"A STUDY ON DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS WITH NORMAL SYSTOLIC FUNCTION"

Dissertation submitted in partial fulfilment of the requirement for the award of the Degree of

DOCTOR OF MEDICINE – BRANCH I

GENERAL MEDICINE

APRIL 2016

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI ,TAMIL NADU.

CERTIFICATE

This is to certify that the Dissertation entitled "**A STUDY ON DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS WITH NORMAL SYSTOLIC FUNCTION"** submitted by **Dr. M.ILAMARAN** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the award of M.D. Degree (GENERAL MEDICINE) is a bonafide work carried out by him under my guidance and supervision during the academic year 2013-2016. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

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I**, Dr.M.ILAMARAN**, solemnly declare that the Dissertation titled "**A STUDY ON DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS WITH NORMAL SYSTOLIC FUNCTION"** has been prepared by me. This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (MEDICINE).

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: TIRUNELVELI

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PROTOCOL TITLE: DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS WITH NORMAL SYSTOLIC FUNCTION.

NAME OF PRINCIPAL INVESTIGATOR: Dr. Ilamaran .M, MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MD General Medicine
DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr. Ilamaran .M, *The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 14.05.14.*

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

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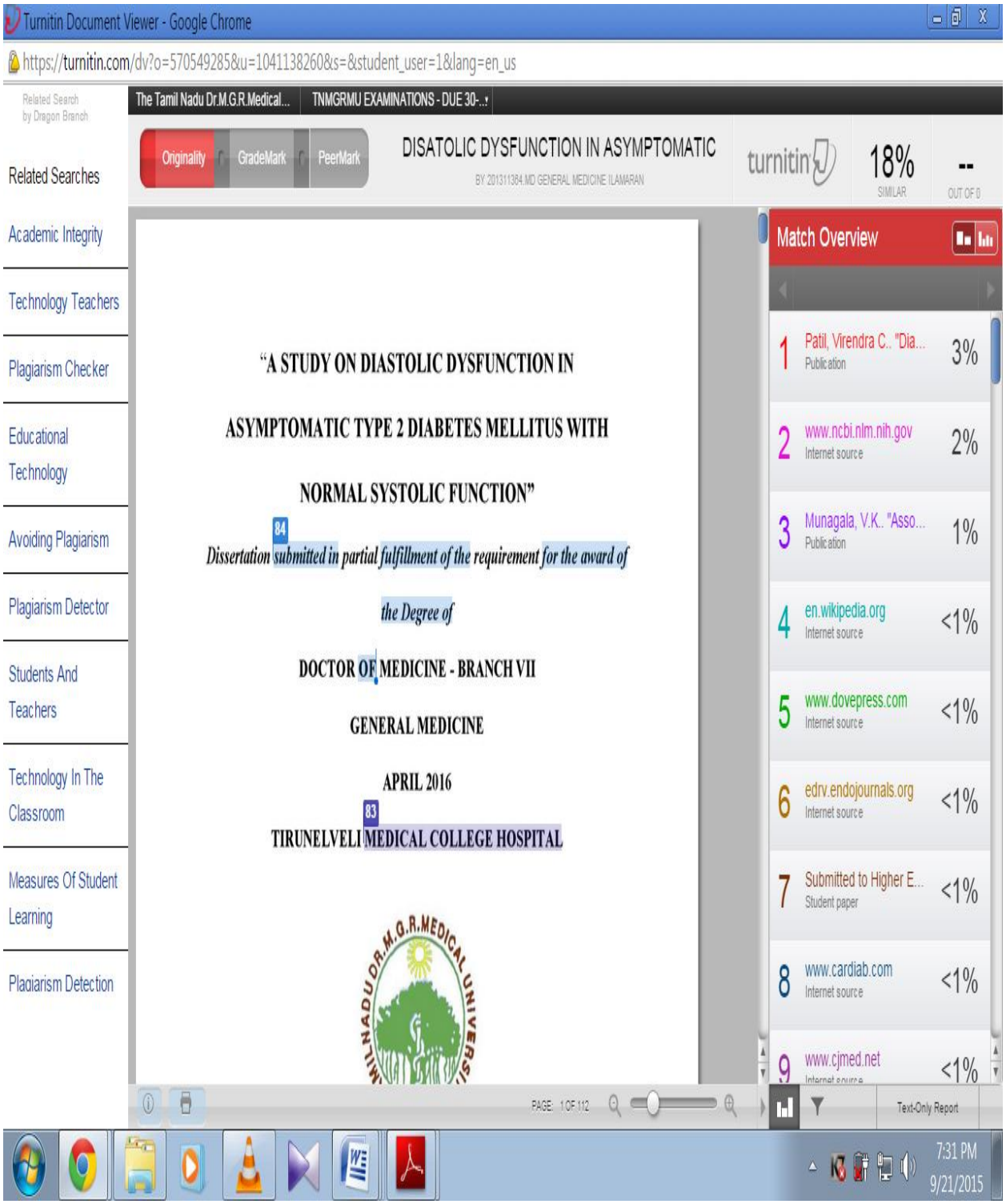
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INTRODUCTION

A STUDY ON DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS WITH NORMAL SYSTOLIC FUNCTION

INTRODUCTION

The incidence of diabetes mellitus (DM) is on the raise across the world and it is turning out to be an epidemic of non communicable disease. Diabetic heart disease and **Diabetic Cardiomyopathy** as a separate entity has been proposed in the last couple of decades. Diastolic heart failure, otherwise called as heart failure with preserved ejection fraction, is common finding of hypertensive heart disease, but various studies report a high incidence of diastolic heart failure in patients with type 2 diabetes mellitus inspite of the absence of coronary artery heart disease and hypertension. Observations point to a diastolic dysfunction occurring before systolic dysfunction in the setting of myocardial damage due to diabetes. There is also prevalence of a pre-clinical diastolic dysfunction in diabetics. The patho-physiology of an impaired diastolic dysfunction in diabetes is poorly understood. Diabetic cardiomyopathy is proposed to be a disease independent coronary artery disease. Metabolic derangements involving hyperglycemia, hyperlipidemia, hyperinsulinemia, myocyte loss, interstitial fibrosis, autonomic neuropathy, microvascular

dysfunction have all been proposed as underlying the development of Diabetic cardiomyopathy. The objective of this study is to find out the association between Type 2 Diabetes Mellitus and Diastolic Dysfunction, even in the asymptomatic diabetic population. To ascertain the prevalence of left ventricular diastolic dysfunction and to determine its correlation with duration of diabetes mellitus, obesity parameters, HbA1c levels, patient's age and diabetic microvascular complications we conducted this case control study.

AIM

AIM

1) To determine the prevalence of dysfunction of left ventricle in diastole in type 2 diabetes mellitus patients with duration greater than 5 years
2) To compare the prevalence of left ventricular diastolic dysfunction of non diabetic individuals with that of asymptomatic type II diabetes patients
3) To know the correlation of diastolic dysfunction in diabetes with age of patients, HbA1c levels, duration of diabetes, duration of diabetes, retinopathy, autonomic neuropathy.

REVIEW OF LITERATURE

Diabetes affects the heart in 3 ways:

(1) Coronary Artery Disease (CAD) due to accelerated atherosclerosis

(2) Cardiac Autonomic Neuropathy (CAN) and

(3) Diabetic Cardiomyopathy (DbCM).

Although there is high awareness among clinicians about the first two disease entities, DbCM is poorly recognized by most physicians and diabetologists.

Various studies have reported the presence of cardiac abnormality apart from coronary artery disease in asymptomatic diabetes patients.

In 1991 Galderisi et al reported the incidence of increased left ventricular mass in diabetes mellitus in women through the **Framingham heart study**. In 1997 Lee et al reported the presence of increased left ventricular mass in diabetes mellitus in both men and women in the cardiovascular health study. In 2000, Devereux et al in **Strong health study** showed that there is increased left ventricular mass, decreased endocardial fractional shortening and midwall fractional shortening in diabetes mellitus. In 2001 Ilercil et al showed that there is increased left ventricular thickness and relative wall thickness in impaired glucose tolerance. In 2003Rutter et al used Framingham heart study and reported the presence of progressive increase in left ventricular mass, relative wall thickness in both impaired glucoe tolerance and diabetes mellitus.

Poulsen et al in a study of 300 patients in 2010 observed that there is high prevalence of diastolic dysfunction in patients with type 2 diabetes with no previous history of coronary artery disease and abnormal left ventricular filling was associated with impaired myocardial perfusion.

Soldatos et al did a case control study with 60 patients and found a significant incidence of diastolic dysfunction in diabetic individuals.

Masugata et al conducted a case control study with 78 patients with normal blood pressure. He found the the presence of diastolic dysfunction with normal systolic function was correlating to duration of type 2 diabetes and age of patients.

Mishra et al observed, from their case control study of 70 patients, that when compared to normal individuals, patients with diabetes have reduced diastolic and systolic function. He also found that the systolic and diastolic disturbances were correlating with diabetes duration and the microvascular complications.

Between 1996-2007 **From et al** conducted a study with 485 subjects and observed that diastolic dysfunction of left ventricle was associated with diabetes mellitus with duration > 4 years.

Sohail et al in a study with 211 patients observed a 30% incidence of diastolic dysfunction in type 2 diabetes.

Exiara et al in a study with 115 patients observed that, patients without hypertension and properly controlled diabetes have diastolic dysfunction and it correlates with duration of diabetes.

Diamant et al found that the echo findings of E, A, E/A ratio and other diastolic function indices were decreased in uncomplicated diabetes that was diagnosed recently.

Bonito et al states that the left ventricular diastolic dysfunction correlates with micro vascular complications.

Aaron et al with a study of 1700 patients found a 23 % incidence of diastolic dysfunction in type 2 diabetes.

Takeda et al in a study of 500 Japanese diabetes patients observed that there is a major role for diastolic dysfunction in producing heart failure with preserved systolic function.

Poanta et al observed, through a study of 50 patients, that left ventricular diastolic dysfunction was associated with cardiac autonomic neuropathy which was asymptomatic.

Patil et al in a study with 122 diabetes patients found that the prevalence of left ventricular diastolic dysfunction was high in diabetics who are asymptomatic, which correlated with HBA1c levels, obesity parameters, duration of diabetes and the microvascular complications.

DIABETES MELLITUS

A group of common metabolic disorders producing a phenotypic expression of hyperglycemia is termed as Diabetes Mellitus. The dysregulation in metabolism due to diabetes affects multiple organ system and leads to a number of complications. Diabetes is one of the major causes of end stage renal disease (ESRD), adult blindness, non traumatic lower limb amputation, coronary artery disease, etc

Diabetes mellitus may be caused by defective production of insulin or by the resistance to respond appropriately to insulin, leading to hyperglycemia.. Type 1 Diabetes mellitus is due to total lack of insulin production caused by auto immune destruction of beta cells of pancreas. In type 2 diabetes, there is a insulin resistance in the peripheral tissues, like skeletal muscles, adipose tissue and liver on which insulin acts, which is the basic patho physiology, leading to initially a relative insulin deficiency that later on progresses to predominant insulin secretory defect with insulin resistance.

Other specific types of diabetes do exist. These include genetic defects in beta cell function due to mutations, defects in insulin action due to genetic mutations, disorders affecting the exocrine pancreas, specific endocrinopathies, drug induced diabetes, gestational diabetes mellitus

The diagnosis of diabetes is made based on the following criteria

TABLE 1: DIAGNOSTIC CRITERIA TO DEFINE DIABETES MELLITUS

SL NO	PARAMETER	NORMAL GLYCEMIC STATUS	PRE-DIABETES	DIABETES
1.	FASTING PLASMA GLUCOSE	<5.6 mmol/l or 100mg/dl	5.6-6.9 mmol/l or 100-125 mg/dl	>/= 7mmol/l or >126mg/dl
2.	2 HOUR PLASMA GLUCOSE AFTER GLUCOSE CHALLENGE	<7.8 mmol/l or 140 mg/dl	7.8-11mmol/l or 140-199 mg/dl	>/=11.1mmol/l or >200mg/dl
3.	HB A 1 C	<5.6%	5.7-6.4 %	>/=6.5%

The above criteria was issued by an International expert committee with members appointed by the American Diabetes Association(ADA), the European Association for the Study of Diabetes and the International Diabetes Federation.

The pre diabetes stage may be either an impaired fasting glucose (IFG) with fasting plasma glucose of 100-125 mg/dl, or, an impaired glucose tolerance following a 75 g of oral glucose tolerance test with plasma glucose levels of 140-199 mg/dl 2 hour following the glucose ingestion.

Diabetes was estimated to affect over 180 million people in 2008 all over the world. Complicating the high burden of disease is the increased incidence and prevalence of type 2diabetes, propelled by increasing age of population, obesity, and sedentary life style as well as by the increased longevity of patients with type 2 DM. It is predicted that by 2030 the presence of diabetes might double the number as it is in the present day.

DIABETIC CARDIOMYOPATHY

Historically most of the attention has been focused on the prevention and treatment of micro-vascular diseases complicating diabetes such as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. But cardiovascular disease is the major cause for disability and death in diabetes mellitus. The most common cardiovascular abnormality is coronary artery heart disease (CAHD). Diabetes also increases the risk of cerebrovascular disease like stroke, peripheral vascular disease due to accelerated atherosclerosis, and also heart failure both systolic and diastolic.

