PROFILE OF ELECTROCARDIOGRAPH IN TYPE 2 DIABETES PATIENTS AND ITS CORRELATION TO CARDIAC DYSAUTONOMIA

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CERTIFICATE

This is to certify that this dissertation entitled "PROFILE OF ELECTROCARDIOGRAPH IN TYPE 2 DIABETES PATIENTS AND ITS CORRELATION TO CARDIAC DYSAUTONOMIA" submitted by DR.VIKRAMAN.G to The Tamil Nadu Dr. M.G.R. Medical University Chennai is in partial fulfillment of the regulations for the award of M.D DEGREE BRANCH-I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

Signature of the Unit Chief

Signature of the Professor and HOD

Signature of the Dean

DECLARATION

I solemnly declare that the dissertation titled "PROFILE OF ELECTROCARDIOGRAPH IN TYPE 2 DIABETES PATIENTS AND ITS CORRELATION TO CARDIAC DYSAUTONOMIA" was done by me at Stanley Medical College and Hospital during 2008-2009 under the guidance and supervision of **PROF. S. SUNDAR, M.D.**

The dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of the regulations for the award of M.D. DEGREE (BRANCH-I) in General Medicine.

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CONTENTS

ANNEXURE

INTRODUCTION

Diabetes mellitus is a multi-metabolic disorder that shares the common phenotype of hyperglycemia.

Globally, Diabetes Mellitus is a major threat to human health. The number of people with Diabetes has increased alarmingly since 1985 and the rate of new cases is escalating. In 1985, an estimated 30 million people worldwide had diabetes; by 2003, it was estimated that approximately 194 million people had diabetes, and this figure is expected to rise to almost 350 million by 2025.

Type 2 Diabetes is a major health problem in India.

The WHO has highlighted that India currently holds the top spot for most no. of people with diabetes and would continue to hold the top position in future also. The estimated burden in India would be around 79.4 million by the year 2030.

Autonomic dysfunction in diabetes is common. Abnormal cardiovascular test suggesting cardiovascular autonomic neuropathy is present in 16-40% of diabetic population.

Patients with diabetic cardiac autonomic neuropathy are more prone for sudden cardiac death probably due to silent myocardial ischemia or infarction or due to primary malignant ventricular arrhythmias.

The ECG, which reflects the electrical activity of heart, is liable to show abnormalities in diabetics more often than in non-diabetics by virtue of the more attendant factors that are more commonly seen in diabetics. In this context the factors that modify impulse generation, conduction, nervous control of heart, vascular supply of the myocardium, state of myocardium, all required to be considered individually.

There is a higher prevalence of RBBB and AV block in diabetics that cannot accounted by the increased incidence of ischemic heart disease alone. Higher incidence of these blocks is seen independent of ischemic heart disease.

Autonomic dysfunction is often asymptomatic. Hence diagnosing asymptomatic cardiac autonomic dysfunction, a precursor of symptomatic cardiac autonomic neuropathy will help in a long way in taking sufficient precaution to delay (or) arrest its progression by various measures.

Recent observations noted that corrected QT interval (QTc) in surface ECG seems prolonged in diabetics with autonomic neuropathy and postulations are made that it may be one of the cause of sudden death or a compounding factor for the predisposition of malignant ventricular arrhythmias.

This highlights the importance of simple noninvasive investigation like ECG in diagnosing asymptomatic cardiac autonomic dysfunction.

This study is performed to study the various ECG abnormalities in type 2 Diabetic patients to estimate the prevalence of cardiac dysautonomia in type 2 Diabetic patients by various ECG markers and to compare with the age and sex matched controls.

AIMS OF THIS STUDY

1) To study the various ECG abnormalities in Type 2 Diabetes mellitus patients as compared to controls.

2) To study the prevalence of cardiac dysautonomia in type 2 diabetes mellitus patients by various ECG markers.

REVIEW OF LITERATURE

Diabetes mellitus, once regarded as a single entity is now regarded as a heterogeneous group of disease characterized by a state of chronic hyperglycemia resulting from diverse etiologies, environmental and genetic factors acting together.

HISTORY

The first documented evidence of Diabetes mellitus was reported by Egyptian papyrus as a polyuric state.

In 1776, Mathew Dobson estimated the presence of sugar in blood and urine of diabetes patients.

Type 2 Diabetes is the commonest form of diabetes in any country.

EPIDEMIOLOGY

The global evidence of Diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025. India has the dubious distinction of having the highest number of diabetics in the world. (1)

The prevalence in India varies from 1.7 to 9.6 % in various studies. A multi center study done by Indian council of medical research showed a prevalence of 1.73 percent in Indians above 15 years of age. According to prevalence of Diabetes in India study (PODIs) the prevalence of type 2 diabetes in India is

Urban-9.6%

Rural-4.2%

Male > female

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS (WHO AND NATIONAL DIABETES DATA GROUP) [(2)]

THE CRITERIA IS BASED ON THE FOLLOWING PREMISES

1) The spectrum of fasting (FPG) and the response to an oral glucose load (OGTT-oral glucose tolerance test) varies among normal individuals.
2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations from population based mean.

CRITERIAS:

1) Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL)[a] or
2) Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b] or
3) Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal

[b]Fasting is defined as no caloric intake for at least 8h.

[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water: not recommended for routine clinical use.

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

DIABETES AND HEART [3]

Diabetes involves heart in the following ways

1. Coronary Artery Disease (CAD)
2. Small vessel disease
3. Diabetic Cardiomyopathy
4. Diabetic autonomic neuropathy

CORONARY ARTERY DISEASE (CAD)

Coronary heart disease is about twice frequent in diabetic men and four times frequent in diabetic women compared to respective non-diabetics.

Coronary artery disease is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease. There is a two to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population.[4] This increase is particularly disproportionate in diabetic women when compared with diabetic men.[4] The protection that premenopausal women have against coronary artery disease is not seen if they suffer from diabetes.

Diabetics are prone for severe, premature and asymptomatic heart disease.

SMALL VESSEL DISEASE

Occlusive disease process affecting the smaller vessel is the hallmark of diabetic heart disease. Pathological changes are seen in the endothelium and intima of small arteries. The resultant ischemia produces widespread fibrosis in the ventricular interstitium with impaired left ventricular (LV) function.

DIABETIC CARDIOMYOPATHY

Diabetic cardiomyopathy refers to the derangement in the myocardium in the absence of extramural coronary atherosclerosis. Functional disturbances of the myocardium with cardiac dilatation are encountered in these subjects. ST and T wave changes in ECG are very early in Diabetic cardiomyopathy.

Diabetic cardiomyopathy is a term used by clinicians to encompass the multi-factorial etiologies of diabetes-related left ventricular failure characterized by both systolic and diastolic function. [5] The Framingham Heart Study showed that men with diabetes who have congestive heart failure were twice as common as their non-diabetic counterpart, and that females with diabetes had a fivefold increase, in the rate of congestive heart failure. The spectrum of heart failure ranges from asymptomatic to overt systolic failure. Diabetes complicated by hypertension represents a particularly high-risk group for the development of congestive heart failure. [6] Diastolic dysfunction is exceedingly common (>50 percent prevalence in some studies) and may be linked to diabetes without the presence of concomitant hypertension.

The etiology of impaired left ventricular function may involve any of the following mechanisms:

(1) Coronary Atherosclerotic Disease,

(2) Hypertension

(3) Left Ventricular Hypertrophy

(4) Obesity

(5) Endothelial dysfunction,

(6) Coronary microvasculature disease

(7) Autonomic dysfunction

(8) Metabolic abnormalities

DIABETIC AUTONOMIC NEUROPATHY

Symptoms relating to autonomic involvement in diabetic patients have been recognized since the last century [(7)], but the frequency with which the autonomic system is affected was first stressed by Jordan in 1936 and then by Rundles in 1945.

Autonomic dysfunction in diabetics is common but in sharp contrast symptomatic autonomic neuropathy is rare. Diabetic autonomic neuropathy usually accompanies peripheral neuropathic disturbances. [(3)]

Besides atherosclerotic vascular diseases and diabetic heart muscle disease, cardiac autonomic neuropathy may also contribute to the excessive cardiovascular morbidity and mortality. The main risk factor for autonomic neuropathy was poor glycemic control but hyperinsulinemia may have predictive role in the development of parasympathetic autonomic neuropathy.

Interestingly both parasympathetic and sympathetic neuropathies predicted 10 year cardiovascular mortality independent of conventional risk factors, hyperglycemia and ischemic ECG. [8]

Diabetic autonomic neuropathy may also associate with an increased risk of stroke and lacunar infarcts. In a power spectral analysis of type 2 diabetic patients and control subjects, both pro-insulin and C peptide levels were associated with sympatho-vagal imbalance of autonomic nervous function [9], and recently it has been shown the autonomic nervous dysfunction may be an early finding in subjects with insulin resistance. [10]

PREVALENCE

The two population based studies, one in Oxford and other in Pittsburgh, recorded mainly cardiovascular autonomic function tests. In the Oxford Community Diabetes study [11], 202 type 2 diabetics were tested from a total of 402 diabetic patients in the community of 29,873. One or more cardiac autonomic tests were abnormal in 15.8% of type 2 patients.

The Pittsburgh epidemiology of Diabetes Complications study [12] found orthostatic hypotension (drop in blood pressure >30 mm Hg) in 3.4% of patients, and the most common symptom suggestive of autonomic dysfunction was unawareness of hypoglycemia (26%). Other symptoms were uncommon (0-8%).

Multicenter clinic based studies such as EURODIABIDDM Complications Study [13] found orthostatic hypotension in 5.9% and abnormal Heart Rate Variability in 19.3% of patients.

Ziegler and colleagues [14] (DiaCAN) reported that, in an unselected cohort of type 2 diabetics, there were borderline cardiac autonomic abnormalities in 12.1% and definite abnormalities in 22.1% of patients. It is also recognized that the autonomic function tests can be abnormal at the time of diagnosis of diabetes.

Diabetes is the most common organic cause of male erectile dysfunction, and data from Massachusetts Male aging Study show that 64% of men with treated diabetes have some degree of erectile problem.[15] Control and duration of diabetes, the presence of neuropathy, retinopathy, or nephropathy, and smoking were identified as risk factors for impotence.

In Gastrointestinal studies which are based on clinical symptoms, only early satiety, fullness after meals and nausea being significant symptoms compared with the controls. Diarrhea was not more frequently encountered in two European studies [16] but was more prevalent in type 2 diabetics in a study from Hong Kong.

PATHOGENESIS OF DIABETIC AUTONOMIC NEUROPATHY

The pathologic basis of diabetic autonomic neuropathy is not completely understood.

A number of investigators have identified abnormalities in para-vertebral sympathetic ganglia, including neurons distended by lipid-rich material [17, 18], vacuolar degeneration of neurons produced by dilation of endoplasmic reticulum, and mononuclear cell infiltration of autonomic nerve bundles and ganglia.

Loss of myelinated nerve fibres has been described in sympathetic communicating rami [19], vagus nerves [21], splanchnic nerves [20], and nerves to the bladder wall [22].

Diabetic neuropathies have multi-factorial pathogenic mechanism and clinical presentation. Hyperglycemia plays a dominant role in the pathogenesis of diabetic neuropathy.

Both the autonomic and somatic neuropathy may share a common pathogenesis. But it is still not clear whether any of the postulated mechanism for somatic nerves also apply to autonomic nerves. Following theories are put forth to explain diabetic neuropathy.

