	1	1	1	1	1	1	A
107	48	M	2	2	2	2	110/80	82	114	150	5.9	1	1	1	1	1	1	A
108	50	M	2	1	2	2	120/70	65	120	189	6	2	2	1	1	2	2	B
109	53	M	2	2	2	2	110/80	74	124	177	6.2	1	1	1	1	1	1	A
110	50	M	2	2	2	2	130/70	82	123	142	6.1	1	1	1	1	1	1	A
111	52	F	2	2	2	2	120/70	92	120	167	6.3	1	1	1	1	1	1	A
112	42	M	2	2	2	2	110/80	86	119	155	5.9	1	1	1	1	1	1	A
113	52	M	2	2	2	2	120/80	88	111	185	5.7	1	1	1	1	1	1	A
114	54	F	2	2	2	2	110/70	82	124	180	6.2	1	1	1	1	1	1	A
115	60	M	2	2	2	2	110/80	78	122	188	6	1	1	1	1	1	1	A
116	63	M	2	2	1	2	100/60	72	119	177	5.8	1	1	1	1	1	1	A
117	65	F	2	2	2	2	110/70	68	120	148	5.7	1	1	1	1	1	1	A
118	53	M	2	2	2	2	110/70	72	117	147	5.9	1	1	1	1	1	1	A
119	54	M	2	2	2	2	120/70	72	123	185	6	1	1	1	1	1	1	A
120	65	F	2	2	2	2	110/70	86	120	180	6.2	1	1	1	1	1	1	A
121	60	F	2	2	2	2	120/70	76	119	188	6.1	1	1	1	1	1	1	A
122	61	F	2	1	2	2	110/80	88	123	177	6.3	1	1	1	1	1	1	A
124	60	F	2	2	2	2	100/60	68	121	172	5.7	1	1	1	1	1	1	A
124	45	M	2	2	2	2	110/70	80	118	148	6.2	1	1	1	1	1	1	A
125	28	M	2	1	2	2	120/70	90	110	147	6	1	1	1	1	1	1	A
126	65	M	2	2	2	2	110/80	74	122	185	5.9	1	1	1	1	1	1	A
127	47	M	2	2	2	2	120/80	82	119	180	6	1	1	1	1	1	1	A
128	46	M	2	2	2	2	110/70	84	120	188	6.2	1	1	1	1	1	1	A
129	63	F	2	1	2	1	110/80	78	117	177	6.1	2	2	2	1	3	3	C
130	60	F	2	1	2	2	100/60	68	120	172	6.3	1	1	1	1	1	1	A
131	44	F	2	2	2	2	110/70	68	114	148	5.9	1	1	1	1	1	1	A
132	42	M	2	2	2	2	130/80	74	120	166	5.7	1	1	1	1	1	1	A
133	33	M	2	2	2	2	110/60	88	124	192	6.2	1	1	1	1	1	1	A
134	35	M	2	2	2	2	120/70	68	123	147	6	1	1	1	1	1	1	A
135	38	F	2	2	2	2	120/70	80	120	185	5.8	1	1	1	1	1	1	A
136	33	M	2	2	2	2	110/80	68	119	180	5.7	1	1	1	1	1	1	A
137	47	M	2	2	2	2	120/80	82	111	188	5.9	1	1	1	1	1	1	A
138	40	M	2	2	2	2	110/70	86	121	177	6	1	1	1	1	1	1	A
139	45	F	2	2	2	2	110/80	74	118	172	6.2	1	1	1	1	1	1	A
140	44	M	2	2	2	2	100/60	88	110	148	6.1	1	1	1	1	1	1	A
141	42	M	2	2	2	2	110/70	72	122	166	6.3	1	1	1	1	1	1	A
142	47	M	2	2	2	2	130/80	64	119	192	5.9	1	1	1	1	1	1	A
143	41	F	2	2	2	2	110/60	78	120	149	5.7	1	1	1	1	1	1	A
144	57	M	2	1	2	2	120/70	84	118	193	6.2	2	2	1	1	2	2	B
145	61	M	2	1	2	1	110/70	84	122	151	6	2	1	1	1	2	2	B
146	52	M	2	2	2	2	130/70	82	119	157	5.9	1	1	1	1	1	1	A
147	45	F	2	2	2	2	120/70	90	120	183	6	1	1	1	1	1	1	A
148	43	M	2	2	2	2	110/80	82	117	150	6.2	1	1	1	1	1	1	A
149	46	F	2	2	2	2	130/70	82	120	148	6.1	1	1	1	1	1	1	A
150	65	M	2	1	2	2	120/70	76	114	147	6.3	2	1	1	2	2	2	B

DBPV DURING HAND GRIP	HR RESPONSE TO VALSALVA			DEEP BREATH TEST			HR IN STANDING		FALL IN SBP ON STANDING	
>= 15 mmhg-1	>=1.21-1			>=15 bpm-1			>=1.04-1		<=10 mmhg-1	
11-15 mmhg-2	1.11-1.20-2			11-14 bpm-2			1.01-1.03-2		11-29 mmhg-2	
<=10 mmhg-3	<=1.10-3			<=10 bpm-3			<=1-3		>=30 mmhg-3	
CAN SCORE										
NO AUTONOMIC NEUROPATHY-A										
EARLY AUTONOMIC NEUROPATHY-B										
SEVERE AUTONOMIC NEUROPATHY-C										
PRESYNCOPE	SYNCOPE	POSTURAL GIDDINESS	PALPITATION	QTc						
1-YES	1-YES	1-YES	1-YES	<440-1						
2-NO	2-NO	2-NO	2-NO	>440-2						