In 1972 Rubler et al first described Diabetic Cardiomyopathy . ***"Diabetic cardiomyopathy is defined as myocardial dysfunction occurring in patients with diabetes in the absence of Coronary Artery heart Disease, hypertension, or valvular heart disease."***

ATHEROSCLEROSIS

When compared with non-diabetic population, patients with diabetes mellitus have a 2-fold to 4-fold increased risk of developing Coronary heart disease and also of dying from it. The occurrence of diabetes mellitus is considered to be a "Coronary Disease Equivalent" meaning that the risk of coronary events in a diabetic patient is equal to that of a non diabetic individual who sustained an Acute myocardial infarction. Of late with more effective therapy and awareness, the coronary artery heart disease risk has been substantially lowered in the last decade.

Diabetes mellitus is associated with an increased risk for Myocardial infarction both the ST elevation Myocardial Infarction and Non-ST elevation Myocardial Infarction, Unstable angina and Chronic stable angina. The incidence of these events is more than 1 in 3 patients. The outcome following these Acute Coronary Syndromes (ACS) is poor in patients with diabetes when compared to that of non diabetes. Inspite of overall improvement in outcome over the past several decades for both patients with diabetes and without diabetes, the graveness of risk associated with diabetes still persists .

In addition to CHD, diabetes increases the risks of stroke and peripheral arterial disease. The diagnosis of diabetes portends a twofold increased stroke

risk compared with non diabetic individuals , with hyperglycemia affecting approximately one in three patients with acute stroke, associated with a twofold to sixfold increased risk for adverse clinical outcomes after stroke. Among patients with symptomatic peripheral arterial disease, diabetes prevalence ranges from 20% to 30% and accounts for approximately 50% of all lower extremity amputations .

HEART FAILURE:

In the ambulatory setting, diabetes associates independently with a twofold to fivefold increase in risk for heart failure (HF), comprising both systolic and diastolic HF, and diabetes patients have worse outcomes once HF has developed. In addition, diabetes is associated with an increased HF risk in the setting of Acute Coronary Syndrome event. The increased risk of HF observed in diabetes is multi factorial, caused by ischemic, metabolic, and functional myocardial perturbations.

Diabetes as risk factor in the development of heart failure is well known and the Framingham Heart Study confirmed that the occurrence of heart failure in diabetic individuals compared to age-matched control subjects very high. Heart failure reduces the quality of life of the affected individual and complicates the management of diabetes by alterations in the pharmacokinetics

of anti-diabetic medications. Therefore, early diagnosis and prompt management of these patients are of utmost importance.

EPIDEMIOLOGY

Heart failure prevalence among diabetic individuals was as high as 20-25% in major clinical trials. However the actual prevalence of Diabetic Cardiomyopathy is not yet established, since there is a lack of large scale study data from different populations with diabetes mellitus. Some studies reported the prevalence upto 30% - 60 %.The small size of sample population limit the utility of these studies. The prevalence of myocardial dysfunction and heart failure was found to be 14.5% and 3.7% respectively at 7 years of follow up in a major prospective study which examined the prevalence of heart failure and myocardial dysfucntion in patients with type 1 diabetes of more than 10 years duration. The annual incidenc of heart failure was 0.01% and myocardial dysfunction was 0.02%. However 85% of patients were found to have a diastolic heart failure in the baseline evaluation.

The question whether diabetes itself, distinct from CAD and hypertension, results in a dilated cardiomyopathy, remains controversial. Analysing the Framingham heart study, it was found, in the population group of age between 35-64 yrs there is a 4 fold increased risk of heart failure in men and risk as high as 8 fold in

women even after the results were adjusted for other variables like lipid profile, age of the population studied, blood pressure ,obesity indices and prior history of CAD. The Washington DC Dilated Cardiomyopathy Study which was concluded recently also in the final analysis showed the association of diabetes with idiopathic cardiomyopathy.

Persons with diabetes, and especially women, have greater left ventricular mass and higher heart rates than their nondiabetic counterparts. Some studies report that patients with diabetes may have an abnormal exercise response, with an attenuation or augmentation of left ventricular EF relative to that of healthy persons without diabetes. Furthermore, various groups have reported diastolic abnormalities using various parameters, including prolonged isovolumic relaxation time decreased rates of left ventricular diastolic filling and abnormal transmitral flow velocities. Increased echo density has also been reported despite normal wall thicknesses, which could suggest increased collagen deposition present in the myocardium .

PATHOGENESIS AND PATHOPHYSIOLOGY

Pathologically, postmortem studies of patients with diabetic cardiomyopathy have revealed that they have features similar to those of patients with other forms of nonischemic cardiomyopathy. This includes myocyte hypertrophy, interstitial fibrosis, and infiltration with periodic acid-Schiff–positive materials, with coronary arterioles having thickened basement membranes, as well as the presence of intramyocardial microangiopathy.

Theories abound regarding the possible mechanism or mechanisms underlying diabetic cardiomyopathy. These include both cellular and molecular perturbations, as well as metabolic abnormalities.

Insulin may play a central role in the cellular and molecular mechanisms of diabetic cardiomyopathy. Studies with a line of transgenic mice in which the gene for the insulin-regulated glucose transporter GLUT4 has been deleted demonstrate hyperinsulinemia and cardiomyopathy. Calcium homeostasis may be altered, suggesting a diminished but prolonged increase in intracellular calcium concentration. Hyperglycemia increases calcium-activated

signaling through protein kinase C, which may in turn result in cardiac dysfunction.

Abnormalities in myofibrillar proteins, such as disturbance in troponin I phosphorylation and myosin light chains phosphorylation, may also play a role in diabetes-associated impairment of contractile function. Advanced glycosylation results in abnormal collagen cross-linking, which may contribute to decreased compliance and in turn to diastolic dysfunction.

Several metabolic perturbations may also be responsible factors leading to diabetic cardiomyopathy. Glucose contributes 10% to 15% of the energy of the heart under normal conditions. However, during insulin stimulation, increased workload, and ischemia, the metabolism of glucose is increased. Studies using diabetic animal models have demonstrated that diabetic hearts have a blunted uptake of basal and insulin-stimulated myocardial glucose. The glucose that is transported into the diabetic heart is often shunted to glycogen because of increased fatty acid utilization. Increased fatty acid uptake and oxidation itself may decrease cardiac function. Ketoacidosis may occur in diabetes. The ketones produced are avidly taken up by the diabetic heart and reduce coenzyme A, which in turn

inhibits the citric acid cycle, thereby reducing the energy capability of the muscle and resulting in myocardial dysfunction.

So the patho-physiology of Diabetic cardiomyopathy has not been delineated completely as yet. It is probably multi-factorial. Number mechanisms have been proposed. These include

1) Metabolic disturbances like hyperglycemia, hyperlipidemia
2) Insulin resistance which is the hall mark of type 2 diabetes,
3) Microvascular disease complicating diabetes,
4) Alterated renin-angiotensin system (RAS) ,
5) Autonomic dysfunction of the heart and
6) Myocardial fibrosis.

Chronic hyperglycemia is thought as the central point in pathogenesis of diabetic cardiomyopathy with contributions from molecular and metabolic perturbations from within the myocardium and also from plasma. The important metabolic alterations in diabetes are hyperglycemia, hyperlipidemia and inflammation, each contributing to the formation of reactive oxygen species (ROS) that is postulated to result in the end point of most of diabetic complications. Adaptive response to these abnormalities do occur but these responses on a chronic course lead to myocardial dysfunction and subsequently to heart failure.

HYPERGLYCEMIA AND HEART

Chronic hyperglycemia results in a number of metabolic and molecular changes in the myocardial cells. Increased glucose metabolism due to hyperglycemia leads to an increases the oxidative stress by generation of reactive oxygen species (ROS) from mitochondria. Overproduction of superoxide by the mitochondrial respiratory chain and the consequent oxidative stress result in reduction of myocardial contractility and eventually myocyte fibrosis. ROS and oxidative stress can cause cellular DNA damage and acceleration of cardiomyocyte apoptosis. DNA damage induced by oxidative stress also activates poly Adenosyl di-phosphate ribose polymerase (PARP), a repair enzyme of DNA. PARP diverts glucose metabolism from its usual glycolytic pathway (through inhibition of glyceraldehyde phosphate dehydrogenase) into alternative biochemical pathways that result in generation of various mediators which causes hyperglycemia leading to cellular injury. Activation of the enzyme protein kinase C, increased production of hexosamine ,sorbitol and advanced glycation end products(AGEs) are the processes through which hyperglycemia induces cell death.

ADVANCED GLYCATION END PRODUCTS AND DBCM

Oxidative stress induced by chronic hyperglycemia has been shown to increase the AGEs in diabetic subjects. AGEs can covalently crosslink various

intra and extracellular proteins that is thought to be a pivotal factor in development of complications of diabetes. The collagen and elastin crosslinks leads to myocardial stiffness and impairment in cardiac relaxation. AGEs are found to induce myocardial damage in both animals and human beings. AGEs also indirectly exert their detrimental effect on the myocardium by interacting and up-regulating their receptors, including receptors of AGE and galectin-3. This results in activation of nuclear transcription factors, like nuclear factor-kB (NF-kB). In turn NF-kB dependent genes activate pathways that produce of inflammation producing cytokines like Tumour necrosis factor-α and cause myocardial damage. NF-kB blockers were found to attenuate mitochondrial oxidative stress and protect against cardiac dysfunction in diabetic mice.

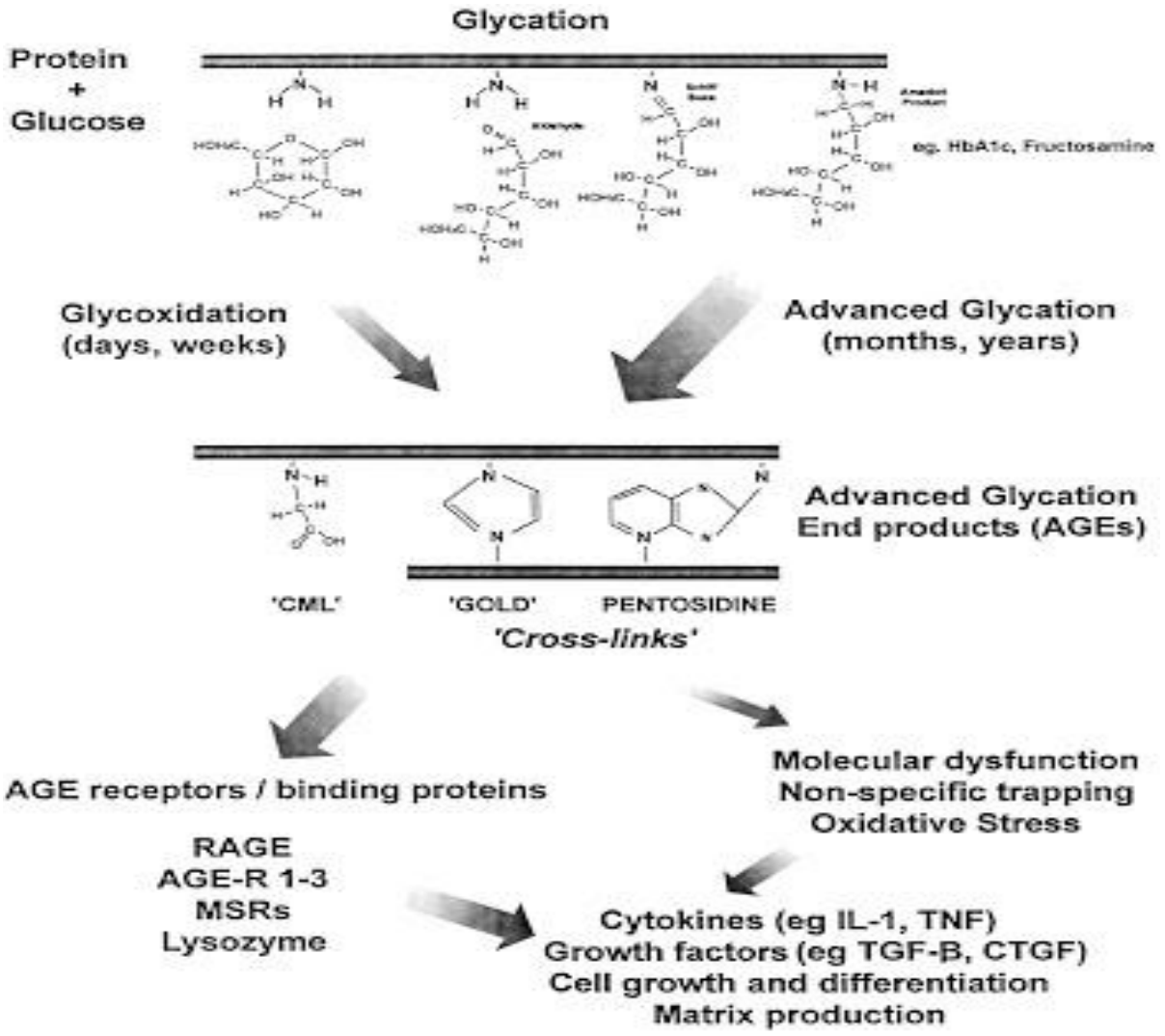


FIGURE 1: MECHANISM OF FORMATION OF ADVANCED GLYCATION END PRODUCTS AND DOWNSTREAM PATHWAYS IN DbCM

HEXOSAMINES AND DBCM

Chronic hyperglycemia can lead to increased flux of glucose into the alternate metabolic pathway known as hexosamine pathway that is implicated in many adverse consequences of diabetes. Increased glucose metabolism in the hexosamine pathway is associated with disruption of normal cardiomyocyte

calcium flux linked to reduced sequestration of calcium in the sarcoplasmic reticulum. This results in reduction in myocardial performance and impaired diastolic relaxation, a possible mechanism for DbCM.