METABOLIC THEORY [23]

A) POLYOL THEORY

The polyol pathway is not dependent on insulin and normally 1% of glucose is metabolized through this pathway. In the presence of hyperglycemia, the excess sugar is converted to sorbitol by an enzyme aldose reductase. Increased sorbitol damages Schwann cells and has delirious effect on nerve conduction velocity.

B) MYO-INOSITOL METABOLISM

Myo-inositol is an important constituent of phospholipids and cell membrane. Increased activity of polyol pathway leads to decreased myo-inositol concentration by unknown mechanism which inhibits Na+/K+ ATPase activity.

C) LIPIDS

Reduction in membrane cholesterol, cerebroside, sphingomyelin, phosphotidyl serine, phosphotidylinositol, is encountered in diabetic neuropathy. The synthesis of myelin which is rich in these lipids is also likely to be reduced contributing to neuropathy.

D) TAURINE

Osmo-regulation, in order to maintain the intracellular milieu, may also result in endo-neurial metabolic changes in diabetic neuropathy. The increase in intracellular osmolality due to shunting of glucose into the polyol pathway and the consequent accumulation of sorbitol may lead to

compensatory depletion of the endo-neurial osmolytes taurine and myo-inositol to maintain osmotic balance.

E) OXIDATIVE STRESS

Oxidative stress also is implicated in the etiology of diabetic neuropathy. There is evidence that activity of oxygen-free radicals is enhanced in diabetes. Indices of increased oxidative stress such as malondialdehyde, conjugated dienes, and lipid hydroperoxides are increased in experimental diabetic neuropathy.

F) PROTEIN KINASE C ACTIVATION

Protein kinase C elevations compromise nerve regeneration in experimental models of diabetic peripheral neuropathy. In experimental models of diabetes, treatment with nonspecific and β-specific protein kinase C inhibitors normalized the observed neurophysiologic abnormalities.

G) POLY (ADP-RIBOSE) POLYMERASE

There is increasing evidence that poly (ADP-ribose) polymerase (PARP) plays a critical role in mediating several pathways of hyperglycemia-induced damage.

H) NEUROTROPHIC FACTORS

The neurotrophins are proteins that promote the growth, maintenance, survival, and differentiation of specific populations of neurons. There is

evidence that failure of neurotrophic support is in part responsible for the pathogenesis of diabetic polyneuropathy.

VASCULAR THEORY

Hyperglycemia-related metabolic alterations produce interposed changes in tissues and the microvasculature that are then responsible for ischemic pathologic changes in nerve fibres.

Lundback proposed a unifying hypothesis of wide spread small vessel angiopathy underlying most diabetic complications of the eye, kidney and nerves. A concept there after arises of a common micro vascular etiology for diabetic neuropathy, retinopathy and nephropathy exemplified by the term “triopathy”.

Support for this hypothesis was provided by histopathological studies of vasovasorum of peripheral nerves from patients with neuropathy showing thickening, hyalinisation and accumulation of PAS positive material in the vessel wall and narrowing or occlusion of the lumen.

Dyck and colleagues[24] observed thickening of capillary walls and documented capillary closure and platelet thrombi occlusions in the small arteries and arterioles that supply peripheral nerves that was more pronounced in patients with diabetic neuropathy than in age-matched controls.

Timperty et al. recently described intraluminal changes of the vasonervorum with intravascular coagulation in several nerve biopsies. The most consistently reported

ultra structural micro vascular abnormalities in diabetic neuropathy are basement-membrane thickening and endothelial-cell hyperplasia.

Several studies have established a correlation between ultra structural micro vascular disease in peripheral nerve and severity of diabetic neuropathy. [24]

It is difficult to pinpoint a particular pathologic mechanism in diabetic neuropathy except in certain mononeuropathies. Metabolic and vascular factors, together with glycosylation of protein, hyper-aggregation of platelets and altered haemo-rheology may contribute to the development of neuropathy.

PATHOLOGY

Duchene had studied the sympathetic ganglia in five diabetics with autonomic neuropathy.

He described vacuolated and granular cell necrosis, loss of myelinated nerve fibres in vagus and splanchnic nerves and loss of neurons in the intermediolateral columns of spinal cord.

Feerman et al (1977) showed changes in the autonomic nerves and ganglia such as beaded thickening, hyperargenophilia in nerves, spindle shaped nerve fibres, fragmentation of fibres and decrease in number of fibres.

Diabetes results in a predominantly axonal neuropathy with an increasing gradient of nerve fibre loss from center to periphery (a dying back neuropathy). There is in addition a disturbance in axonal transport in experimental diabetes produced by streptozotocin. There is a decrease in fast component of axonal transport, segmental demyelination independent of axonal damage is also found.

It is also thought to be the result of damage to Schwann cells in the diabetic process. Myelin degeneration and regeneration may give rise to onion bulb formation. There is also a depletion of small myelinated and unmyelinated fibres. Microvasculature of endo-neurial capillaries show thickening and widening of the peri-neural basement membrane. Small vessel occlusion may also be present.

Total cardiac denervation is possible but usually the parasympathetic fibres are involved earlier than the sympathetic fibres. However both may be differentially involved. Evidence would now suggest that there is a simultaneous impairment of both the sympathetic and parasympathetic pathways rather than a progressive model of parasympathetic dysfunction preceding damage of the sympathetic neurons. [25]

CLINICAL FEATURES OF AUTONOMIC NEUROPATHY [26]

1. CARDIOVASCULAR

- Postural hypotension
- Painless Myocardial Infarction/ischemia
- Resting tachycardia
- Loss of heart rate variation
- High peripheral blood flow
- Rigidity/calcification of arteries
- Neuropathic edema
- Diabetic cardiomyopathy

2. GASTROINTESTINAL

- Dyspepsia, Dysphagia and esophageal ulcerations- Impaired esophageal motility
- Gastroparesis-Gastric atony
- Diarrhea- small intestinal dysfunction
- High incidence of cholesterol stones (Gall bladder motility impaired)
- Constipation- Colonic atony

3. UROGENITAL

- Bladder dysfunction
- Impaired bladder sensation
- Bladder over distension
- Impotence

- Retrograde ejaculation
- Loss of testicular sensation
- Female sexual dysfunction

4. SUDOMOTOR AND THERMO REGULATORY DISORDERS

- Diabetic anhydrosis
- Gustatory sweating
- Nocturnal sweating
- Abnormal vasomotor responses

5. PUPILLARY ABNORMALITIES

- Reducing resting diameter
- Delayed (or) absent response to light
- Diminished hippus
- Iritis

6. VASOMOTOR

- Loss of skin vasomotor responses
- Peripheral vascular changes
- Dependent edema

7. RESPIRATORY

- Respiratory arrest
- ?Sleep apnea
- Cough reflex reduced

8. HYPOGLYCEMIA UNAWARENESS

- Decreased catecholamine release with loss of warning symptoms of hypoglycemia
- Decreased pancreatic glucagon and pancreatic polypeptide release

9. NEUROENDOCRINE

- Catecholamines reduced
- Glucagon reduced
- Pancreatic polypeptide reduced

10. OTHER CONSEQUENCES OF DIABETIC AUTONOMIC NEUROPATHY

- Contribution to pathogenesis of Diabetic foot
- Worsening of diabetic retinopathy

PROGNOSIS

Autonomic function declines with age, but in diabetes it deteriorates, on average, faster than in normal subjects. Thus variation in heart rate which normally decreases at about 1 beat/min every 3 years declines about three times faster in diabetic patients, although there is substantial variation. [35]

Most patients who develop abnormal autonomic function do not become symptomatic. Mortality of asymptomatic patients with autonomic dysfunction may be increased but the prognosis is generally good, and 90% of our patients (all under 50 years old at the beginning of the study) were alive 10 years later. By contrast, the outcome for those with

symptomatic autonomic neuropathy is not as good, although even in this group, 73% were still alive after a decade.

Ewing *et al* [36] reported a poorer prognosis, although patient selection was different: the patients were older and some had renal damage. Those with orthostatic hypotension seem to have the highest mortality, perhaps because of the premature development of left ventricular hypertrophy.

Most deaths in these patients are from renal failure or myocardial infarction. There are a few sudden unexplained deaths among patients with autonomic neuropathy, which might be due to respiratory arrest rather than cardiac arrest or arrhythmia.

Established symptoms of autonomic neuropathy, including diarrhea, vomiting from Gastroparesis and postural hypotension run a very protracted although intermittent course and rarely become disabling, even over a 10 to 15 year period. [35]

Postural hypotension fluctuates substantially with a corresponding variation in the intensity of symptoms. Gustatory sweating also tends to persist without remission, although many patients describe disappearance of this symptom after renal transplantation.

The general absence of progression to debilitating disease remains unexplained and contrasts with devastating and, indeed, often fatal progression of the primary autonomic failure.

Malins made many of these observations some years ago and wrote that "The prognosis for autonomic manifestations is poor although the disability is often surprisingly slight." [37]

AUTONOMIC NERVOUS SYSTEM OF THE HEART

Autonomic nervous system innervates every visceral organ of the body. It controls sympatho-vagal actions via neurotransmitters like acetyl-choline and nor-epinephrine to maintain internal homeostasis. These actions are largely automated (or) involuntary, possibly because of their complex and important nature.

Their importance was well recognized by Claude Bernaud who said "the nature thought it provident to remove these important phenomenon from the caprice of ignorant will".

The heart possesses an inherent ability to impulse generation and conduction, but autonomic nervous system plays an important role in myocardial excitability and contractility.

Parasympathetic fibres from the vagus and sympathetic fibres from upper 4 to 5 thoracic ganglion innervate heart and mediate autonomic control. These innervations inform the stretch receptors in systemic and pulmonary vessels continuously and thus monitor intravascular pressure.

The highlight of autonomic control is that it acts rapidly and constantly to the changes threatening internal environment. Important function under autonomic regulation include maintenance of blood column and tissue perfusion, blood pressure, extracellular fluid and its composition, smooth muscle and glandular functions.

AUTONOMIC NEURAL CONTROL OF THE HEART

Autonomic regulation of the heart and vasculature is primarily controlled by special regions within the medulla oblongata of the brainstem that contain the cell bodies of sympathetic and parasympathetic (vagal) efferent nerves. The hypothalamus plays an integrative role by modulating medullary neuronal activity (e.g., during exercise).

Sensory information from peripheral baroreceptors (e.g., carotid sinus baroreceptors) synapses within the medulla at the nucleus tractus solitarius, which modulates the activity of the sympathetic and vagal neurons within the medulla.

PARASYMPATHETIC INNERVATION

Preganglionic parasympathetic efferent nerves exit the medulla as the tenth cranial nerve and travel to the heart within the left and right vagus nerves. Preganglionic fibres synapse within ganglia located within the heart; short postganglionic fibres innervate the myocardial tissue.

Parasympathetic activation decreases heart rate, inotropy, and dromotropy, and it produces vasodilation in specific organs through the release of acetylcholine, which binds to postjunctional muscarinic (M2) receptors.

SYMPATHETIC INNERVATION

Preganglionic sympathetic efferent nerves exit from the spinal cord and synapse within paravertebral or prevertebral ganglia before sending out postganglionic fibres to target tissues in the heart and blood vessels.

Sympathetic activation increases heart rate, inotropy, and dromotropy through the release of norepinephrine, which binds primarily to postjunctional cardiac β1-adrenoceptors.

Norepinephrine released by sympathetic nerves constricts blood vessels binding to postjunctional α-1 and α2- adrenoceptors. The release of norepinephrine from sympathetic nerve terminals is modulated by prejunctional α2-adrenoceptors, β2-adrenoceptors and muscarinic (M2) receptors.

BARORECEPTOR FEEDBACK REGULATION OF BP

Baroreceptors are mechanoreceptors that respond to stretch induced by an increase in pressure or volume.

Arterial baroreceptor activity (e.g., carotid sinus and aortic arch receptors) tonically inhibits sympathetic outflow to the heart and blood vessels, and it tonically stimulates vagal outflow to the heart.

Decreased arterial pressure, therefore, decreases the firing of arterial baroreceptors, which leads to reflex activation of sympathetic influences acting on the heart and blood vessels and withdrawal of the vagal activity to the heart.

EFFECT OF SYMPATHETIC AND PARASYMPATHETIC STIMULATION OF CARDIAC AND VASCULAR FUNCTION

HEART	SYMPATHETIC	PARASYMPATHETIC
Chronotropy(rate)	+++	_ _ _
Dromotropy (conduction velocity)	+++	_ _ _
Inotropy(contractility)	++	_1

1 more pronounced in the atria than in the ventricles

CHEMORECEPTORS FEEDBACK REGULATION

Peripheral chemoreceptors (e.g., carotid bodies) and central chemoreceptors (e.g., medullary chemoreceptors) respond to decreased pO2 and pH or increased pCO2 of the blood.

Their primary function is to regulate respiratory activity, although chemoreceptor activation generally leads to activation of the sympathetic nervous system to the

vasculature, which increases arterial pressure. Heart rate responses depend upon changes in respiratory activity.

CARDIAC DYSAUTONOMIA [27]

Cardiac dysautonomia refers to autonomic dysfunction of the heart. It appears to be the most frequent complication of diabetes. It includes

1. **Autonomic neuropathy**

   Refers to combined clinical and objective evidence of autonomic involvement.

2. **Autonomic dysfunction**

   Refers to abnormal cardiovascular tests in absence of clinical symptoms.

Autonomic dysfunction in diabetes is common (20-50%) but symptomatic autonomic neuropathy is less common (12% in IDDM and 1% in NIDDM).

NATURAL HISTORY

A 10 year study of type 2 diabetics in Finland [28] found that cardiac autonomic function assessed with an E:I ratio [(sum of six longest R-R intervals occurring during 6 expirations) / (sum of the shortest R-R intervals occurring during 6 inspirations)] rose from 5%(controls 2%) at the beginning to 65%(controls 28%) at the end of the study. Changes in systolic blood pressure on standing increase from 7 to 24 %(controls 6% to 9%).

The development of autonomic neuropathy correlated with poor glycemic control. This was also noted by Ziegler and co-workers [29] in a clinic based study in Germany.

Further evidence supporting a gradual progression of autonomic neuropathy with time comes from clinic based studies showing a deterioration in autonomic function test scores in 57% of type 2 diabetics over 5 years [30] and a separate study of older patients showed that autonomic function test abnormalities increased from 41% at baseline to 64%[31].

EFFECTS OF SYMPATHOVAGAL IMBALANCE [32]

1. Impairs angina recognition

   Silent ischemia and infarction

2. Alters threshold for ischemia

   Increased resting heart rate and blunted chronotropic response to exercise.

   Impaired coronary vasomotor regulation.

3. Abnormality in diastolic and systolic function

   Contributes to cardiomyopathy

4. Increased risk of ventricular arrhythmia

   Contributes to sudden cardiac death

5. Altered circadian pattern of triggering of acute cardiac events

   Leads to loss of nocturnal protection against acute Myocardial infarction

6. Altered circadian blood pressure regulation leads to

   Increased cardiac mass

Risk factor of microalbuminuria and diabetic nephropathy

Adversely affects the natural history of congestive cardiac failure

Causes hemodynamic instability in peri-operative period

CLINICAL PRESENTATION

Autonomic damage may be asymptomatic and thus be detected incidentally, even if symptomatic, the condition often goes unnoticed for a considerable time partly of the vagueness of many of early symptoms. The proportion of asymptomatic subjects increases with increasing duration of diabetes.

The features of cardiac autonomic neuropathy include

1) Exercise intolerance
2) Postural hypotension
3) Resting tachycardia
4) Fixed heart rate
5) Painless (or) silent myocardial infarction

Although insidious in onset, autonomic neuropathy may be associated with substantial morbidity. In fact, sudden death and cardio respiratory arrest in diabetes have been attributed to cardiac autonomic dysfunction.

Mortality associated with autonomic neuropathy after clinical diagnosis has been reported to be as high as 50% in 3 years and its presence has been suggested to serve as a poor prognostic indicator. In a five year follow up study, the mortality rate of diabetes

with autonomic neuropathy was 56% as against 21% in those without autonomic neuropathy [33].

Patients with autonomic neuropathy are also at a higher risk of sudden death.

1) Exercise intolerance

Diabetic with autonomic neuropathy achieve a lower heart rate, blood pressure and cardiac output on exercise compared to diabetics without this complication. It results in poor exercise tolerance.

2) **Postural hypotension**.

The most serious clinical consequence of vascular denervation is orthostatic hypotension. It is due to diminished peripheral vasoconstriction and some failure of splanchnic blood flow reduction on standing, but these defects are not as marked as would be expected even in severe cases. Noradrenaline concentrations are normally reduced in these patients, whereas renin responses may or may not be abnormal.

Measured orthostatic hypotension, defined as a decrease of systolic blood pressure on standing of more than 30 mm Hg, is not uncommon in diabetic neuropathy although symptoms are rare. Patients may then complain at the least of mild giddiness and at most may be disabled by the condition, unable to stand for more than a few minutes at a time, although this state is very rare.

Symptoms range from mild giddiness or muzzy headedness on standing up, progressing to a grey mistiness of vision followed by a curious pain in the back of the neck and shoulders in a "coat hanger" distribution [40] and later unconsciousness. Distortion of vision can occur.

Symptoms are often worse on rising from bed in the morning, but they vary substantially both through the day and from week to week, ranging from negligible to severe. They do not show very close correlation with actual fall of blood pressure although when the systolic pressure is less than 70 mm Hg few patients can remain upright.

Orthostatic hypotension is exacerbated by insulin administration, [38, 39] and just occasionally episodes of loss of consciousness from insulin induced orthostatic hypotension are confused with those from hypoglycemia. Orthostatic hypotension can persist over many years and apart from the rare patients who develop disabling disease it often fails to progress even during 10-15 years. It never remits completely.

In 1945, Rundles first linked postural hypotension with autonomic neuropathy in diabetics [34]. The blood pressure fall may be worsened by a variety of drugs including hypotensive agents, diuretics, tricyclic antidepressants, phenothiazines, nitrates, vasodilators etc. Insulin may aggravate postural hypotension possibly through a direct vasodilator action on peripheral blood vessels. Conversely fluid retention in congestive cardiac failure (or) nephritic syndrome may mask postural hypotension.

3) Resting heart rate

There are several reports of resting heart rate in excess of 95/minute in diabetics with autonomic damage and some times more rapid rates up to 130/minute occur. An overall increase in mean heart rate of about 10/minute has been reported.

Diabetics with cardiac parasympathetic damage had the fastest rates (may represent the initial stages of autonomic dysfunction) and those with additional sympathetic damage have slightly slower heart rate.

4) Fixed heart rate

Heart rate show less diurnal variation with increasing autonomic damage. The loss of the normal cardiac slowing at night occurs as a result of vagal damage. With severe damage there is a loss of minute and second to second variation in heart rate, resulting in relatively fixed rate.

5) Painless (or) silent Myocardial Infarction

Autonomic neuropathy may reduce the perception of cardiac ischemic pain. Diabetic patients admitted to the hospital with Myocardial infarction have been reported to have less intense pain than non diabetic patients.

Margolis [41] et al reviewed the ECG of all patients in Framingham heart study and found that 23% of myocardial infarction was silent.

The significance of reduction in ischemic pain is that, silent myocardial damage may occur more likely and this may be the basis for the increased prevalence of ischemic cardiomyopathy in diabetes. It may be responsible for diabetic patients suffering from infarction reaching late to hospital.

ECG CHANGES IN DIABETICS

The QT interval in the ECG reflects the total duration of ventricular myocardial depolarization and repolarization.

A role of autonomic neuropathy in duration of QT interval in diabetic patient has been proposed because the diabetic patient with autonomic dysfunction show longer QTc compared with those without autonomic dysfunction [43].

The men with impaired heart rate variability (an index of autonomic dysfunction) showed significantly higher QTc compared with men without these complications suggesting a role for autonomic dysfunction in QTc prolongation in men [43].

Diabetics have a prolonged PR interval and more leftward frontal QRS axis than their non diabetic counterparts [44].

There is no significant difference in QRS duration between diabetics and non diabetics.

There is an increase incidence of intraventricular conduction blocks in diabetic patients than that of normal [45].

PATHOLOGY OF CONDUCTION

The arrhythmias which occur in Diabetics are related to the complication of the disease (i.e.) arteriosclerotic coronary heart disease, aging, sclerosing the left side of cardiac skeleton and monkeburg's sclerosis of the arteries.

Sinuatrial block or atrioventricular block can occur acutely in Myocardial infarction and in chronic states due to atherosclerosis of large arteries (or) fatty infiltration of the node itself isolating from the rest of the myocardium. (10)

Various types of bundle branch blocks such as RBBB, LBBB, LAHB, LPHB, alternating bundle branch block may occur in diabetes. In the acute type it is usually caused by infarction and in the chronic type it is due to arteriosclerosis of the left side of the skeleton, a process accelerated in diabetics. (10)

ASSESSMENT OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Objective evidence of autonomic nerve damage is based on cardiovascular reflexes as these are reliable and quantitative non invasive methods to assess autonomic nervous system function.

Implicit in the use of cardiovascular reflex test is the assumption that it reflects damage throughout the autonomic nervous system. This is largely true except for the very early manifestation such as sweating loss on the feet and impotence which may antedate abnormal cardiovascular tests.

TESTS FOR PARASYMPATHETIC FUNCTION

1) Heart rate response to deep breathing (HRBD)
2) Heart rate response to standing
3) Heart rate response to valsalva maneuver

TESTS FOR SYMPATHETIC FUNCTION

1) BP response to standing
2) BP response to sustained handgrip

HEART RATE RESPONSE TO DEEP BREATHING (HRBD)

The patient sits quietly and breaths deeply at 6 breaths a minute (5 seconds in and 5 seconds out) for one minute. An ECG is recorded throughout the period of deep breathing with a marker used to indicate the onset of each inspiration and expiration.

The maximum and minimum R-R intervals during each breathing cycle are measured and converted into beats/minute. The result is then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute.

(Normal response $\geq$ 15 beats/minute, Borderline 11-14 beats/minute, Abnormal response $\leq$ 10 beats/minute).

The normal acceleration and deceleration of heart rate during respiration (sinus arrhythmia) is reduced early in course due to cardiac vagal involvement. This phenomenon provides the basis for the simplest and most sensitive test for the presence of cardiac autonomic dysfunction.

HEART RATE RESPONSE TO STANDING

The test is performed with the patient lying quietly on a couch while heart rate is recorded continuously on ECG machine. The patient is asked to stand up unaided and the point at starting to stand is marked on ECG.

The shortest R-R interval at or around the 15th beat and largest R-R interval at or around the 30th beat after starting to stand are measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratio, which is normal if > 1.04, borderline between 1.01and 1.03 and abnormal if < 1.00.

BLOOD PRESSURE RESPONSE TO STANDING UP

The test is performed by measuring the patient's BP while he is lying down quietly and again when he stands up. The postural fall in BP is taken as the difference between systolic BP lying and the systolic BP standing (Normal response ≤ 10 mm Hg, Borderline 11-29 mm Hg, Abnormal response ≥ 30 mm Hg).