SORBITOL AND DIASTOLIC DYSFUNCTION

Polyol pathway is also activated by chronic hyperglycemia. Sorbitol is produced from glucose by the action of the enzyme aldose reductase in the presence of nicotinic acid adenine dinucleotide phosphate (NADPH) that is oxidized to NADP+. NADPH is a co-factor essential for regeneration of reduced glutathione, an important scavenger of ROS in the body, and increased utilization of NADPH in the polyol pathway disturbs the redox balance of cells. The consequent increase in oxidative stress can lead on to DNA damage and cardiomyocyte apoptosis. Sorbitol can also glycate proteins that results in

formation of AGEs, which are mediators of tissue injury in diabetes .

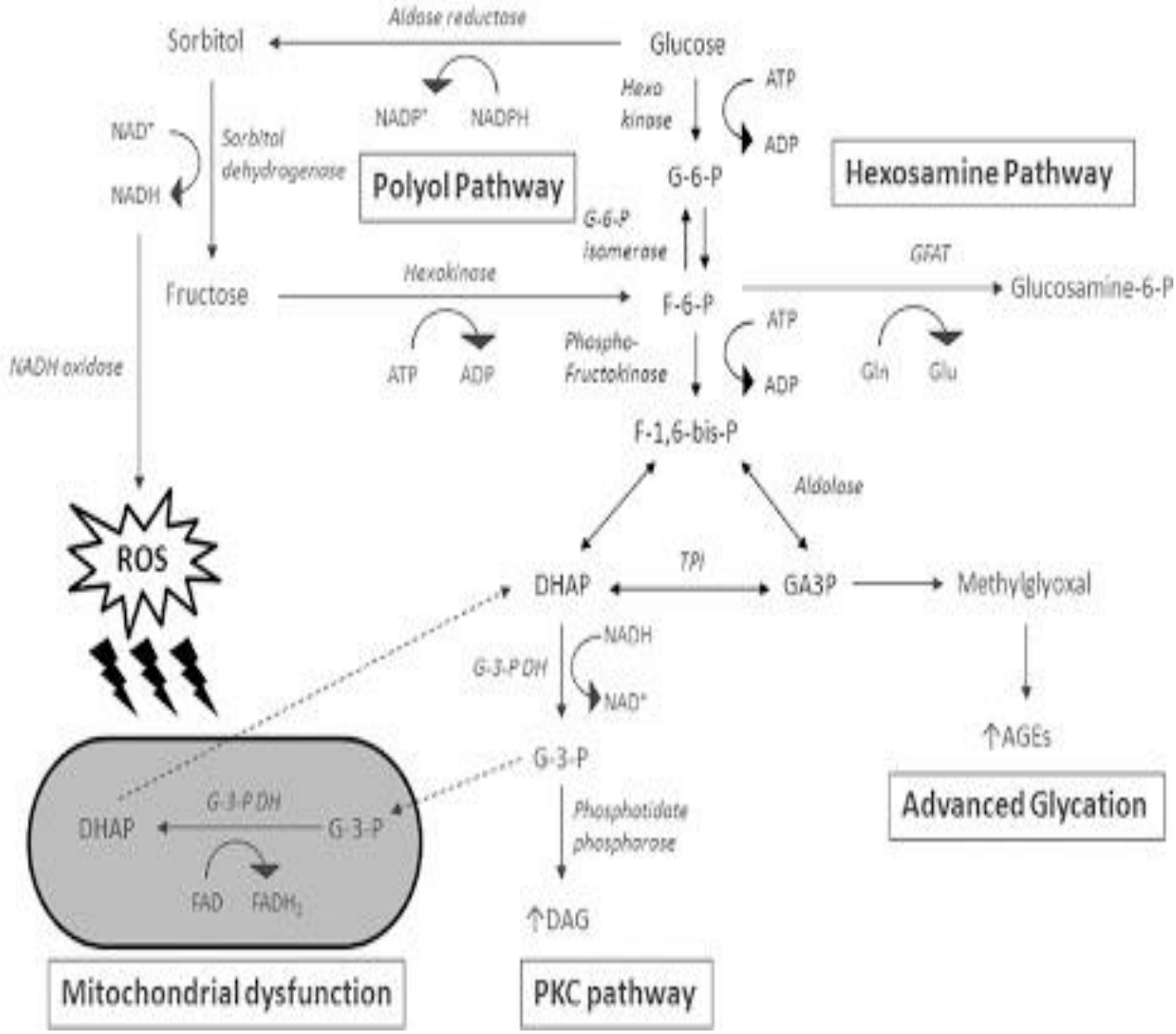


FIGURE 2: SHUNTING OF GLUCOSE INTO HEXOSAMINE AND POLYOL PATHWAY. FORMATION OF AGEs, PKC ACTIVATION. ROS FORMATION AND MITOCHONDRIAL DYSFUNCTION

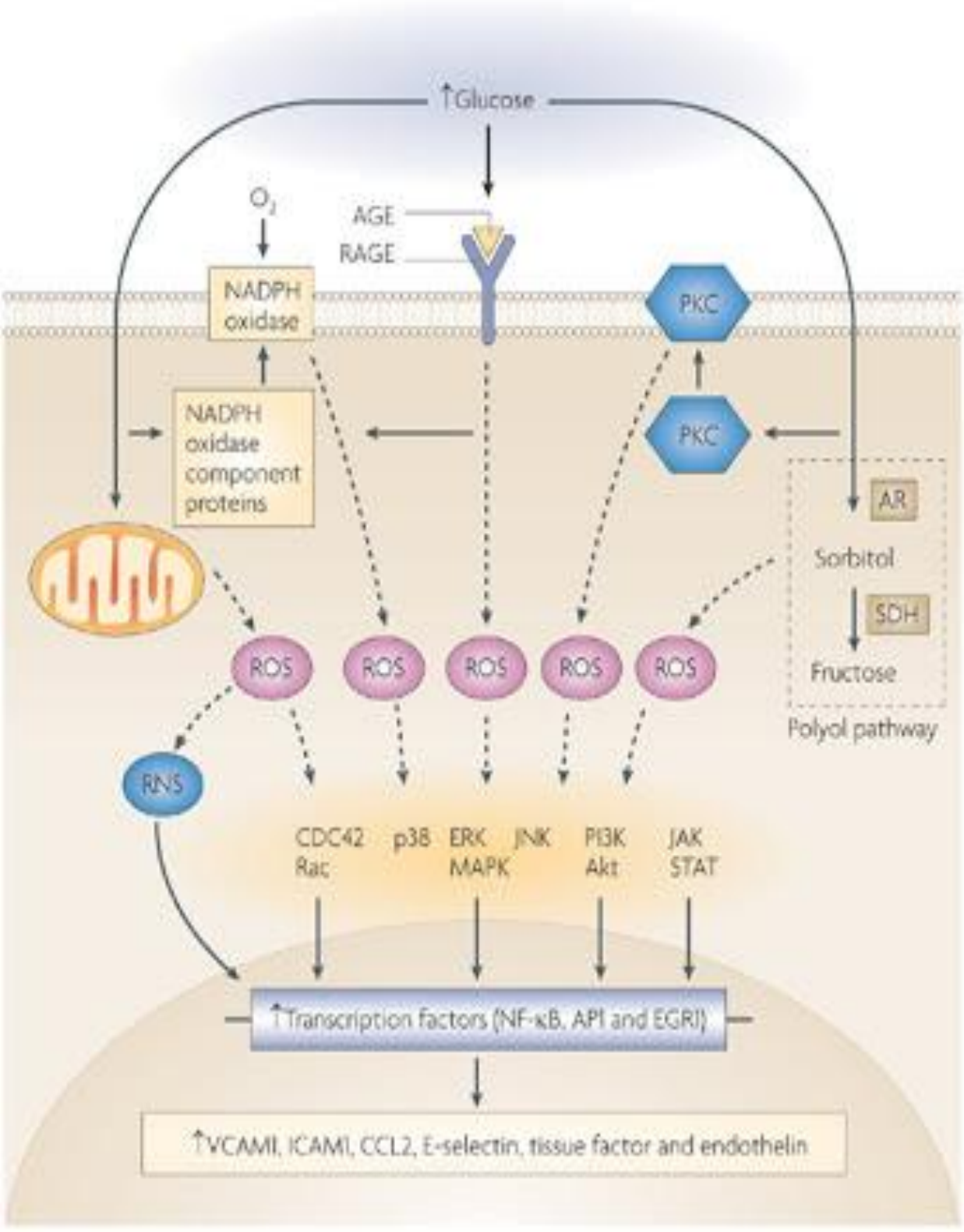


FIGURE 3: FINAL COMMON PATHWAY – NFKB ACTIVATION AND INCREASED TRANSCRIPTION

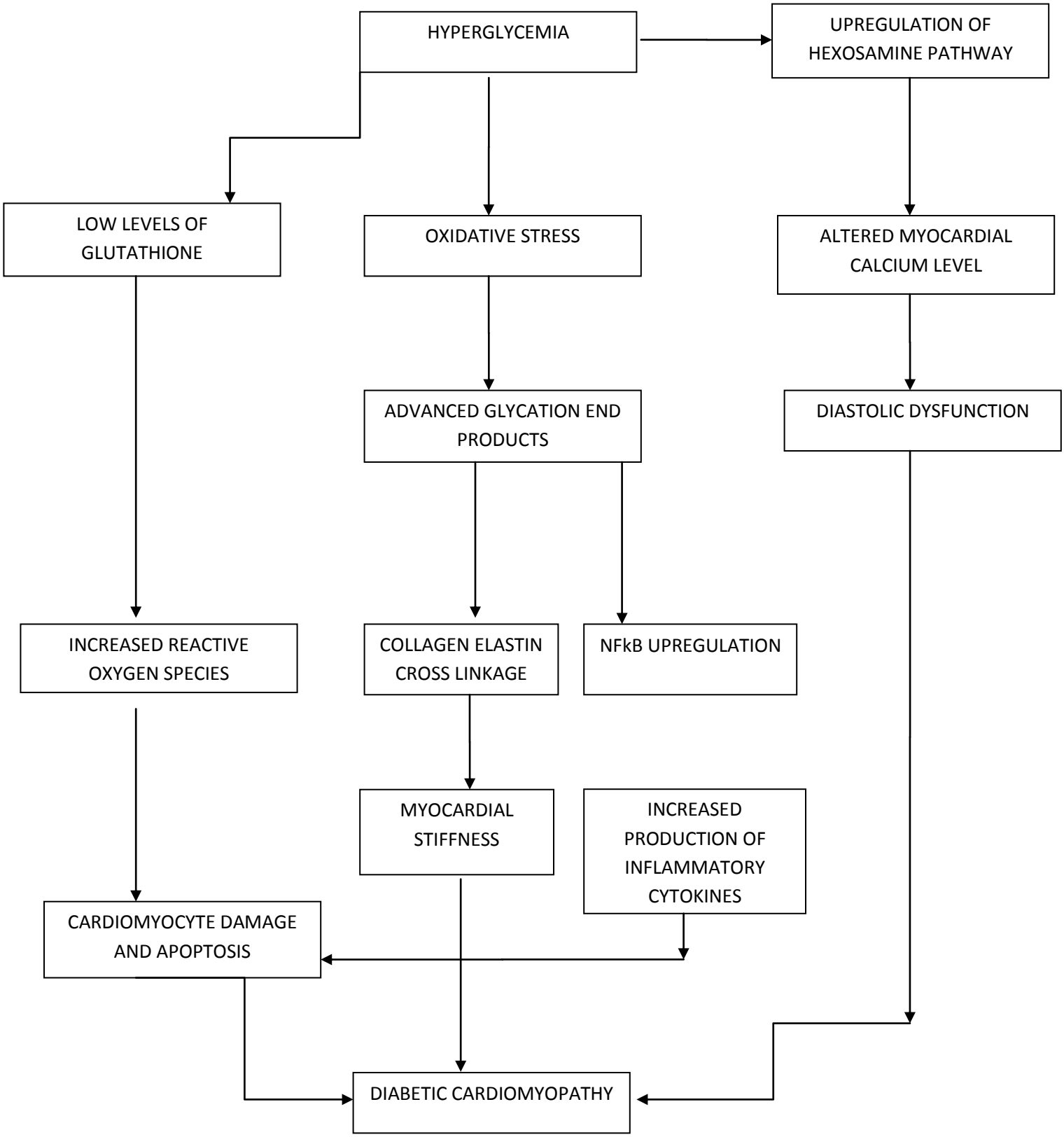


FIGURE 4: PROPOSED MECHANISM OF DIABETIC CARDIOMYOPATHY DEVELOPMENT FROM HYPERGLYCEMIA

LIPID METABOLISM AND THE MYOCARDIUM

Increase in strain of cellular oxidation in diabetes leads to lipid accumulation in tissues like heart, skeletal muscle, liver. This leads to more deposition of lipids in myocardium also termed as **Cardiac steatosis**, which is an important reason for DbCM. Hyperinsulinemia, hyperglycemia, increased blood levels of free fatty acids (FFA) in diabetes lead to cardiac steatosis. Studies have shown the presence of varying degrees of cardiac steatosis in patients with diabetes, impaired glucose tolerance and obesity. Decrease in glucose oxidation and increased use of fatty acid for metabolism represents the characteristic cardiac energetics modification in type 2 diabetes. Increased levels of plasma free fatty acid in patients with diabetes, lead to excessive uptake of FFA by cardio myocytes leading on to triglyceride deposition. This exceeds the normal capacity of mitochondrial oxidative potential and leads on to a lipotoxic injury of heart. Toxic intermediates like ceramide, derived from non-oxidative mechanisms, disrupt normal cellular signaling and cause mitochondrial dysfunction, cellular damage, apoptosis, and eventually leading on to myocardial fibrosis and contractile dysfunction. Intracellular triglyceride accumulation alone is relatively inert and unlikely to be the cause for myocardial injury. Toxic intermediates like ceramide may be the reason for lipid mediated cardiac injury leading to cell death.