HEART RATE RESPONSE TO VALSALVA MANEUVER

The test is performed by the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mm Hg for 15 seconds while a continuous ECG is recorded.

The maneuver is performed 3 times with interval of one minute in between. The result is expressed as the Valsalva ratio which is the ratio of the longest R-R interval after

the maneuver to the shortest R-R interval during the maneuver. The mean of three Valsalva ratio is taken as the final value.

(Normal Valsalva ratio ≥ 1.21, Borderline between 1.11 and 1.20, Abnormal ≤ 1.10).

BLOOD PRESSURE RESPONSE TO SUSTAINED HAND GRIP

Blood pressure is measured with 30% of maximum voluntary contraction using a hand grip dynometer for 5 minutes. The difference between the diastolic blood pressure just before starting and just before releasing the hand grip is taken as a measure of response. (Normal ≥ 16mmHg., Borderline 11-15 mm Hg., Abnormal ≤10 mm Hg.)

MATERIALS AND METHODS

MATERIALS

STUDY POPULATION

1) Study group- 50 patients with type 2 diabetes mellitus
2) Control group- 50 age and sex matched controls

PLACE OF STUDY

Out patients department,

Department of medicine,

Department of diabetology,

Stanley medical college,

Chennai-1.

PERIOD OF STUDY

Feb 2008 to September 2009

METHODS

All the study population and controls were subjected for thorough physical examination. Blood samples were drawn and subjected to estimation of causal blood glucose and renal function tests.

INCLUSION CRITERIA

Type 2 diabetes patients except the ones with the following exclusion criteria

EXCLUSION CRITERIA

1) Age > 60 years

2) Documented CAD/ischemic heart disease

3) Documented valvular heart disease/congenital heart disease.

4) Hypertension

5) Uremia

6) Drugs-any drug which alters the sinus node impulse generation and AV conduction.

7) Features of hypo and hyperthyroidism.

8) Fever and features suggestive of infections

9) Chronic obstructive pulmonary disease and other chronic lung disorders.

10) Parkinsonism and other movement disorders

11) Dyselectrolytemia

Autonomic dysfunction was assessed by the following maneuvers

PARASYMPATHETIC FUNCTION

1) Tachycardia in resting ECG
2) Heart rate response to deep breathing (HRBD)

SYMPATHETIC FUNCTION

1) Blood pressure response to standing
2) QTc prolongation

Various parameters that will be obtained are to be compared between study and control group using either unpaired‘t’ test.

ELECTROCARDIOGRAM

Resting ECG was taken both in the study and control group using a three leaded Schillar Cardiovit AT machine.

ECG during deep breathing was recorded only in study group (diabetics) using single leaded BPL ECG machine. The lead preferred is Lead II.

The subjects were made to lie down quietly. Then they were asked to The patient takes deep breath and evenly at a rate of six breaths per minute (i.e.) five seconds for inspiration and five seconds for expiration. A continuous ECG was recorded for one minute.

. The maximum and minimum R-R intervals during each breathing cycle were measured and converted into beats/minute. The result was then expressed as the mean of

the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute. <10 beats variation is taken as abnormal.

QTc INTERVAL

R-R and QTc intervals were measured with a meter on the resting ECG tracing. The lead considered here is lead V2.

The QT interval was measured from the beginning of QRS Complex to the down slope of the T wave (crossing the iso-electric line)

When a U wave was present, the QT interval was measured to the nadir of T wave and U wave.

The corrected QT interval for the previous cardiac cycle length (QTc) was calculated using Bazett's formula

$$QTc = QT / \sqrt{R - R\ interval(sec)}$$

A QTc > 460 msec is considered abnormally prolonged.

OBSERVATIONS AND DATA ANALYSIS

1) AGE AND SEX DISTRIBUTION

YEAR	CONTROL GROUP				STUDY GROUP			
	MALES	FEMALES	TOTAL	%	MALES	FEMALES	TOTAL	%
21-30	1	0	1	2%	1	0	1	2%
31-40	8	5	13	26%	8	5	13	26%
41-50	13	15	28	56%	13	15	28	56%
51-60	3	5	8	16%	3	5	8	16%

More than half of the study population belongs to the age group of 41-50 years (56%).

2) DURATION OF DIABETES

STUDY GROUP (DIABETICS)

DURATION	NO.	%
0-5 YRS	28	56%
6-10YRS	14	28%
11-15YRS	6	12%
16-20YRS	1	2%
>20YRS	1	2%

More than 50% of the study population has duration of diabetes less than 5 years.

ECG ABNORMALITIES

3) RESTING HEART RATE

GROUPS	RESTING HEART RATE	
	Range(bpm)	**Mean(bpm)**
Study(diabetics)	56-110	84.2±12.86
Control	56-100	75.2±10.65

*p Value= 0.0001 *Unpaired 't' test

The mean resting heart rate of study (diabetics) group (84.2±12.86bpm) is significantly higher ($p<0.05$) than that of control group (75.2±10.65).

4) R-R INTERVAL

GROUPS	R-R INTERVAL	
	Range(msec)	**Mean(msec)**
Study(diabetics)	550-1070	725.4±121.49
Control	600-1070	815.4±114.41

*p value-0.0002 *Unpaired 't' test

The R-R interval of study group (725.4±121.49msec) is significantly lower ($p<0.05$) than that of controls (815.4±114.41msec) correlating with the increased heart rate signifying parasympathetic damage.

5) **PR INTERVAL**

GROUPS	**P-R INTERVAL**	
	Range(msec)	**Mean(msec)**
Study(diabetics)	120-240	162.4±11.67
Control	120-180	138.2±16.99

*p value-0.0001 *Unpaired 't' test

The PR interval of study group (162.4±11.67msec) is significantly ($p<0.05$) higher than that of control group (138.2±16.99msec).

6) QRS DURATION

GROUPS	**QRS DURATION**	
	Range(msec)	**Mean(msec)**
Study(diabetics)	60-100	68.4±11.67
Control	60-80	65±8.69

*p value- 0.1016 * Unpaired 't' test.

The QRS duration in prolonged in study group (68.4±11.67msec) as compared to that of controls (65±8.69msec). But it is not statistically significant. ($p>0.05$).

7) QRS AXIS

GROUPS	QRS AXIS	
	Range(degrees)	**Mean(degrees)**
Study(diabetics)	-45 - +90	26.4±30.54
Control	-15 - +100	67.6±27.82

*p value-0.0001 *Unpaired 't' test

The QRS axis of study group is more towards left (26.4±30.54 degrees) as compared to that of controls (67.6±27.82 degrees) which is statistically significant($p<0.05$).

8) QTc INTERVAL

GROUPS	QTc INTERVAL	
	Range(msec)	**Mean(msec)**
Study(diabetics)	345-595	405.16±40.38
Control	302-415	365.38±25.3

*p value-0.0001 * Unpaired 't' test

The QTc interval in study group (405.16±40.38 msec) is significantly prolonged ($p<0.05$) than the controls (365.38±25.3 msec).

9) ECG CHANGES OF ISCHEMIA AND INFARCTION

GROUPS	EVIDENCE OF ISCHEMIA		EVIDENCE OF INFARCTION	
	NO.	%	NO.	%
Study(diabetics)	13	26%	5	10%
Control	6	12%	3	6%

The ECG changes of ischemia and infarction is significantly higher in the study group (26%&10% respectively) when compared to the control group (12%&6%).

10)CORRELATION BETWEEN ECG AND SYMPTOMS OF IHD

GROUPS	ECG CHANGES	SYMPTOMATIC		ASYMPTOMATIC	
		NO.	%	NO.	%
Study(diabetics)	18	13	72.22%	5	27.78%
Control	9	8	88.89%	1	11.11%

Prevalence of asymptomatic heart disease in the study group (27.78%) is higher when compared to the control group (11.11%).

11) INCIDENCE OF INTRAVENTRICULAR CONDUCTION BLOCKS

GROUPS	NUMBER	%
Study Group	4	8%
Control Group	1	2%

The prevalence of intraventricular conduction defect is higher in the study group when compared to that of controls.

12) HEART RATE RESPONSE TO DEEP BREATHING (HRBD)

STUDY GROUP (DIABETICS)

HRBD	NUMBER	%
NORMAL HRBD (>15 beats per min)	36	72%
ABNORMAL HRBD (<10 beats per min)	14	28%

28% of study group have abnormal HRBD suggesting early parasympathetic dysfunction.

13) SIGNIFICANT POSTURAL DROP OF SBP (>30 mm Hg)

Postural fall of SBP (>30 mm Hg)	Number	%
Study (Diabetics)	3	6%
Control	0	0%

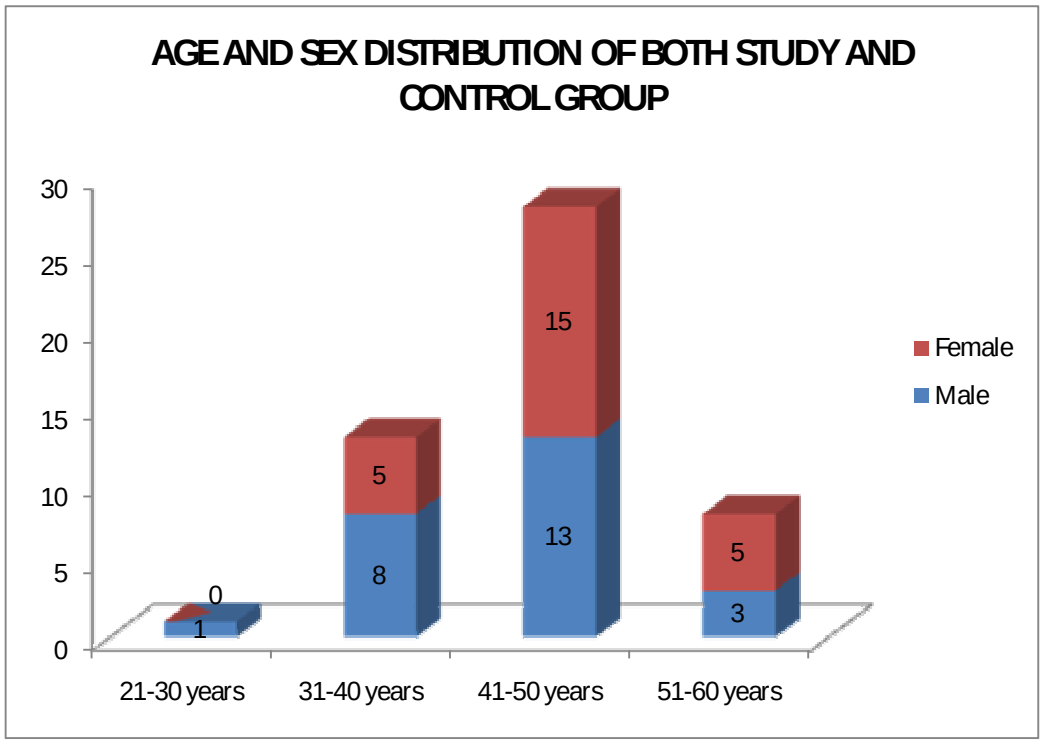
6% of the study group show significant postural drop of SBP (>30 mm Hg) on standing which probably indicates sympathetic nervous system dysfunction.

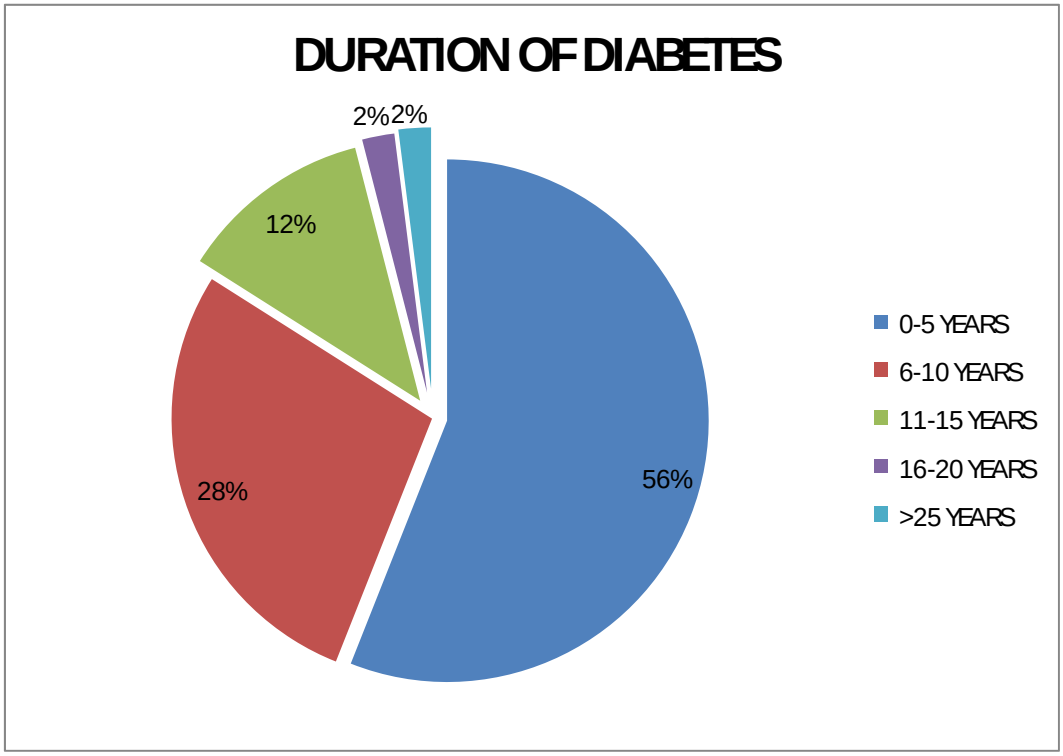
14) QTc INTERVAL CORRELATION WITH SIGNIFICANT POSTURAL DROP IN SBP (SBP>30 mmHg)

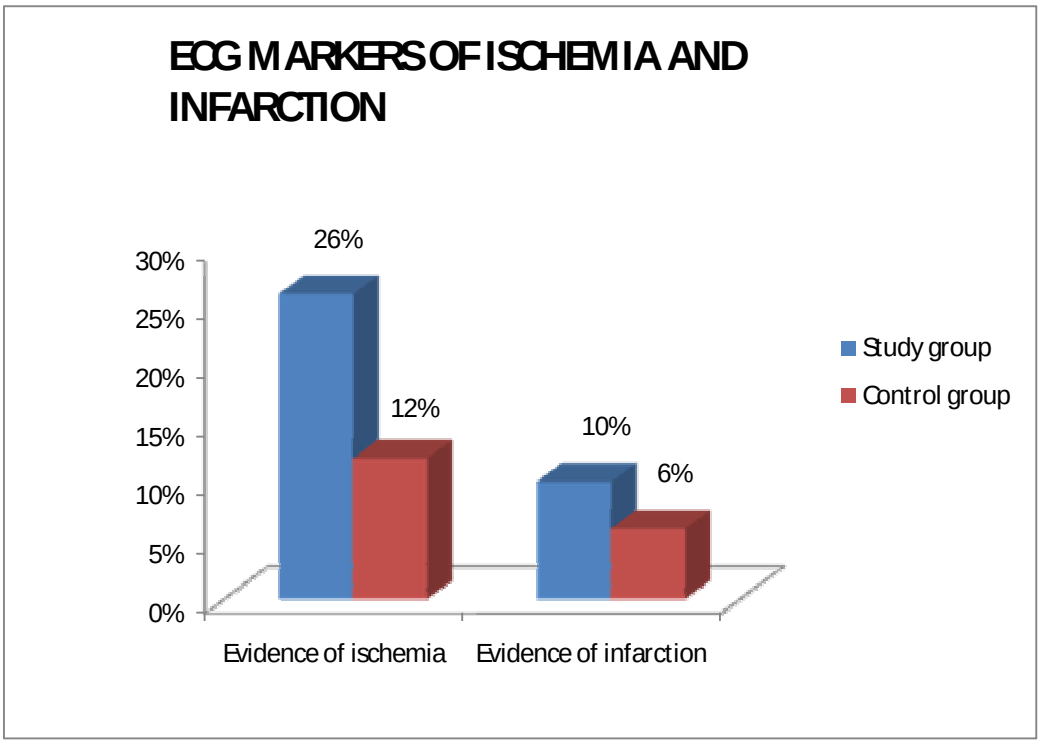
STUDY GROUP (DIABETICS)

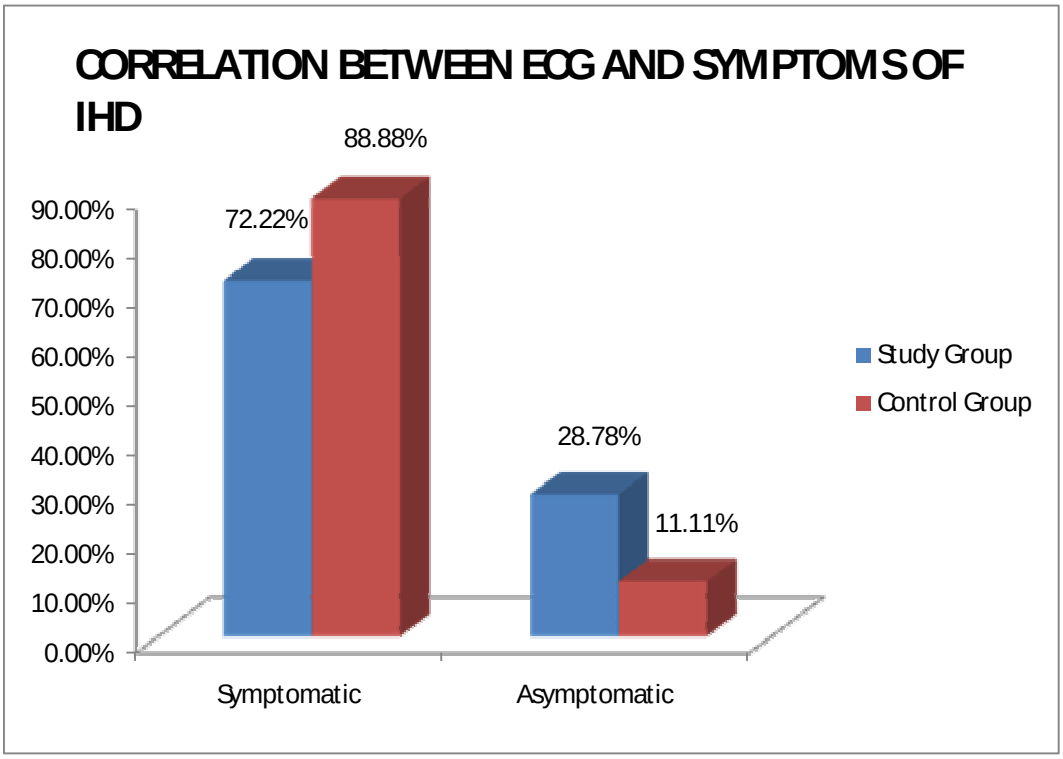
PARAMETERS	NUMBER	%
QTc >460msec	4	8%
Fall in SBP > 30 mm Hg	3	6%

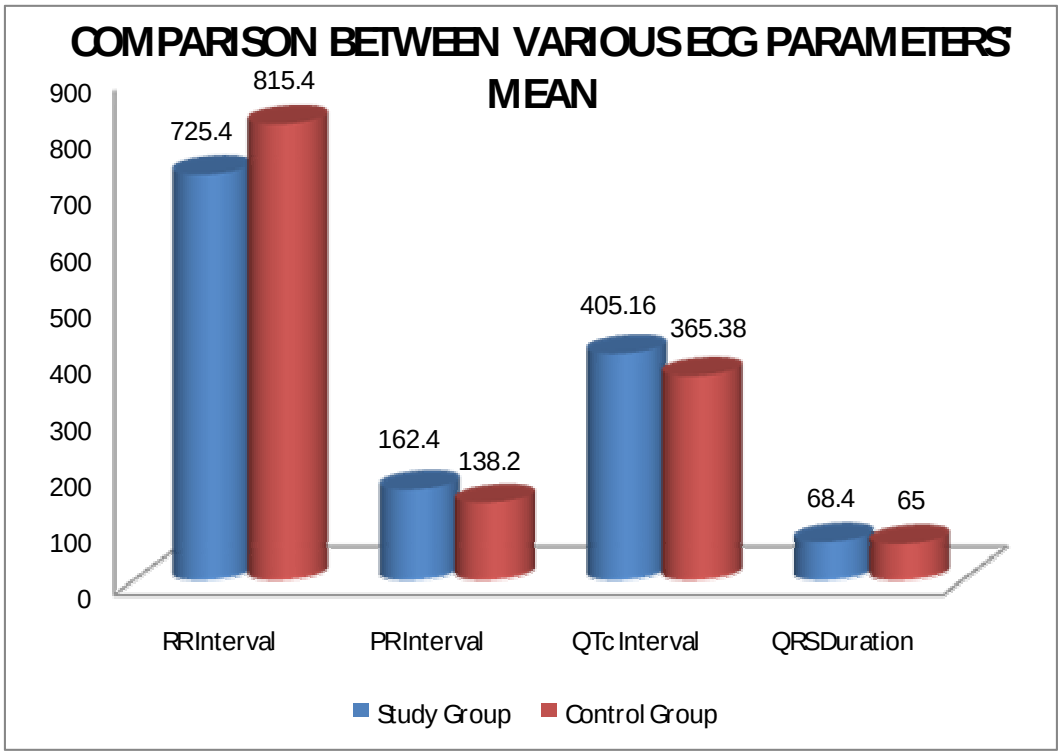
There is a positive correlation between QTc prolongation and significant postural fall in SBP. All the three patients had significant QTc prolongation.