Increased FA oxidation in the mitochondria is associated with an increase in generation of Reactive oxygen species that oxidizes cytoplasmic lipids into lipid peroxides. Reactive oxygen species and lipid peroxides in turn cause cellular and mitochondrial damage and uncoupling of mitochondrial oxidative metabolism. Consequently, impaired myocardial generation of energy and reduced cardiac contractility results. Decreased production of energy leads to an altered calcium handling in the mitochondria causing cardiac dysfunction.

Cellular apoptosis that results from lipo toxicity is commonly referred to as **lipo apoptosis**. Mechanisms involved in lipoapoptosis are inflammation, membrane destabilisation, endoplasmic reticulum stress, toxicity due palmitate, diacyl glycerol (DAG) and ceramide. Structural damage and myocardial fibrosis are the results of lipoapoptosis that compromise the cardiac function. Elevated levels of plasma FFA also induce cellular insulin resistance by various mechanisms. These include protein kinase C activation, and activation of peroxisome proliferator-activated receptor-gamma and α (PPAR-γ and PPAR-α).

PKC is a family of several isoenzymes that regulates various complex cellular metabolic pathways, and plays an important role in development of insulin resistance. Similarly, the activation of PPAR-γ and PPAR-α also results

in hyperinsulinemia and insulin resistance, mediated through different complex mechanisms.

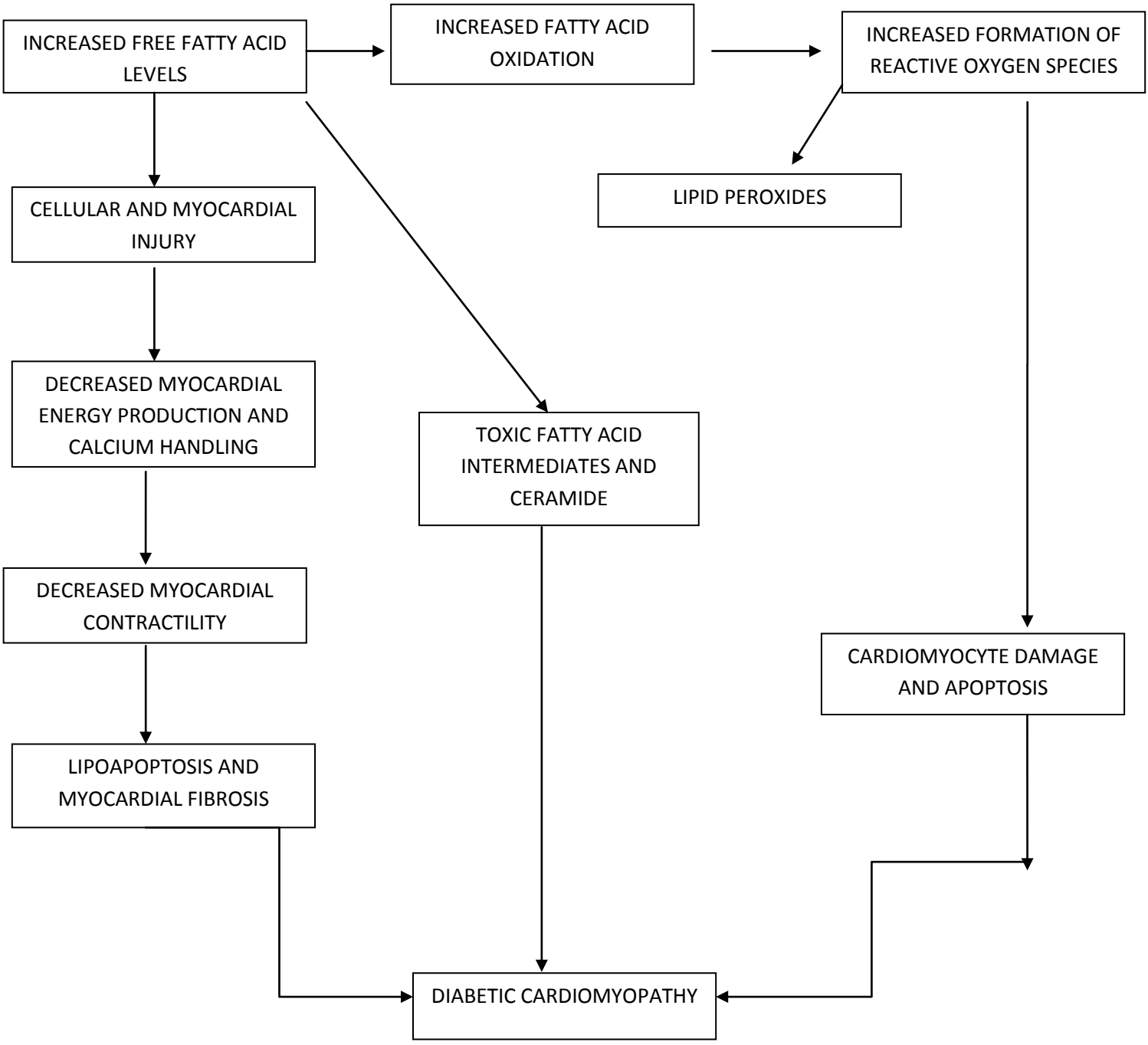


FIGURE 5: PROPOSED MECHANISM OF DIABETIC CARDIOMYOPATHY DEVELOPMENT FROM IMPAIRED LIPID METABOLISM

ROLE OF HYPERINSULINEMIA AND INSULIN RESISTANCE

Hyperinsulinemia and insulin resistance are the characteristic pathological abnormalities in T2DM and prediabetic states. Hyperinsulinemia results in cardiomyocyte hypertrophy by various mechanisms. Brain natriuretic peptide (BNP), a biomolecule which the ventricles release in response to stretch is increased in patients with heart failure. BNP is also an important molecular marker of cardiac hypertrophy. *BNP* gene expression was found to be significantly higher in animal models with hyperinsulinemia and insulin resistance. Increase in left ventricular mass and left ventricular hypertrophy is found in these animal models. Recently, BNP has emerged as a useful biomarker for screening subclinical ventricular diastolic dysfunction in patients with uncontrolled diabetes.

Hypertrophy of cardiac myocytes in diabetes was found to be regulated at the transcriptional level. Various genetic and epigenetic alterations resulting from hyperinsulinemia, leads on to activation of multiple transcription factors that modulate cellular and extracellular protein expression. Activation of such transcription factors have been shown to result in cardiomyocyte hypertrophy and deposition of extracellular matrix proteins causing focal cardiac fibrosis in diabetes.

CONTRIBUTION FROM MICROVASCULAR ISCHEMIA

The pathological hallmark of diabetes-related vascular complications is damage to the microvasculature throughout the body. Classical examples of microvascular complications are diabetic retinopathy, nephropathy and neuropathy. Hyperglycemia confounded by other factors such as hypertension, lipid abnormalities and smoking impose oxidative stress on the vascular endothelium that leads on to endothelial dysfunction, the earliest abnormality in patients with diabetes. Nitric oxide (an endothelium-derived vasodilatory factor) production in relation to vascular stretch is also reduced due to down regulation of endothelial nitric oxide synthase enzyme in diabetes. Hyaline change of the medial layers of arterioles and reduction of capillary length density throughout the cardiac circulation is seen in diabetics. The microvascular diasease resulting in reduced blood supply affects the vasa vasorum in diabetes, damages the small and medium arterioles of the diabetic heart. Capillary basement membrane, microaneurysms of small vessels, perivascular fibrosis and interstitial changes are the other vascular abnormalities causing cardiac microvascular ischemia in diabetes. Ischemia contributes to myocardial stiffness, fibrosis and cardiac dysfunction in DbCM.

ROLE OF RENIN ANGIOTENSIN SYSTEM

Recent evidence from animal and human experiments have demonstrated significant role of RAS in diabetes induced cardiac dysfunction. The major components of RAS, *i.e.*, renin, angiotensinogen, angiotensin converting enzyme (ACE), angiotensin II(AGT II) receptors are expressed in the heart. Intra cardiac RAS is activated by hyperglycemia and has varying effects on the myocardium. When compared to non diabetic, patients with diabetes were found to express higher levels of intracellular AGT II.

Cytoplasmic AGT II has been shown to induce cell growth in animal models. AGT II may cause myocyte hypertrophy and fibroblast proliferation. In addition to above effects inflammation, oxidative stress and aldosterone, may also contribute to the deleterious effects of AGT II on the heart producing myocardial damage in diabetes.

CARDIAC AUTONOMIC NEUROPATHY AND DBCM

Cardiac autonomic neuropathy (CAN) complicates long standing diabetes that causes abnormal vascular hemodynamics and control of heart rate. The prevalence of varying degrees of CAN may be as high as 60% in individuals with prolonged history of diabetes. CAN affects blood flow in the coronary vasculature and also alters the contractile function of the myocardium. Patients with CAN were found to have a reduction in the vascular elasticity and

an increased systemic vascular resistance due to abnormal sympathetictone. Reduction in myocardial perfusion reserve also was shown by other investigators. This may partly explain the ventricular dysfunction associated with diabetic CAN. Correlation between the severity of CAN and the prevalence of diastolic dysfunction also have been demonstrated. Alterations in the myocardial contractility responses in relation to stress is seen in patients with diabetic CAN, and even in those with normal ventricular function at rest, exerciseinduced myocardial dysfunction have been demonstrated.

STRUCTURAL AND FUNCTIONAL ALTERATIONS IN DBCM

Significant functional and anatomical changes occurs in diabetic cardiomyopathy. Changes like formation of Advanced Glycation End products, reactive oxygen species, microvascular ischemia of vaso vasorum,imapaired compliance cause myocardial contractile dysfunction. Later on changes like perivascular fibrosis, interstitial fibrosis and myocardial hypertrophy occur. Earliest change in DbCM is an altered diastolic function which is followed by a systolic dysfunction at later stages. Diastolic dysfunction is characterized by impaired relaxation of the ventricular musculature during diastole with a resultant increase in left ventricular end diastolic filling pressure and diastolic heart failure. When systolic dysfunction supervenes the cardiac output diminishes progressively with the severityof disease.

CARDIAC REMODELING IN DBCM

DbCM results from the structural, functional and regulatory remodeling of the heart induced by diabetes mellitus. Different stages of remodeling has been proposed: the **early stage, middle stage and the late stage**.

The **early stage** is usually asymptomatic with myocardial changes mostly at the molecular level. Ventricular hypertrophy and diastolic dysfunction with a normal LVEF are the only gross abnormalities demonstrable at this stage.

The **middle stage** of DbCM is characterized by progressive cardiomyocyte hypertrophy and myocyte fibrosis. Increasing ventricular wall thickness and muscle mass at this stage result in worsening of the diastolic dysfunction and the development of mild systolic dysfunction.

Further progression of the disease in the **late stage** is associated with abnormalities like CAN, microvascular/macrovascular CAD, hypertension, and overt diastolic and systolic dysfunction.

INTERACTION WITH COEXISTENT HYPERTENSION AND CAD

The diagnosis of DbCM is made only when co existent coronary artery heart disease and hypertension are excluded. However, when both hypertension and CAD complicate the already existing diastolic dysfunction in a diabetic patient there is rapidity in progression to advanced stages of heart failure. Diagnostic evaluation may be complicated by clinically silent coronary artery disease.

Coexisting hypertension was found in upto 35% of Type1 Diabetes Mellitus and upto 75% with type 2 diabetes mellitus. Cardiac dysfunction was shown to be worsened by hypertension in animal models of DbCM. Also the presence of hypertension has been found to be independently associated with diastolic dysfunction in diabetic patients. Similarly, myocardial structural abnormalities were found to occur in diabetic patients with CAD.