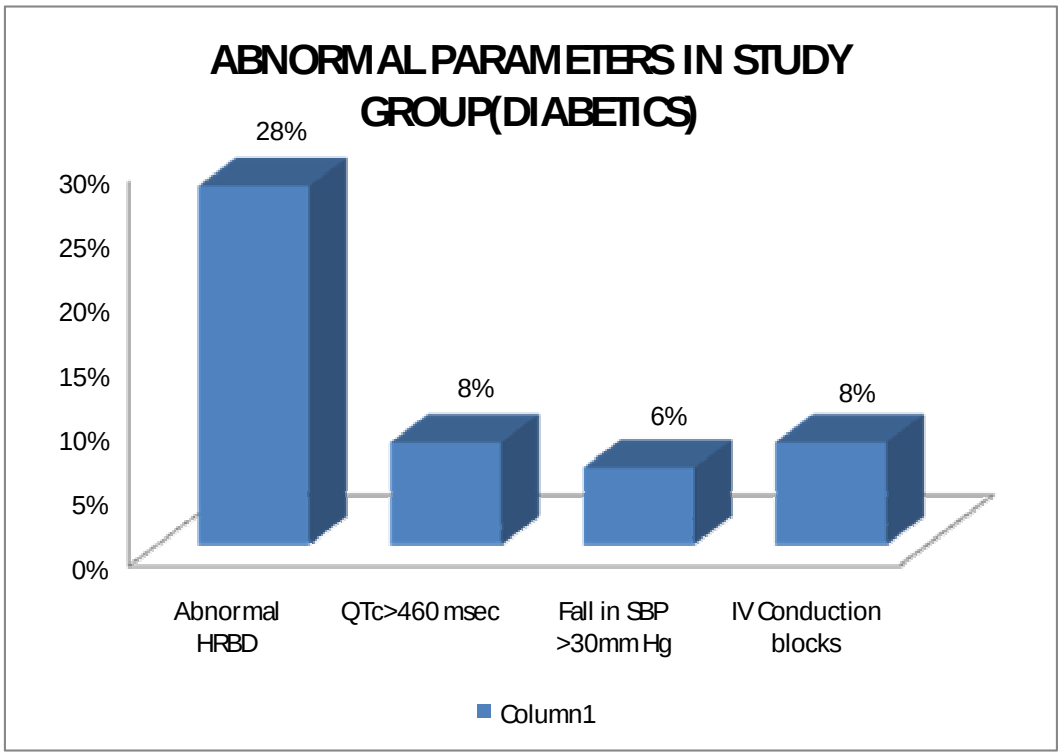

AGE AND SEX DISTRIBUTION OF BOTH STUDY AND CONTROL GROUP
30
25
20
15
10
5
0
0
1
5
8
15
13
5
3
21-30 years
31-40 years
41-50 years
51-60 years
Female
Male


DURATION OF DIABETES
2%
2%
12%
28%
56%
0-5 YEARS
6-10 YEARS
11-15 YEARS
16-20 YEARS
>25 YEARS


ECG MARKERS OF ISCHEMIA AND INFARCTION
30%
25%
20%
15%
10%
5%
0%
26%
12%
10%
6%
Evidence of ischemia
Evidence of infarction
Study group
Control group


CORRELATION BETWEEN ECG AND SYMPTOMS OF IHD
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
72.22%
88.88%
28.78%
11.11%
Symptomatic
Asymptomatic
Study Group
Control Group


COMPARISON BETWEEN VARIOUS ECG PARAMETERS' MEAN
900
800
700
600
500
400
300
200
100
0
725.4
815.4
162.4
138.2
405.16
365.38
68.4
65
RR Interval
PR Interval
QTc Interval
QRS Duration
Study Group
Control Group


ABNORMAL PARAMETERS IN STUDY GROUP(DIABETICS)
30%
25%
20%
15%
10%
5%
0%
28%
8%
6%
8%
Abnormal HRBD
QTc>460 msec
Fall in SBP >30mm Hg
IV Conduction blocks
Column1

RESULTS

1. The mean resting heart rate of study (diabetics) group (84.2±12.86bpm) is significantly higher ($p<0.05$) than that of control group (75.2±10.65).
2. The R-R interval of study group (725.4±121.49msec) is significantly lower ($p<0.05$) than that of controls (815.4±114.41msec).
3. The PR interval of study group (162.4±11.67msec) is significantly ($p<0.05$) higher than that of control group (138.2±16.99msec).
4. The QRS duration is prolonged in study group (68.4±11.67msec) as compared to that of controls (65±8.69msec). But it is not statistically significant. ($p>0.05$).
5. The QRS axis of study group is more towards left (26.4±30.54 degrees) as compared to that of controls (67.6±27.82 degrees) which is statistically significant($p<0.05$).
6. The QTc interval in study group (405.16±40.38 msec) is significantly prolonged ($p<0.05$) than the controls (365.38±25.3 msec).
7. The ECG changes of ischemia and infarction is significantly higher in the study group (26%&10% respectively) when compared to the control group (12%&6%).
8. Prevalence of asymptomatic heart disease in the study group (27.78%) is higher when compared to the control group (11.11%).

9. The prevalence of intraventricular conduction blocks in diabetics (8%) is higher than that of controls (2%).
10. 28% of study group have abnormal HRBD suggesting early parasympathetic dysfunction.
11. 6% of the study group show significant postural drop of SBP (>30 mm Hg) on standing which probably indicates sympathetic nervous system dysfunction.
12. There is a positive correlation between QTc prolongation and significant postural fall in SBP (>30 mm Hg). All the three patients had significant QTc prolongation.

DISCUSSION

This study compares the ECG changes of 50 type 2 diabetes patients with equal number of age and sex matched controls to find out any differences in abnormalities, if any, in diabetic patients. By using conventional ECG parameters, this study also delineates the prevalence of autonomic dysfunction in the diabetic population.

The mean resting heart rate in diabetics was found to be 84.88±12.86msec as compared to that of non-diabetic controls which was 74.28±10.65msec. Thus diabetic patients had a mean resting heart rate that was significantly higher than of non-diabetics. (p value<0.05).

Kahn J.K. et al found that patients with cardiac dysautonomia have higher resting heart rates and lower maximal heart rates during exercise than diabetic patients with-out autonomic neuropathy [57].

The measurement of PR interval that reflects the AV conduction showed that mean PR interval was (162.4±31.72) in diabetics as against (138.2±16.986) in non-diabetic population, which was statistically significant.

According to Uuisipta and M.Mushronan, the PR interval was prolonged in diabetics than normal.

The QRS duration in diabetics was not significantly prolonged than that in non-diabetics in this study.

The QRS axis in diabetics was significantly shifted leftwards (26.4±30.54 degrees) as compared to that of non-diabetics (67.6±27.82 degrees), indirectly reflecting the higher incidence of Ischemic Heart Disease in them.

The QTc interval in diabetics (405.16±40.375) was significantly ($p<0.05$) prolonged as compared to that of non-diabetics (365.38±25.3).

A Pourmoghaddas, et al [45] found that the prevalence of prolonged QTc interval was significantly higher in the case group in comparison with the control group, 8 vs. 2% respectively (p value = 0.012, OR = 4.3). It is comparable with our study which also shows long QTc in 8% of diabetics as compared to 0% in non-diabetics.

Abnormality of parasympathetic nervous system is more common than (3 fold) abnormality in sympathetic nervous system.

Mathur et al [46] found that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other ANF tests. Further, QTc prolongation has linear positive correlation with the degree of CAN. QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance.

Clinical significance of prolonged QTc interval

An association between abnormally prolonged QT interval and syncope, malignant ventricular arrhythmias and sudden cardiac death has been found in various idiopathic and acquired disorders.

Hisayoshi Oka [47] et al. in 1995, attempted to clarify the relationship of the QTc interval to α and β sympathetic as well as parasympathetic function tests and concluded that QTc prolongation is an indicator of cardiac dysautonomia. And found that the QTc interval in diabetics was 420 msec v/s 385 msec in nondiabetics and thus was significant.

The ECG changes of ischemia and infarction was significantly higher in diabetics (36%) compared to nondiabetics (18%).

Kannel et al [48] found that the risk of cardiovascular risk in diabetics is double that of nondiabetics. Various studies [49, 50] had established that prevalence of IHD is high in diabetics without doubt.

The prevalence of asymptomatic silent ischemia was significantly higher in diabetics (27.78%) compared to non-diabetics (11.11%) in our study.

Negrusz-Kaweck et al [51] found that the incidence of silent ischemia in type 2 Diabetics was 20.22%.

Other studies [52, 53] also reported a similar prevalence of asymptomatic ischemia in diabetics.

O'sullivan, et al. [54] found that silent ischemia was present in 64.7% with autonomic neuropathy against 41.1% without autonomic neuropathy. They concluded that autonomic neuropathy may prevent the development of angina pain.

There is an increased incidence of conduction blocks in diabetics as compared to non-diabetics.

Partman and Bradkey [55] found that the incidence of RBBB in diabetics is about 2.5%.

In this study there was an increase prevalence of both incomplete RBBB/LAFB in diabetics (4%/4% respectively) as compared to non-diabetics (2%/0%).

Reduced heart ate variability is the earliest indicator of CAN (i.e., abnormalities of heart rate control and vascular dynamics).

The HRBD (Heart Rate response to Deep Breathing) is abnormal in diabetics indicating parasympathetic damage. It was positive in 28% of diabetics in this study.

I.Domuschiev, et al [56] found that the heart rate response to deep breathing was the most sensitive test, positive in 33.3% followed by heart rate response to standing (31%).

The QTc interval correlated well with postural hypotension. All patients who had both symptoms and signs of postural hypotension (three) had significant QTc prolongation.

H. Oka [47] et al found that QTc interval prolongation significantly correlates with postural drop in SBP. In short, QTc interval may be taken as a marker of sympathetic nervous system dysfunction.

Decreased sympathetic outflow to the heart and resistance vessels accompanies a decrease in SBP, exercise capacity and maximum heart rate. [58]

This inability to increase rate variation may contribute to postural hypotension. [59, 60].

CONCLUSIONS

The following ECG manifestations were present in type 2 Diabetic patients compared to non-diabetic population.

1. High resting heart rate
2. Prolongation of PR interval
3. Increased prevalence of ischemia and infarction
4. Increased incidence of asymptomatic IHD
5. Left ward QRS axis
6. No significant difference in QRS duration.

   Following manifestations suggestive of cardiac dysautonomia in type 2 Diabetics were

   1. Abnormal HRBD≤10bpm
   2. Prolonged QTc interval (QTc>460 msec) in 8%
   3. Significant postural drop in SBP (>30 mm Hg) in 6%
   4. There is a positive linear correlation between QTc prolongation (QTc>460 msec) and postural drop on SBP (>30 mm Hg)

Thus, the evaluation of various cardiovascular reflexes in type 2 diabetics gives an easy and feasible bedside technique to determine the presence of cardiac dysautonomia.

BIBLIOGRAPHY

1. Prevalence of type 2 Diabetes in India (PODIS) by Indian task force on Diabetes 2001. Convener M. Sadikot, Mumbai.
2. Textbook of Internal Medicine. Harrison 17th edition P2275-2304..
3. Handbook of diabetes mellitus- Ed V.Seshaih. 1st Ed P: 127-140.
4. The Heart, Hurst's, 12th edition, diabetes and cardiovascular diseases
5. Jain A, Avendaro G, Dharamsey S, et al. Left ventricular diastolic dysfunction in hypertension and role of plasma glucose and insulin: comparison with diabetic heart. *Circulation* 1996; 93:1396–1402. [PMID: 8641029]
6. Palmieri V, Bella JN, Arnett DK, et al. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects. *Circulation* 2001; 103:102–107. [PMID: 11136693]
7. Buzzard.: Illustrations of some less known forms of peripheral neuritis, especially alcoholic monoplegia and diabetic neuritis. BMJ 1:1419, 1890.
8. Toyry et al. Diabetes 1996.
9. Toyry et al Circulation 1997
10. Vasomotor tone in diabetic neuropathy. Annuals of int Med. 17 P: 353-1972.
11. Neil, H. A., Thompson, A., Thorogard, m., et al.: Diabetes in the elderly: the Oxford Community Diabetes study. Diabet. Med. 6:608, 1989

12. Maser, R. et al.: Diabetic autonomic neuropathy and cardiovascular risk. Pittsburgh Epidemiology of Diabetes Complications Study III. Arch. Intern Med. 150: 1218, 1990.
13. Stephenson, J.M., et al: Microalbuminuria is not rare before 5 years of IDDM. EURODIAB IDDM Complications study Group and the WHO Multinational Study of vascular disease in Diabetes Study Group. J. Diabetes Complications 8:166, 1994.
14. Ziegler, D., et al: The epidemiology of diabetic neuropathy. DiaCAN Multicenter Study Group. Diabetic. Med. 10(suppl. 2):82S, 1993.
15. Feldman, H. et al.: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J. Urol. 151:54, 1994.
16. Enck, P., et al.: Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects. Z. Gastroenterol. 32:637,1994.
17. Appenzeller O, Richardson EP Jr. The sympathetic chain in patients with diabetic and alcoholic polyneuropathy. *Neurology* 1966; 16:1205–1209.
18. Duchen LW, Anjorin A, Watkins PJ, et al. Pathology of autonomic neuropathy in diabetes mellitus. *Ann Intern Med* 1980; 92:301–303.
19. Olsson Y, Sourander P. Changes in the sympathetic nervous system in diabetes mellitus: a preliminary report. *J Neurovasc Relat* 1968; 31:86–95.

20. Low PA, Walsh J: C, Huang CY, et al. The sympathetic nervous system in diabetic neuropathy: a clinical and pathological study. *Brain* 1975; 98:341–356.
21. Kristensson K, Nordborg C, Olsson Y, et al. Changes in the vagus nerve in diabetes mellitus. *Acta Pathol Microbiol Scand* 1971;79[A]:684–685.
22. Faerman I, Glocer L, Celener D, et al. Autonomic nervous system and diabetes: histological and histochemical study of the autonomic nerve fibers of the urinary bladder in diabetic patients. *Diabetes* 1973; 22:225–237.
23. Greene DA, Lattimer SA. Impaired rat sciatic nerve sodium-potassium adenosine triphosphatase in acute streptozocin diabetes and its correction by dietary myo–inositol supplementation. *J Clin Invest* 1983; 72:1058–1063.
24. Yasuda H, Dyck PJ. Abnormalities of endoneurial microvessels and sural nerve pathology in diabetic neuropathy. *Neurology* 1987; 37:20–28.
25. Bellavave F, Balzenil, Demasi G, Carraro M, Carenza P, Cobelli C, Tomoseth K, power spectral analysis of heart rate variation improves assessment of cardiac autonomic neuropathy. Diabetes 1992; 41:63-640.
26. International textbook of diabetes mellitus 2nd Ed 1997. Ed by K.G.M.M. Alberti P: 1447-1507.

27. Medifacts-cardiac dysautonomia volume 24 2003 page 2-5.
28. Toyry, J et al: occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM: ten-year follow-up from the diagnosis. Diabetes 45:308, 1996.
29. Ziegler, d. Mayer, P., et al.: The natural history of somatosensory and autonomic nerve dysfunction in relation to glycemic control during the first 5 years after diagnosis of diabetes mellitus. Diabetologia 34:882, 1991.
30. Quadric R, Ponzani P., et al.: Changes in autonomic nervous function over a 5-year period in non-insulin-dependent diabetic patients. Diabet. Med. 10:916, 1993.
31. Mustonen, J., Uusitpa, M., et al.,: changes in autonomic nervous function during the 4-year follow-up in middle-aged diabetic and nondiabetic subjects initially free of coronary artery disease. J. Intern. Med. 241:227, 1997.
32. Braunwald heart disease 6th Ed P: 2143-2146.
33. Ewing et al. The natural history of diabetic autonomic neuropathy QJ Med. 1980; 49:95-108.
34. Rundles RW diabetic neuropathy: General review with report of 125 cases. Medicine (Baltimore) 24, P: 111-160, 1945.
35. Sampson MJ, Wilson S, Karagiannis P, *et al*. Progression of diabetic autonomic neuropathy over a decade in insulin dependent diabetics.*Q J Med* 1990;75:635–46.
36. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; 193:95–112.
37. Malins JM. *Clinical diabetes mellitus.* Margate: Eyre and Spottiswoode, 1968

38. Porcellati F, Fanelli C, Bottini P, *et al*. Mechanisms of arterial hypotension after therapeutic dose of subcutaneous insulin in diabetic autonomic neuropathy. *Diabetes* 1993; 42:1055–64.
39. Purewal TS, Watkins PJ. Postural hypotension in diabetic autonomic neuropathy: a review. *Diabet Med* 1995; 12:192–200.
40. Mathias CJ, Bleasdale-Barr K, Smith G, *et al*. Intermittent muscle ache, particularly in the suboccipital/paracervical (coathanger) region in autonomic failure: frequency in associated neurological conditions and relationship to postural hypotension. *J Neurol* 1994; 214(suppl 1):S85.
41. Margolis JR et al: Clinical features of unrecognized myocardial infarction in diabetic patients; silent and symptomatic; 18 years follow up American Journal of Cardiology 1973 page 1-7.
42. Siveri R Vagliam, Chinglie A, Sagoline L, prevalence of QT prolongation in diabetic population and its association with autonomic neuropathy. Diabetic medicine 10:920-924.1993.
43. Quantitative Electro cardiographic and Vector cardio graphic study on newly diagnosed NIDDM and non diabetic control subjects. Uusitpa, M. Mushronan Cardiology 75(1) P:1-9,1988.
44. Tharaindottir IS et al: The Epidemiology of right bundle branch block in association with cardiovascular mortality: European heart Journal 1993, DEC. 14(@) P: 1590-96.

45. A Pourmoghaddas, A Hekmatnia et al: The relationship between QTc interval and cardiac autonomic neuropathy in diabetes mellitus: Mol Cell Biochem (2003) 249: 125-8.
46. CP Mathur*, Deepak Gupta**, :QTc Prolongation in Diabetes Mellitus – An Indicator of Cardiac Autonomic Neuropathy :JIACM 2006; 7(2): 130-2
47. H Oka et al – diabetes mellitus proceedings at 14th international Federation page 1304(68-71).
48. Kannal et al- Diabetes and cardiovascular diseases, the Framingham Heart Study JAMA 241:2035.1975.
49. Diabetes mellitus and anterior myocardial infarction-Acta. Med.Scandineve 200 P: 151-153.
50. Silver et al: Myocardial infarction in diabetes mellitus QJM 44:125-1975.
51. Negrusz-kawecki m et al.:Frequency of silent ischemic heart disease in patients with diabetes mellitus: Pol Merkuriusz Lek: 1997 Aug3(14)53:6
52. Polmerkuriuszlek: 1997 August 39(14)53:6.
53. Pathophysiology of diabetic autonomic neuropathy, cardio vascular, hormonal and metabolic structures. Diabetes 31 page 730-1982.
54. O'sullivan JJ,Conroy R, et al.: silent ischemia in diabetic men with autonomic neuropathy. British Heart Journal 1991; 66:313-15.
55. Partiman J.O., Bradley R.F., Acute myocardial infarction in 258 cases of diabetes, immediate mortality and five year survival; New England Journal of Medicine 273;455-461,1965.

56. I. Domuschiev: Cardiac autonomic neuropathy and its correlation with retinopathy in type 2 Diabetics: Biotechnol. & Biotechnol. Eq. 19/2005/3
57. Kahn J.K., Sisson J.C., Vinik A.I. (1988) J. Nucl. Med., 29, 1605-06.
58. Sudden death the heart- The Heart – William Hurst V-II, 10th edn.
59. Vacek J et al: Silent myocardial infarction in diabetic population. American journal of Medicine 1984 April 76(4) page 59.
60. Electro physiological studies in denervated transplanted human heart. Circulation 32 268:1973.

PROFORMA

1. Name
2. OP/IP no.
3. Address
4. Age
5. Sex
6. Age of onset of diabetes
7. Duration of diabetes
8. Treatment history
9. H/o smoking
10. H/o alcoholism
11. H/o anginal pain
12. Dietary habits
13. Body mass index
14. Pulse
15. Blood pressure
    1. Supine
    2. Standing

CARDIOVASCULAR SYSTEM

ELECTROCARDIOGRAM

1. Rate
2. RR interval
3. PR interval
4. QRS duration
5. QRS axis
6. QTc interval
7. HRBD
    a. RR interval Inspiration(Rate)
    b. RR interval Expiration(Rate)
    c. HRBD
8. ST-T changes
9. Conduction abnormalities
10. Other abnormalities

MASTER CHART

STUDY GROUP (DIABETICS)																				
							Blood pressure		Electrocardiogram											
SI.NO.	NAME	IP/OP NO.	AGE/SEX	H/o anginal pain	H/o postural giddiness	Pulse (bpm)	Supine (mm Hg)	Standing (mm Hg)	Rate (bpm)	R-R (msec)	P-R (msec)	QRS Durat.(msec)	QRS axis (degrees)	QT Interval	QTc Interval (msec)	HRBD	ST –T Changes	Conduction abnormalities	Other abnormalities
1	Vasantha	251585	40/F	-	-	88	130/80	124/80	88	680	140	80	90	340	412	5	-	-	-
2	Muthulingam	78157	37/M	-	-	92	122/78	120/78	92	650	160	60	0	320	396	9	-	-	-
3	Suresh	77096	32/M	-	-	58	134/88	134/88	58	1030	240	60	45	380	374	15	-	-	-
4	Mallika	245572	48/F	+	-	82	112/86	110/86	82	730	120	60	60	320	374	17	T↓II,III,aVF	-	-
5	Radha	76424	43/F	-	-	102	100/70	98/70	102	590	160	60	60	300	390	17	-	-	-
6	Manoharan	71608	47/M	-	-	88	110/82	110/82	88	680	140	60	45	320	388	8	T↓I,aVL,V5,6	-	-
7	Jeeva	.81947	37/F	-	-	94	116/78	116/78	94	640	120	60	45	280	350	15	-	-	-
8	Radhakrishnan	78179	45/M	-	-	70	124/82	124/82	70	860	200	80	75	320	345	4	T↓II,III,aVF	-	-
9	Charles	76979	40/M	-	-	90	130/82	126/82	90	670	180	60	30	360	440	15	-	-	-
10	Srinivasan	42552	50/M	+	-	80	122/80	122/80	80	750	140	60	30	340	392	19	T↓V1-V4	-	-
11	Annamary	19558	50/F	-	-	84	110/70	108/70	84	710	160	60	60	340	403	18	-	icRBBB	-
12	KasthuriBai	76365	42/F	-	-	86	120/86	118/86	86	700	140	60	30	360	412	18	-	-	-
13	Premavathy	33261	52/F	+	-	60	136/86	136/86	60	1000	200	60	-45	400	400	15	QV1-V4	LAFB	-
14	Pappathy	77835	42/F	-	-	76	110/70	108/70	76	790	180	80	45	340	382	13	-	-	-
15	Radha	28989	50/F	-	+	56	126/80	94/76	56	1070	220	60	30	500	483	5	-	-	-
16	Munusamy	15750	48/M	+	-	96	110/76	108/76	96	620	140	80	30	320	406	17	T↓V1-V3	-	-
17	Mahendran	40831	44/M	+	-	64	130/80	118/80	64	940	220	60	45	360	371	15	T↓II,III,aVF	-	-
18	Ambika	76467	45/F	-	-	70	126/80	124/80	70	860	160	100	0	340	367	4	T↓I,aVL,V5,V6	-	-
19	Senthamarai	76408	41/F	-	-	86	110/80	108/80	86	700	160	90	-30	320	382	17	-	-	-
20	Anbalagan	1013	55/M	+	-	96	116/86	116/86	96	620	120	60	45	320	406	4	T↓I,aVL	-	-
21	Dhanalakhsmi	36996	35/F	-	-	82	116/76	108/76	82	730	140	70	0	320	374	16	-	-	-
22	Yasodha	76403	45/F	+	-	94	112/86	110/86	94	640	160	60	-30	320	400	16	QII,III,AVF	-	-
23	Krishnan	50676	43/M	-	-	98	126/80	122/80	98	610	140	80	45	300	384	4	-	icRBBB	-
24	Kesavan	6458	46/M	-	-	88	110/70	108/68	88	680	160	80	30	360	437	17	-	-	-
25	Parvathy	76282	42/F	-	-	90	120/80	118/80	90	670	160	60	30	320	391	15	-	-	-