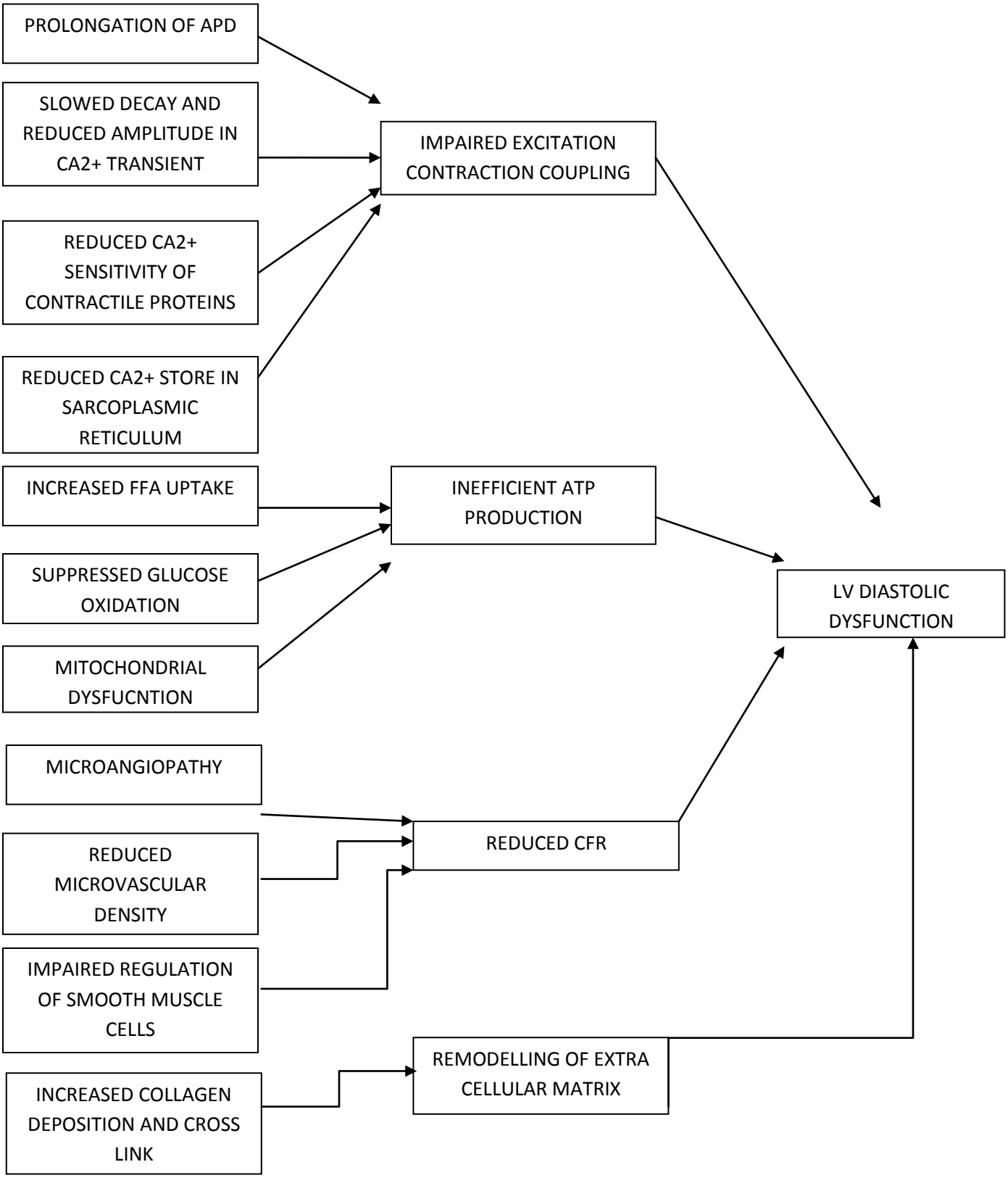


FIGURE 6: PROPOSED MECHANISM OF DEVELOPMENT LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

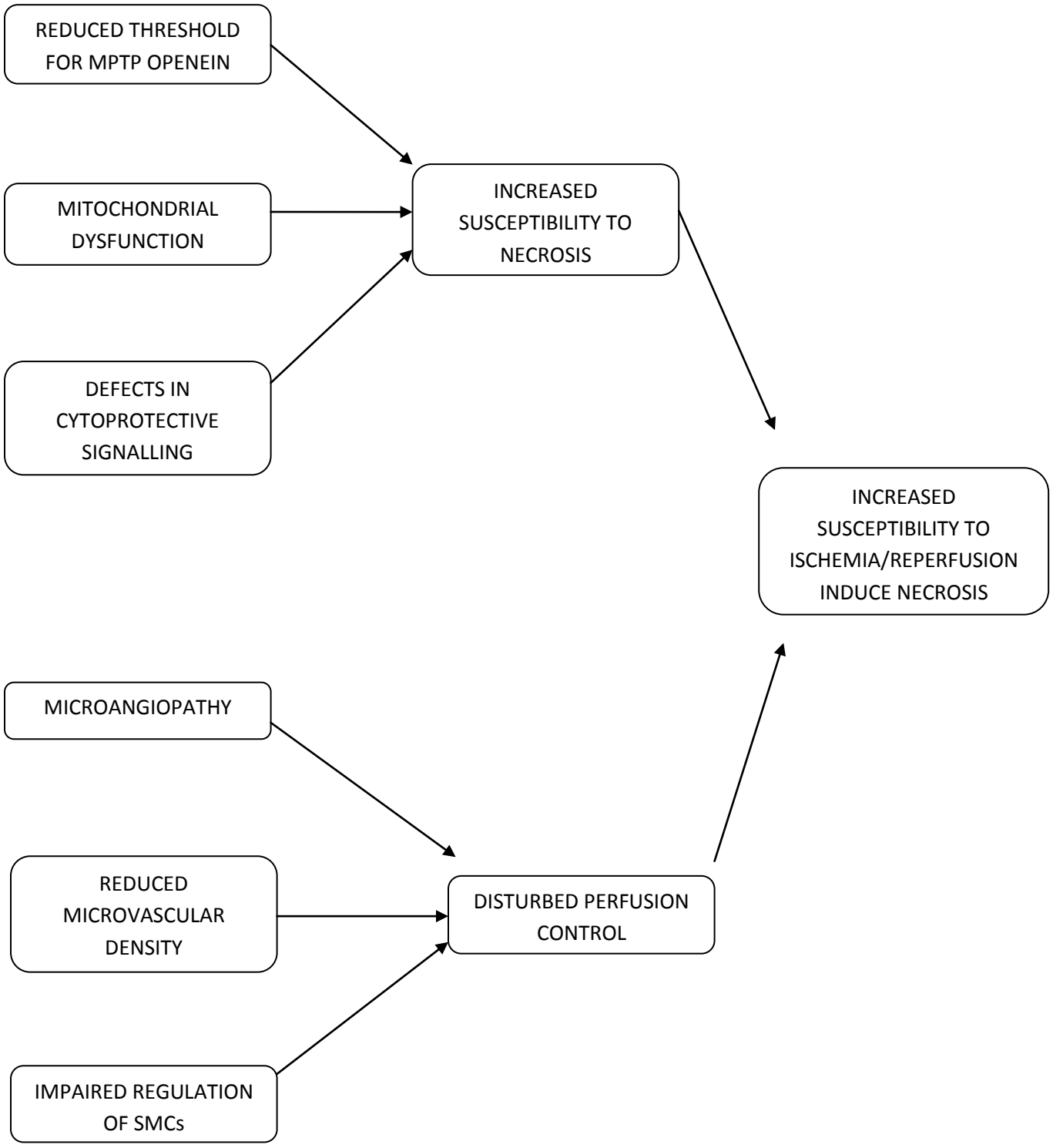


FIGURE 7: PROPOSED MECHANISM OF DEVELOPMENT OF MICRO VASCULAR ISCHEMIA

ASSESSMENT OF DIASTOLIC FUNCTION

Assessment of diastolic function should be an integral part of an evaluation of cardiac function because about 50% of patients with heart failure have preserved LVEF. Assessment of diastolic function requires an understanding of diastology and various means to evaluate diastolic function. Currently, echocardiography is the best non invasive way to evaluate diastolic function and to estimate filling pressures. M-mode, two-dimensional, and Doppler (blood flow, tissue, and color) echocardiography are all helpful in evaluating diastolic function. Recently, the ASE and the European Association of Echocardiography (EAE) published a guideline for assessment of diastolic function by echocardiography. The following steps will ensure comprehensive assessment of diastolic function and the identification of heart failure related to diastolic dysfunction:

1. Look for M-mode and two-dimensional echocardiographic evidence of diastolic dysfunction. Abnormal myocardial relaxation, an integral part of diastolic dysfunction, decreases the slope (in M-mode) and mitral annulus motion of early diastolic filling and increases LA size. LV wall thicknesses is usually but not necessarily increased.
2. Mitral inflow velocities reflect the transmitral pressure gradient, which is

usually characteristic of various stages of diastolic dysfunction. Assessment of ventricular compliance is possible from the configuration (velocities and flow duration) of mitral inflow velocities. Pulmonary vein flow velocities are also helpful.

3 Myocardial relaxation by TDI can be evaluated. Mitral annulus velocity (e′) during early diastole correlates reasonably well with the status of myocardial relaxation (tau).

4 Mitral inflow velocities (E and A), e′, propagation velocity at inflow of mitral valve, and their combination can estimate LV filling pressure in diastole with exercise and at rest.

5 These steps allow diagnosis of diastolic heart failure and separation of myocardial diastolic heart failure from pericardial diastolic heart failure

LV diastolic filling consists of a series of events that are affected by numerous factors, including myocardial relaxation, compliance, cardiac rhythm, and pericardial compliance. Normal diastolic function ensures adequate filling of the ventricles during rest and exercise without an abnormal increase in diastolic pressure or pulmonary venous congestion. Early rapid diastolic filling occurs when Left Ventricular pressure falls below corresponding atrial pressure, and mitral valve opens. The principal determinant of early diastolic filling is the

elastic recoil caused by normal relaxation of the left ventricle. Normally, 75% to 80% of LV filling occurs during this phase. During early diastolic filling, LV pressure continues to decrease until completion of myocardial relaxation (normally about 100 milliseconds) before rising after reaching minimal pressure; this loss of positive driving force results in the deceleration of mitral inflow. Later, atrial contraction produces a positive pressure gradient for transmitral inflow, accounting for 20% to 25% of LV filling in normal subjects.

The proportion of LV filling during the early and late diastolic phases depends on elastic recoil (suction), rate of myocardial relaxation, chamber compliance, LA pressure, and heart rate. The LV filling pattern is the result of the transmitral pressure gradient produced by these various factors.

The transmitral pressure gradient or the relationship between LA and LV pressures is accurately reflected by mitral inflow Doppler velocities. Diastolic filling is usually classified initially on the basis of the peak mitral flow velocity of the early rapid filling wave (E), peak velocity of the late filling wave caused by atrial contraction (A), E/A ratio, and deceleration time (DT), which is the time interval for the peak E velocity to reach zero baseline .

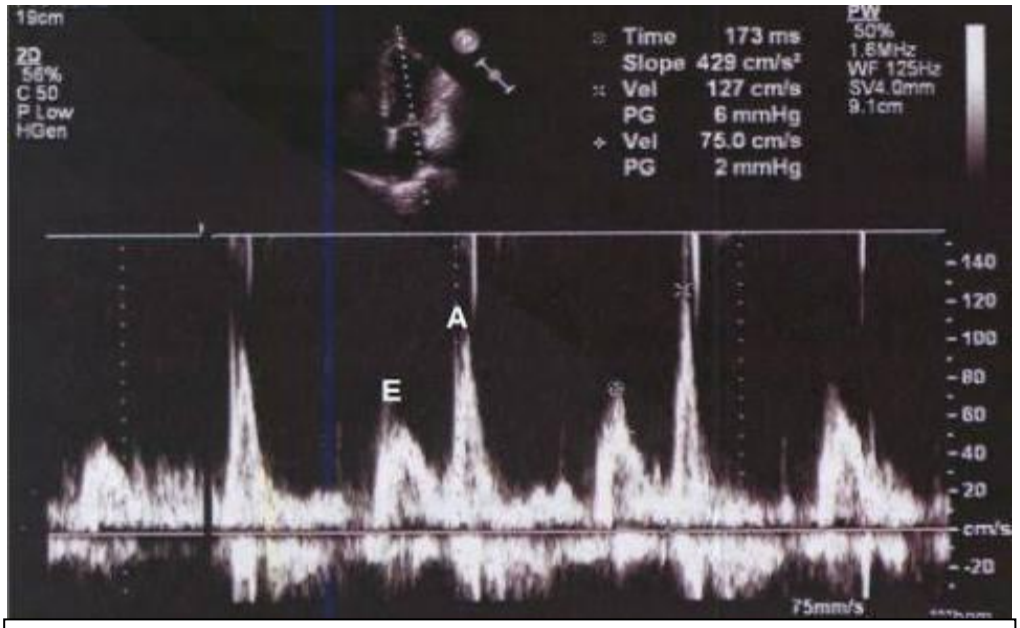


FIGURE 8: ECHO CARDIO GRAPHIC WINDOW TO SHOW THE E AND A WAVE

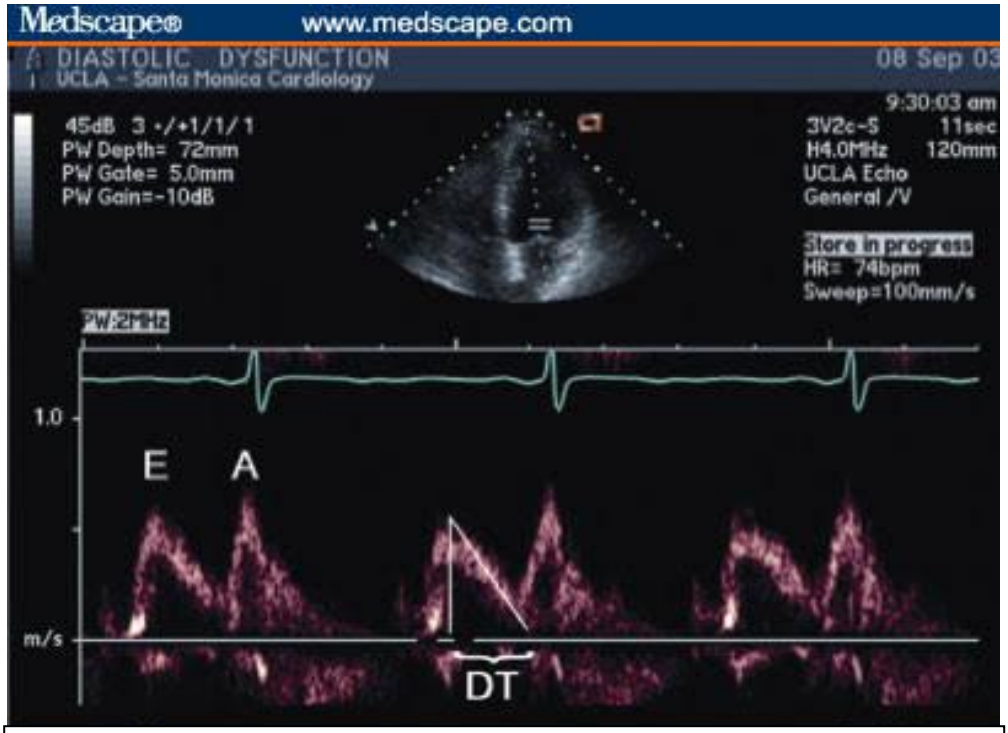


FIGURE 9: ECHO CARDIO GRAPHIC WINDOW TO SHOW THE DECERATION TIME

With myocardial relaxation, the LV cavity elongates, expands laterally, and rotates. The longitudinal motion of the mitral annulus has been shown to correlate with the rate of myocardial relaxation. The velocity of the mitral annulus can be recorded by TDI, which has become an essential part of evaluation of diastolic function by echocardiography. Radial and circumferential function can also be assessed with speckle tracking strain imaging.