STUDY GROUP (DIABETICS)																				
							Blood pressure		Electrocardiogram											
SI.NO.	NAME	IP/OP NO.	AGE/SEX	H/o anginal pain	H/o postural giddiness	Pulse (bpm)	Supine (mm Hg)	Standing (mm Hg)	Rate (bpm)	R-R (msec)	P-R (msec)	QRS Durat.(msec)	QRS axis (degrees)	QT Interval	QTc Interval (msec)	HRBD	ST –T Changes	Conduction abnormalities	Other abnormalities
26	Fathima.S	17828	55/F	-	-	96	110/76	106/72	96	620	200	60	45	320	406	6	-	-	-
27	Vijaya	77860	45/F	-	-	92	110/80	108/80	92	650	160	60	-30	320	397	5	-	-	-
28	Ravindran	17998	45/M	+	-	76	120/80	120/80	76	790	180	60	-45	360	405	17	QV1-V4	*LAFB*	-
29	Jeeva	76240	32/F	-	-	102	112/82	110/80	102	590	140	80	60	320	417	13	-	-	-
30	Chandrasekar	78169	45/M	-	-	90	120/80	116/78	90	670	140	60	45	320	391	6	QI,aVF,V5,V6	-	-
31	Vasantha	76515	42/F	-	-	76	132/86	130/86	76	790	200	60	60	360	405	14	-	-	-
32	Dilliammal	88328	56/F	-	-	110	120/82	120/82	110	550	140	60	45	300	405	15	-	-	-
33	Jayavel	76769	39/M	+	-	70	110/70	108/70	70	860	160	80	0	380	410	15	T↓V1-V4	-	-
34	Mathivanan	78099	38/M	-	-	106	100/70	100/70	105	570	140	60	30	320	424	17	-	-	-
35	Daksinamoorti	39916	35/M	-	-	102	120/86	118/86	102	590	160	60	0	320	417	5	-	-	-
36	Rubavathy	72608	40/F	-	-	106	100/70	98/70	104	580	160	80	30	300	394	5	-	-	-
37	Murali.K	7443	50/M	-	-	66	128/88	128/88	66	910	220	60	15	360	377	15	-	-	-
38	Panchavarnam	12442	55/F	-	+	92	118/70	82/68	92	650	140	60	30	480	595	16	-	-	-
39	Zeenath	245592	50/F	+	-	70	126/82	126/82	70	860	220	80	0	380	410	13	T↓V1-V3	-	-
40	Selvi	39710	48/F	-	-	78	118/86	116/86	78	770	160	60	45	320	387	15	-	-	-
41	Panneerselvam	76862	37/M	-	-	80	136/86	134/86	80	750	120	60	45	380	439	16	-	-	-
42	Krishnan	83007	41/M	+	-	78	120/78	120/78	78	770	140	80	30	320	365	16	T↓V1-V4	-	-
43	Poomalai	81945	52/F	-	+	86	126/86	94/74	86	700	160	60	0	400	478	5	T↓V1-V4	-	-
44	Sairam	78204	42/M	+	-	82	120/82	118/82	82	730	120	60	-30	340	398	15	QII,III,aVF	-	-
45	Syed Ameed	2892	50/M	-	-	96	110/80	100/80	96	630	120	60	0	300	378	16	-	-	-
46	Suresh	76746	29/M	-	-	100	110/70	106/70	100	600	140	80	45	380	491	13	-	-	-
47	Thenmozhi	24667	47/F	-	-	90	138/82	128/78	90	670	140	80	45	300	367	15	-	-	-
48	Ramachandran	50747	58/M	-	-	74	110/70	110/70	74	810	200	80	30	360	400	18	-	-	-
49	Loorthusamy	43204	40/M	+	-	78	118/70	118/70	78	770	220	100	30	380	433	13	T↓II,III,aVF	-	-
50	Mohan	76239	54/M	-	-	78	120/82	118/80	78	770	180	80	30	360	410	16	-	-	-

CONTROL GROUP																			
SI.NO.	NAME	IP/OP NO.	AGE/SEX	H/o anginal pain	H/o postural giddiness	Pulse (bpm)	Blood pressure		Electrocardiogram										
									Rate (bpm)	R-R(msec)	P-R (msec)	QRS Durat.(msec)	QRS axis (degrees)	QT Interval (msec)	QTc Interval (msec)	ST –T Changes	Conduction abnormalities	Other abnormalities
1	Amutha	10357	45/F	-	-	82	130/80	128/80	82	730	160	80	30	300	352	-	-	-
2	Adhilakhsmi	37736	43/F	-	-	92	138/80	136/80	92	650	160	60	60	300	372	-	-	-
3	Malarkodi	29156	47/F	-	-	80	130/82	126/82	82	730	130	60	0	320	375	-	-	-
4	Palaniammal	11172	36/F	-	-	90	126/80	124/80	90	670	140	60	60	340	415	-	-	-
5	Annapoorani	25775	47/F	+	-	76	110/80	108/80	76	790	160	80	-15	360	405	Q II,III,aVF	-	-
6	Shanthi	14422	41/F	-	-	66	126/80	120/78	66	910	140	60	45	360	377	-	-	-
7	Arul	45866	36/M	-	-	84	116/86	116/86	83	790	140	60	30	300	338	-	icRBBB	-
8	Krishnan	34325	36/M	-	-	78	120/82	120/82	78	770	140	80	100	340	387	-	-	-
9	Lilli	36777	48/F	-	-	92	128/82	126/80	92	650	150	60	70	260	322	-	-	-
10	Lingammal	29993	43/F	-	-	62	110/80	110/80	62	960	120	60	45	340	347	-	-	-
11	Jayalakhsmi	32674	40/F	-	-	68	112/82	110/80	68	880	140	60	60	360	384	-	-	-
12	Bakiya	6983	55/F	-	-	72	120/80	120/80	72	830	120	80	45	340	373	-	-	-
13	Subramani	51588	51/M	+	-	82	132/86	130/86	82	730	120	60	30	300	351	T↓V1-V4	-	-
14	Srinivasan	38234	38/M	-	-	78	120/82	120/82	78	770	140	60	60	300	342	-	-	-
15	Varadhan	4801	35/M	-	-	78	110/70	108/70	78	770	140	60	60	320	365	-	-	-
16	Shanthi	14421	41/F	-	-	90	100/70	100/70	90	670	120	60	60	340	415	-	-	-
17	Moorthy	52282	40/M	-	-	70	120/86	118/86	70	860	180	70	70	340	366	-	-	-
18	Pushpalatha	25102	45/F	-	-	60	136/86	136/86	60	1000	120	60	60	360	360	-	-	-
19	Sumathy	15912	50/F	-	-	70	110/70	108/70	70	860	120	60	50	380	410	-	-	-
20	Kasthuri	32763	48/F	-	-	86	120/80	114/80	86	700	120	80	60	300	359	-	-	-
21	Prabhu	44137	28/M	-	-	80	110/76	108/76	80	790	160	60	90	300	338	-	-	-
22	Jothi	7808	45/F	-	-	62	110/80	108/78	62	970	160	60	30	360	366	-	-	-
23	Thirunavukarasu	600	55/M	+	-	80	120/80	120/80	79	760	140	80	-15	320	367	Q II,III,aVF	-	-
24	Veeraiah	19805	40/M	-	-	78	112/82	110/82	78	770	120	60	0	300	342	-	-	-
25	Raju	26624	32/M	-	-	70	120/80	116/78	70	860	140	60	45	360	388	-	-	-

CONTROL GROUP																			
SI.NO.	NAME	IP/OP NO.	AGE/SEX	H/o anginal pain	H/o postural giddiness	Pulse (bpm)	Blood pressure		Electrocardiogram										
							Supine (mm Hg)	Standing (mm Hg)	Rate (bpm)	R-R(msec)	P-R (msec)	QRS Durat.(msec)	QRS axis (degrees)	QT Interval (msec)	QTc Interval (msec)	ST –T Changes	Conduction abnormalities	Other abnormalities
26	Venkatesan	11636	46/M	+	-	74	106/82	104/82	74	810	150	60	45	360	400	QV1-V4	-	-
27	Muthammal	14429	40/F	-	-	68	110/86	110/86	68	880	140	60	45	380	405	-	-	-
28	Guru	40829	45/M	-	-	78	100/70	98/70	78	770	120	60	60	320	365	-	-	-
29	Pattammal	17064	55/F	-	-	68	110/82	110/82	68	880	160	80	60	360	384	-	-	-
30	Rajan	38989	48/M	-	-	74	116/78	116/78	74	810	130	60	90	320	356	-	-	-
31	Kalavathy	13633	52/F	-	-	72	124/82	124/82	68	880	140	60	30	360	364	-	-	-
32	Anjaladevi	31687	50/F	-	-	56	130/82	126/82	56	1070	160	60	60	400	387	-	-	-
33	Annamalai	44144	45/M	-	-	58	120/86	118/86	58	1030	120	80	30	340	335	T↓V1-V4	-	-
34	Kattan	15110	40/M	-	-	86	136/86	136/86	86	700	140	60	0	300	359	-	-	-
35	Dhas	20723	45/M	-	-	88	126/80	120/78	87	680	130	60	90	300	364	-	-	-
36	Venkatesh	22227	50/M	-	-	86	116/86	116/86	86	700	120	80	40	280	335	-	-	-
37	Venkatesan	1305	50/M	-	-	70	120/82	120/82	70	860	120	60	30	340	367	-	-	-
38	Mala	406101	41/F	-	-	60	128/82	126/80	61	980	120	80	45	340	344	-	-	-
39	Mallika	12708	34/F	-	-	76	112/86	110/86	76	790	130	60	0	360	405	-	-	-
40	Parthiban	18112	46/M	+	-	58	126/80	124/80	58	1030	150	60	30	340	335	T↓V1-V4	-	-
41	Kuppan	10766	59/M	-	-	100	100/70	100/70	100	600	120	80	0	280	361	-	-	-
42	Anand	50665	41/M	-	-	70	120/80	118/80	70	860	120	60	90	320	345	-	-	-
43	Yamuna	29749	52/F	+	-	72	126/80	124/80	72	830	120	60	70	320	351	T↓II,III,aVF	-	-
44	Gopinath	24724	41/M	-	-	66	110/80	108/80	66	910	140	80	45	320	335	-	-	-
45	Palanisamy	6808	48/M	+	-	98	116/86	116/86	98	610	120	60	90	300	384	T↓V1-V4	-	-
46	Loganayagi	10389	35/F	-	-	82	110/76	108/76	82	730	160	60	75	320	375	-	-	-
47	Kamurunnisha	31764	57/F	-		68	110/80	108/78	68	880	140	60	60	340	362	-	-	-
48	Ravi	12634	43/M	-	-	70	110/82	110/82	70	860	180	6`0	60	280	302	-	-	-
49	Mani	16901	43/M	-	-	80	130/82	126/82	80	750	140	60	60	340	393	-	-	-
50	Muthulaksmi	36721	42/F	+	-	60	126/80	124/80	60	1000	160	60	45	340	340	T↓II,III,aVF	-	-