Comprehensive assessment of diastolic filling and estimation of filling pressures by echocardiography require TDI, pulmonary vein Doppler, hepatic vein Doppler, and color M-mode of mitral inflow for propagation velocity—sometimes with an alteration in a loading condition .The Valsalva maneuver is used most frequently to decrease venous return by increasing intrathoracic pressure

Grading of Diastolic Dysfunction (or Diastolic Filling Pattern)

The grading of the diastolic filling pattern (or diastolic dysfunction) is based on several parameters. In many cardiac disease , the initial abnormality in diastole is impaired relaxation. With further progression of disease and a mild to moderate increase in LA pressure, the dysfunction shows a normal filling pattern (pseudonormalized). With further decreased Left Ventricular compliance and increased Left

Atrial pressure, diastolic filling becomes restrictive. Most patients with restrictive filling are symptomatic and have a poor prognosis unless the restrictive filling can be reversed by treatment. However, restrictive filling may be irreversible and represent the end stage of diastolic heart failure. Therefore, diastolic dysfunction can be graded according to the diastolic filling pattern.

A grade 1 diastolic filling pattern usually implies a normal filling pressure despite a background of impaired myocardial relaxation. However, in patients with a marked relaxation abnormality, as in HCM, the filling pressure can still be elevated with grade 1 mitral inflow velocity pattern (E/A ratio <1.0 and DT >240 milliseconds).

NORMAL DIASTOLIC FILLING PATTERN

In healthy subjects, the Left Ventricular recoil elasticity is vigorous because of normally relaxing myocardium; therefore, most filling is completed during early diastole. Thus, the E/A ratio is usually 1.5 or higher, DT is 160 to 240 milliseconds (septal), e′ is 10 cm/sec or higher, E/e′ is less than 8, and Vp is 50 cm/sec or higher.

With normal myocardial relaxation, the longitudinal mitral annulus diastolic velocity pattern mirrors that of normal mitral inflow: early diastolic

velocity (e′) is higher than late diastolic velocity (a′). Lateral annulus velocity is always higher (normal, >15 cm/sec) than septal e′. Thus, e′ increases with exercise in healthy subjects so that E/e′ is similar at rest and with exercise (usually <8). With aging, there is a gradual decrease in the rate of myocardial relaxation as well as in elastic recoil, resulting in slower decline of LV pressure, and filling becomes slower, producing a diastolic function pattern similar to grade 1 dysfunction. At roughly the age of 65 years, E velocity approaches A velocity, and in persons older than 70 years, the E/A ratio is usually less than 1.0. The reversal of e′/a′ occurs about 10 to 15 years earlier than that of E/A.

TABLE 2: REFERENCE RANGES FOR DIASTOLIC FUNCTION PARAMETERS BY AGE* QUOTED FROM BRAUNWALD'S HEART DISEASE-9th EDITION

PARAMETER	*Age Groups (yr)*					
	45-49	**50-54**	**55-59**	**60-64**	**65-69**	**≥70**
Mitral inflow						
E, m/sec	0.7 (0.5-0.9)	0.6 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.6 (0.4-0.8)	0.6 (0.4-1.0)
A, m/sec	0.5 (0.3-0.7)	0.5 (0.4-0.8)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.7 (0.4-1.0)	0.8 (0.5-1.1)
E/A	1.3 (1.0-2.0)	1.2 (0.8-2.0)	1.2 (0.7-1.8)	1.0 (0.7-1.6)	1.00 (0.6-1.50)	0.8 (0.6-1.3)
E/(A-E at A)	1.50 (1.0-2.67)	1.40 (1.0-2.33)	1.29 (0.83-2.25)	1.20 (0.83-2.0)	1.00 (0.75-1.67)	1.00 (0.67-1.60)
DT, msec	208 (180-258)	217 (178-266)	210 (183-187)	222 (180-282)	227 (188-298)	242 (188-320)
A_{dur}, msec	140 (122-170)	147 (130-172)	147 (127-173)	147 (129-172)	150 (122-180)	150 (128-183)
Pulmonary vein flow						
P_S, m/sec	0.60 (0.40-0.80)	0.60 (0.40-0.80)	0.60 (0.40-0.80)	0.60 (0.40-0.80)	0.60 (0.50-0.80)	0.60 (0.40-0.80)
P_D, m/sec	0.40 (0.30-0.60)	0.40 (0.30-0.60)	0.40 (0.30-0.60)	0.40 (0.30-0.60)	0.40 (0.30-0.60)	0.40 (0.30-0.60)
P_S/P_D	1.25 (0.86-2.00)	1.40 (1.00-2.00)	1.40 (1.00-2.00)	1.50 (1.00-2.25)	1.60 (1.00-2.50)	1.67 (1.00-2.50)
$PVAR_{dur}$, msec	118 (100-140)	122 (103-142)	123 (105-157)	123 (103-160)	127 (110-152)	130 (112-170)
$PVAR_{dur} - A_{dur}$,	−25.0 (−53.3-	−25.0 (−51.7-	−21.6 (−50.0-	−23.3 (−51.7-	−21.7 (−55.0-	−22.3 (−51.7-

PARAMETER	*Age Groups (yr)*					
	45-49	**50-54**	**55-59**	**60-64**	**65-69**	**≥70**
msec	0)	0)	11.7)	13.4)	12.5)	31.6)
TDI, mitral annulus						
Septal						
E'_S, m/sec	0.10 (0.07-0.14)	0.09 (0.06-0.14)	0.09 (0.05-0.12)	0.09 (0.06-0.13)	0.08 (0.05-0.11)	0.07 (0.05-0.11)
A'_S, m/sec	0.10 (0.07-0.14)	0.10 (0.08-0.14)	0.11 (0.08-0.15)	0.11 (0.09-0.15)	0.11 (0.09-0.15)	0.11 (0.09-0.15)
E/E'_S	6.67 (4.62-11.25)	7.00 (4.55-11.67)	7.78 (4.62-13.33)	7.64 (5.0-12.0)	8.57 (5.45-13.33)	8.57 (4.55-16.67)
Lateral						
E'_L, m/sec	0.13 (0.09-0.17)	0.12 (0.08-0.16)	0.11 (0.07-0.15)	0.10 (0.07-0.15)	0.09 (0.07-0.12)	0.08 (0.05-0.11)
A'_L, m/sec	0.11 (0.07-0.16)	0.11 (0.07-0.15)	0.11 (0.08-0.16)	0.12 (0.08-0.17)	0.12 (0.09-0.16)	0.12 (0.08-0.18)
E/E'_L	5.38 (3.75-7.78)	5.45 (3.75-8.89)	6.0 (3.85-10.0)	6.67 (4.62-8.89)	7.0 (4.17-11.25)	7.78 (5.0-14.0)
Valsalva maneuver						
VS E/A	1.00 (0.60-1.33)	1.00 (0.57-1.33)	0.80 (0.44-1.25)	0.71 (0.43-1.20)	0.60 (0.40-1.00)	0.57 (0.30-1.00)
VS E/(A-E at A)	1.33 (0.80-2.50)	1.25 (0.67-3.00)	1.00 (0.60-2.50)	1.00 (0.50-2.00)	0.75 (0.50-1.67)	0.71 (0.33-1.50)
ΔE/A	0.37 (0-1.0)	0.40 (−0.05-1.0)	0.37 (0-1.0)	0.36 (−0.04-0.80)	0.31 (0-0.64)	0.29 (−0.04-0.70)
ΔE/(A-E at A)	0.0 (−1.3-1.0)	0.07 (−1.33-0.75)	0.17 (−1.0-0.77)	0.13 (−0.83-0.75)	0.17 (−0.58-0.57)	0.17 (−0.75-0.63)
Index of myocardial performance						
LIMP	0.30 (0.10-0.50)	0.30 (0.20-0.60)	0.30 (0.20-0.60)	0.40 (0.20-0.60)	0.40 (0.20-0.60)	0.40 (0.20-0.60)

Modified from Munagala VK, Jacobsen SJ, Mahoney DW, et al: Association of newer diastolic function parameters with age in healthy subjects: A population-based study. J Am Soc Echocardiogr 16:1049, 2003.

A = late diastolic mitral flow velocity; A_{dur} = duration of late mitral flow; A'_L = lateral mitral annulus velocity with atrial contraction; A'_S = late diastolic lateral annular velocity; DT = deceleration time of early diastolic mitral flow; E = early diastolic mitral flow velocity; E'_L = early diastolic lateral annular velocity; E'_s = early diastolic septal annular velocity; ΔE/A =

change in E/A with Valsalva; ΔE/A-E = change in E/A-E at A with Valsalva; LIMP = left ventricular index of myocardial performance; P_D = pulmonary vein diastolic flow velocity; P_S = pulmonary vein systolic flow velocity; $PVAR_{dur}$ = duration of pulmonary vein atrial flow reversal; TDI = tissue Doppler imaging; VS = peak Valsalva.

* Data are median (5th and 95th percentiles).

Grade 1 Diastolic Dysfunction or Mild Diastolic Dysfunction

An early abnormality of diastolic filling is abnormal myocardial relaxation. Typical cardiac conditions that produce abnormal relaxation are LV hypertrophy, HCM, and myocardial ischemia or infarction as well as aging. During this stage of diastolic dysfunction, an adequate diastolic filling period is critical to maintain normal filling without increasing filling pressure. As long as LA pressure remains normal, the pressure crossover between the left ventricle and left atrium occurs late, and the early transmitral pressure gradient is decreased. Consequently, the isovolumic relaxation time (IVRT) is prolonged. Mitral E velocity is decreased and A velocity is increased, producing an E/A ratio of less than 1, with prolonged DT. Pulmonary vein diastolic forward flow velocity parallels mitral E velocity and is also decreased with compensatory increased flow in systole. The duration and velocity of pulmonary vein atrial flow reversal are usually

normal, but they may be increased if atrial compliance decreases or LV end-diastolic pressure (LVEDP) is high. The e′ and mitral flow propagation velocity are reduced, usually less than 7 cm/sec (at the septal annulus) and less than 50 cm/sec, respectively. In most patients with the described mitral inflow velocity pattern, diastolic filling pressure is not increased and the E/e′ ratio is 8 or higher. In a subgroup of patients, E/e′ ratio is higher than 15, with an E/A ratio less than 1. This pattern has been designated grade 1a diastolic dysfunction to emphasize that filling pressure is increased while there is a typical grade 1 mitral inflow velocity pattern.

Grade 2 Diastolic Dysfunction or Moderate Diastolic Dysfunction

This stage is otherwise referred to as the pseudonormalized mitral flow filling pattern, and it indicates a moderate stage of diastolic dysfunction. With worsening diastolic function, the mitral inflow pattern resembles a normal diastolic filling pattern, i.e, an E/A ratio of 1 to 1.5 and normal Deceleration Time of 160 to 240 milliseconds. This is due to a moderately increased LA pressure over and above the

delayed myocardial relaxation. There are several ways to differentiate the pseudonormal pattern from a true normal pattern in patients with grade 2 dysfunction:

1 The e′ is usually less than 7 because of impaired myocardial relaxation.

2 Frequently, there is mid-diastolic flow because the myocardial relaxation is markedly impaired.

3 A decrease in preload, by asking the patient to sit or to perform the Valsalva maneuver, the underlying impaired relaxation of the left ventricle may be unmasked, decreasing the E/A ratio by more than 0.5. An increase in A velocity with the Valsalva maneuver, is a positive sign.

4 Normal-appearing mitral inflow may occur in the setting of systolic dysfunction or increased wall thickness because impaired relaxation is expected as the baseline diastolic function without increased filling pressure in those situations, and a normal E/A ratio suggests that increased LA pressure is masking the abnormal relaxation.

5 Colour M-mode of mitral inflow shows decreased rate of flow propagation (<45 cm/sec).Although this is a less reliable in patients with normal LV cavity size.

Grade 3-4 Diastolic Dysfunction or Severe Diastolic Dysfunction

Severe diastolic dysfunction is termed as restrictive filling or restrictive physiology and can be seen in any cardiac abnormality or in a combination of abnormalities that results in decreased Left Ventricular compliance and increased Left atrial pressure.

Therefore, the characteristics of restrictive filling with severe diastolic dysfunction include

a)Increased E velocity,

b)Decreased A velocity (markedly less than E)

c)E/A ratio > 2, and

d)Shortened Deceleration Time of <160 milliseconds and

e)Iso-Volumetric Relaxation Time <70 milliseconds.

Pulmonary venous systolic forward flow velocity is decreased because of increased Left Atrial pressure and decreased Left Atrial compliance.

Since the myocardial relaxation is impaired in heart with a restrictive filling pattern, mitral annulus velocity (Ea) is decreased (<7 cm/sec). The E/e′ ratio is usually more than 15. In case of normal systolic function and small left ventricular cavity the flow propagation velocity may not be reduced. The Valsalva maneuver may reverse back the restrictive filling pattern from grade 3 to a grade 1 to 2 pattern, indicating the reversible high filling pressure (grade 3 diastolic filling). However, if the restrictive filling pattern does not change with the Valsalva maneuver, reversibility cannot be excluded because the Valsalva maneuver may not alone be adequate or filling pressure is very high to be changed by the Valsalva maneuver.

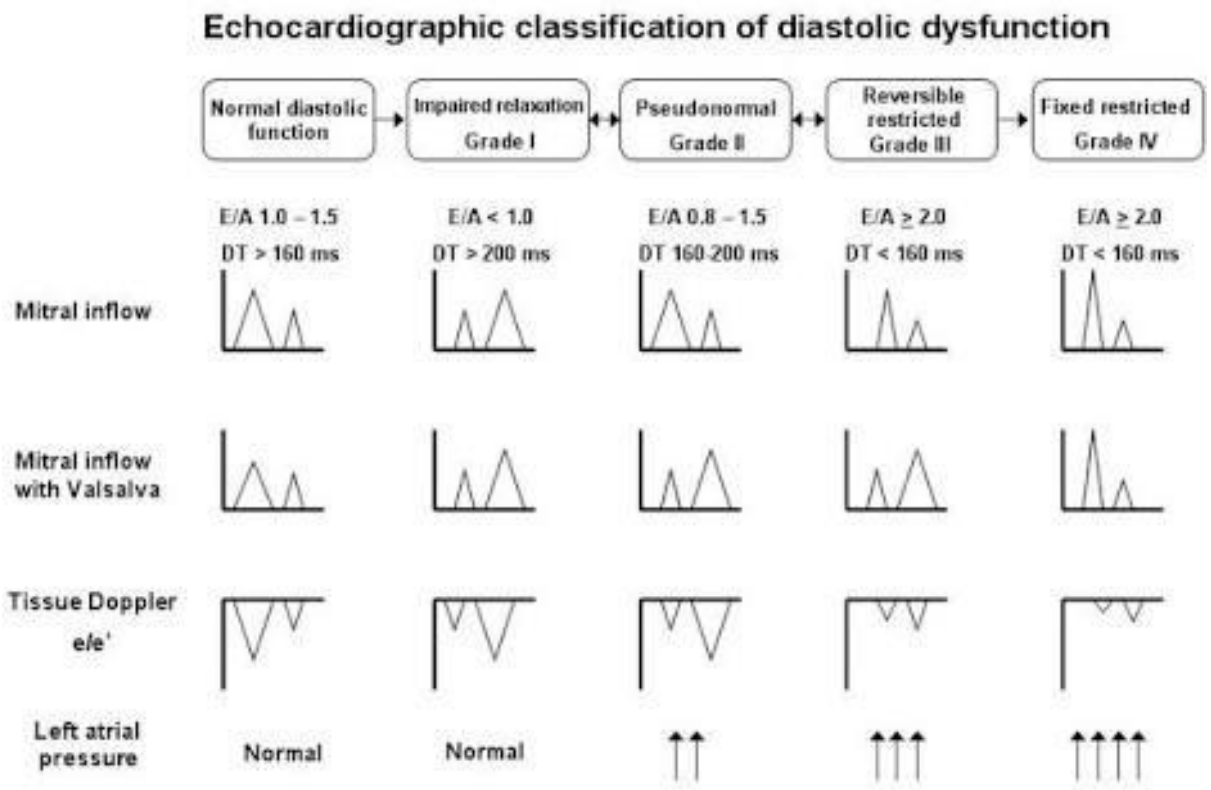


FIGURE 9: ECHO CARDIO GRAPHIC GRADING OF DIASTOLIC DYSFUCNTION

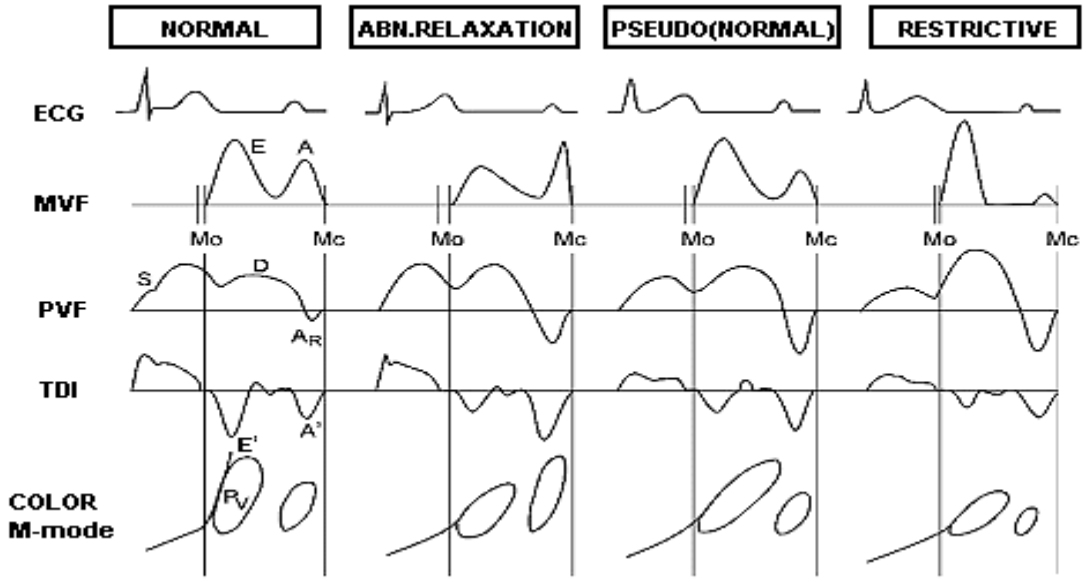


FIGURE 10: ECHO CARDIO GRAPHIC TISSUE DOPPLER IMAGING AND M-MODE FEATURES -VARIOUS STAGES IN DIASTOLIC DYSFUNCTION

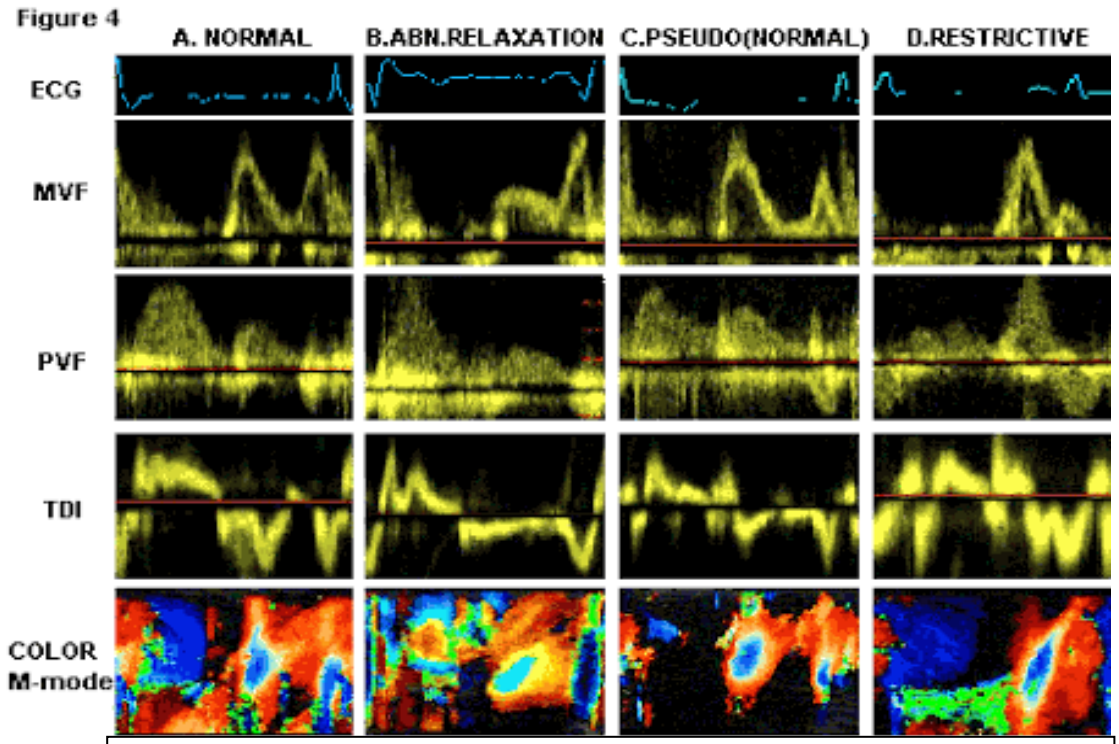


FIGURE 10: ECHO CARDIO GRAPHIC TISSUE DOPPLER IMAGING AND M-MODE FEATURES- VARIOUS STAGES- DIASTOLIC DYSFUNCTION

CLINICAL APPLICATIONS OF DIASTOLIC FUNCTION ASSESSMENT

Assessment of diastolic function echocardiographically has the following clinical applications

1 Estimation of filling pressures with exercise and at rest. In patients with reduced Left Ventricular systolic function i.e., Left Ventricle Ejection Fraction <35%, mitral inflow E/A ratio of 1.5 or more and Deceleration Time of 140 milliseconds or more indicate increased filling pressures.

However, these parameters do not have a good correlation with filling pressure in patients with normal LVEF and diastolic heart failure. For all degrees of LVEF, the parameter E/e′ is the best find out pressures of filling ; pulmonary capillary wedge pressure (PCWP) is 20 mm Hg or more if E/e′ is 15 or higher, and PCWP is normal if E/e′ is less than 8. When E/e′ is 8 or higher but less than 15, duration of pulmonary vein flow, Valsalva maneuver can help estimate PCWP. In an important subset of patients with diastolic dysfunction, at rest Pulmonary Capillary Wedge Pressure is normal and casuses effort dyspnoea because it is increased only on effort. Mitral inflow and annulus velocity can be used to measure pulmonary capillary wedge pressure. Filling pressures do not rise with exertion when the diastolic function is normal. Exertion induced high pressues during filling occurs mainly when the relaxation of myocardium is impaired. In such patients cardiac output increases with associated increase in filling pressure. Because of this, mitral E velocity increases and annulus E velocity does not increase , leading to increased E/e′ ratio. E/e′ correlates well with simultaneously measured PCWP with exercise as well as during resting stage, and a ratio higher than 15 indicates PCWP greater than 20 mm Hg with exercise.

2 Diagnosis of diastolic heart failure, cardiomyopathies, and constrictive pericarditis. Knowledge of the diastolic filling pattern and filling pressures allows the detection of cardiac diseases that are frequently missed or not suspected clinically, especially when the LVEF is normal. Patients with diastolic heart failure and normal LVEF have a large LA volume and evidence of impaired relaxation as well as increased filling pressure. There are several reports that TDI of myocardial relaxation can diagnose various forms of cardiomyopathy (HCM, Fabry disease, and amyloidosis) even before frank phenotypic manifestation.The detection of constrictive pericarditis has been made much easier with the use of echocardiographic diastolic parameters and TDI.

3 Prognosis. Diastolic echocardiographic parameters, E, E/A, DT, E/e′, and LA volume, have been found to be powerful prognostic indicators for various conditions. Even in asymptomatic patients, the presence of diastolic dysfunction portends a poor clinical outcome.

Although diastolic filling is affected by various factors, the direction of its change or progression is predictable in patients with known heart disease. Therefore, assessment of the diastolic filling pattern allows

LV filling pressures and LV compliance and relaxation to be estimated and understood so that optimal treatment strategies can be offered to symptomatic patients with diastolic dysfunction.

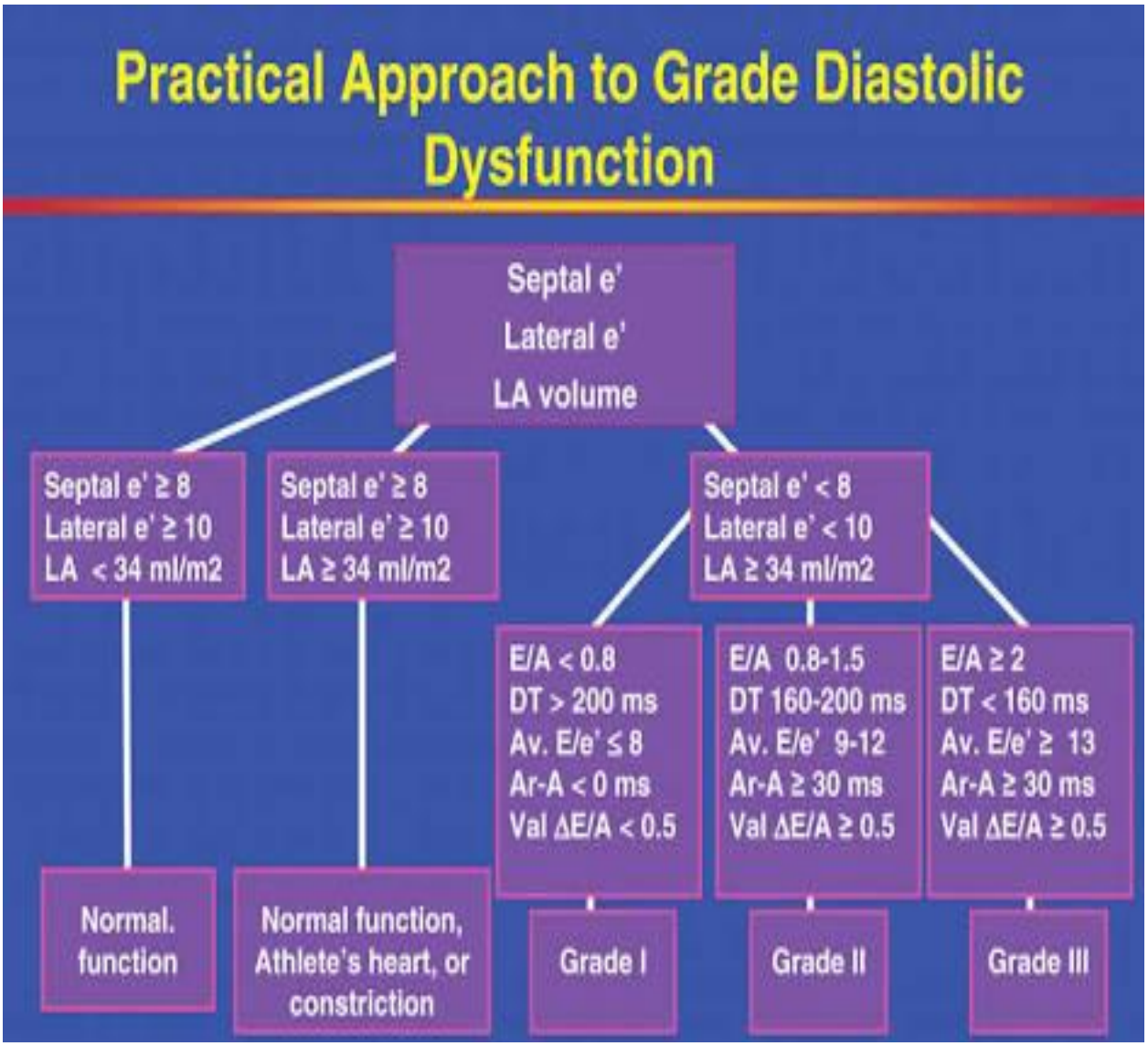


FIGURE 11: A PRACTICAL APPROACH TO CLASSIFICATION OF DIASTOLIC DYSFUNCTION

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted in Tirunelveli medical college hospital over a period of 12 months. Patients were recruited to the study from medical OPD and DIABETIC OPD. A total of about 120 patients were selected and 20 of them were excluded as per exclusion criteria used. The remaining 100 patients were included in the study. Among them 50 patients were diabetics and 50 were non diabetic controls. Informed consent was obtained from all patients. Diastolic dysfunction was measured with standard echocardiographic parameters and the results were computed with corresponding variables of the patients. For the purpose of the study it was hypothesized that the diastolic dysfunction occurring in diabetes would worsen with age of patients, duration of diabetes, hba1c values, obesity indices.

Study Design:

A case control study done prospectively at the tertiary care hospital over 1 year.

Sample size- 100

Inclusion Criteria

1) Asymptomatic type 2 diabetes patients who presented to the medical opd and diabetic opd
2) Healthy individuals between the age of 20-60

Exclusion criteria

1) Patients with evidence of previous coronary artery heart disease- determined by

i)Previous history of angina

ii)Electrocardiographic changes in the form of ST elevation/ST depression/significant q waves

iii)Echo cardiographic evidence of regional wall motion abnormalities

iv)Treadmill testing with positive testing for ischemia

2) Patients with evidence of valvular heart disease as confirmed by standard echocardiographic observation

3) Patients with evidence of systemic hypetersion- determined by

i)History of systemic hypertension

ii)History of drug intake for the hypertension

iii)Evidence of left ventricular hypertrophy with characteristics ST-T changes on the electrocardiogram

4) Patients with poor trans thoracic window

METHODOLOGY

For all the 100 cases admitted ,detailed clinical examination and history regarding diabetes, hypertension, coronary heart disease, valvular heart disease were obtained.

Patients' anthropometric measurements were done. BMI and Waist hip ratio were calculated.

Examination for autonomic dysfunction was done.

Fundus examination for diabetic retinopathy was done.

Investigations like Blood sugar ,ECG ,HBA1C,lipid profile were obtained.

Echocardiographic assessement of both systolic and diastolic dysfunction were done.

DEFINING THE STUDY POPULATION

Diabetes Mellitus was defined as the presence of a fasting plasma glucose level greater than 126 mg/dl or a 2 hour post prandial plasma glucose level greater than 200 mg/dl or an HBA1 C level greater than 6.5%.

Patients with a known history of diabetes with duration of more than 5 years and on treatment were selected as cases for the purpose of studying diastolic dysfunction. Careful history was taken to rule out exclusion criteria if present.

An equal number of healthy individuals with no history of prior diabetes were chosen. Blood sugar levels and HBA1C levels were obtained. Patients' age was between 20-60 yrs and they were selected randomly.

GLYCATED HEMOGLOBIN (HBA1C)

Hb A1c is formed by non-enzymatic glycation of hemoglobin's by plasma glucose. HbA_{1c} is a measure of the beta-N-1-deoxy fructosyl component of hemoglobin. Normal levels of plasma glucose produce a normal amount of glycated hemoglobin. If the average plasma glucose increases, the fraction of glycated hemoglobin increases. Hb A1c is a marker for average plasma glucose levels over the previous 3 months prior to the measurement as this is the half life of RBCs.

In diabetes mellitus, increased glycated hemoglobin, indicates poorer control of blood glucose levels, have been associated with micro vascular complications like cardiovascular disease, nephropathy, and retinopathy.

Huisman and Meyering in 1958 first separated HbA1c from other forms of hemoglobin by using a chromatographic column. Bookchin and Gallop in

1968 first characterized it as a glycoprotein. Samuel Rahbar *et al* described the increase of HbA1c in diabetes in 1969. Bunn and his coworkers described the reactions leading to its formation in 1975.

Blood sugar and HBA1C levels were measured using standard biochemical tests.

DIABETIC RETINOPATHY

Retinopathy is hall mark of microvascular complications of in diabetes mellitus. The exact pathophysiology though remains unclear. Diabetic retinopathy is one of the common causes of preventable blindness. Patients are usually asymptomatic in the early stage of the disease but as the disease progresses there is plethora of symptoms like blurred vision, floating particles in the visual field, visual distortion, decrease in visual acuity progressively. Micro aneurysms, flame shaped haemorrhages, dot-blot haemorrhages, cotton wool spots, retinal edema, hard exudates, venous beading, intra retinal microvascular abnormalities and macular edema are some of the signs in diabetic retinopathy.

- Microaneurysms are the earliest clinical sign of diabetic retinopathy. These are capillary wall outpouching secondary to pericyte loss which are seen as tiny, red dots in the superficial layers of retina

- Flame-shaped hemorrhages are splinter hemorrhages found in the superficial nerve fiber layer
- Dot and blot hemorrhages occur in the deep layers of retina like the inner nuclear and plexiform layers due to rupture of the micro aneurysms. When the are small they look similar to micro anusrysms.
- Cotton-wool spots are whitish spots which are at times surrounded by microaneurysms . These occur due occlusion of precapillary arterioles that leads on to infarction of the nerve fiber layer.
- Retinal edema and hard exudates are due to the breakdown of the blood-retina barrier. This break in blood retina barrier leads to leak in serum lipids and proteins which lead to interstitial edema that subsequently become hard exudates.
- Venous loops and venous beading are signs of progression from non proliferative retinopathy to proliferative retinopathy. Due to increasing retinal ischemia there is poor perfusion of nearby retinal layers leading to venous abnormalities..
- Intraretinal microvascular abnormalities (IRMA) are found in the retina layers with near absent perfusion. Its due to capillary remodeling with no associated proliferative changes.

Diabetic retinopathy is usually classified as non proliferative diabetic retinopathy and proliferative diabetic retinopathy.

Nonproliferative diabetic retinopathy (NPDR)

It may be of 3 stages

- Mild NPDR is presence of at least 1 microaneurysm.
- In Moderate NPDR characterized by microaneurysms, retinal hemorrhages and hard exudates.
- Severe NPDR includes microaneurysms and hemorrhages in all 4 quadrants, venous beading in at least 2 quadrants and intraretinal microvascular (IRMA) abnormalities in at least 1 quadrant.

Proliferative diabetic retinopathy

It includes the following (PDR)

- Neovascularization which is pathognomic of PDR
- Preretinal hemorrhage which are pockets of blood collected between the posterior hyaloids membrane and retina.
- Vitreous Hemorrhage which appear as a diffuse haze or as clumps of blood clots within the gel
- Fibrovascular tissue proliferation
- Traction retinal detachments

- Macular edema

The evaluation of diabetic retinopathy is done clinically using fundus examination after dilation with tropicamide 1 % eye drops. Investigations that are helpful in evaluation are fundus flourescien angiography (FFA), B-scan ultrsonography and optical coherence tomography (OCT).

FIGURE 1: FUNDUS PICTURE OF BACKFROUND RETINOPATHY WITH FEATURES OF MICROANEURYSMS

CARDIAC AUTONOMIC NEUROPATHY

Cardiac Autonomic Neuropathy causes significant mortality and morbidity in diabetics. It results in very high risk of arrhythmias and sudden cardiac death (SCD) probably due to silent myocardial infarctions.

CAN results from interaction between various factors like blood pressure both systolic and diastolic, glycemic control, duration of disease. Hyperglycemia produces advanced glycation end products, activation of polyol pathway, activation protein kinase C. These changes result in increased ROS production. The microvascular ischemia of vaso vasarum and free radical damage are proposed as the cause for nerve cell damage in diabetes leading on to autonomic neuropathy.

Long standing hyperglycemia causes dying back neuropathy. The longest nerve of the body Vagus supplies parasympathetic innervations to heart. Since the neuropathy affects the nerves with long course, the first manifestation of diabetic autonomic neuropathy is parasympathetic denervation. There is an associated increase in sympathetic tone. As the disease progresses there is abnormal nor adrenaline signalling and its metabolism is altered within heart in diabetics. Co- existent free radical injury, mitochondrial stress, calcium dependent cellular destruction may contribute to myocyte loss and the high risk of arrhythmias and sudden cardiac death.

The clinical symptom in cardiac autonomic neuropathy is exercise intolerance and postural giddiness. Signs include an impaired Heart rate variability (HRV), resting tachycardia, nocturnal hypertension and orthostatic hypotension.

Impaired HRV

Beat to beat variation in heart rate and heart rate changes with respect to respiration is a function of both parasympathetic and sympathetic activity. In normal subjects there is high degree of beat to beat heart rate variability and this HRV increases with inspiration and decreases with expiration. A decreased HRV is seen very early in the course of development of CAN.

Resting tachycardia

Sympathetic over activity along with a parasympathetic denervation produces a resting tachycardia with rates > 100 /mt. A complete cardiac denervation is indicated by a fixed heart rate not responding stress, exercise or sleep.

Exercise intolerance

Decreased heart rate, blood pressure and cardiac output response to exercise occur due to CAN in diabetics.

Abnormal Blood Pressure regulation

Normally a dominant vagus output and decrease in adrenrgic output at night produces a reduced blood pressure at night. An altered pattern with

parasympathetic denervation and sympathetic over activity in CAN produces nocturnal hypertension in diabetic patients.

Orthostatic hypotension

As the diasease progresses there is sympathetic denervation in diabetic patients resulting in impaired vasoconstriction of peripheral vascular beds which results in orthostatic hypotension.

DIASTOLIC DYSFUNCTION :

Two dimensional echo cardiographic evaluation of diastolic dysfunction was done in all subjects both cases and control. Echocardiography was done using harmonic imaging by standard protocol. In the apical 4 chamber view Transmitral inflow velocities was obtained using pulsed wave dopppler. All measurements were averaged over three consecutive cardiac cycles. Echocardiographer was unaware of the research to prevent any observer bias in interpretation. Following measurements were done

1) E-wave –Transmitral-early rapid filling velocity in diastole

2) A-wave –late filling velocity- atrial contraction wave

3) E/A ratio

4) IVRT-Isovolumetric relaxation time

5) DT-Deceleration time

6) E/e’ ratio

Diastolic dysfunction was defined to be present if any of the following finding was observed

1) E/A ratio <1 or >2
2) DT < 150 msec or > 220 milliseconds
3) IVRT < 60 ms or > 100 milliseconds
4) E/e’ ratio >15

The diastolic dysfunction can be graded by the following grade

Grade 1 (mild dysfunction): impaired relaxation with normal filling pressure

Grade 2 (moderate dysfunction): pseudonormalized mitral inflow pattern

Grade 3 (severe reversible dysfunction): reversible restrictive (high filling pressure)

Grade 4 (severe irreversible dysfunction): irreversible restrictive (high filling pressure)

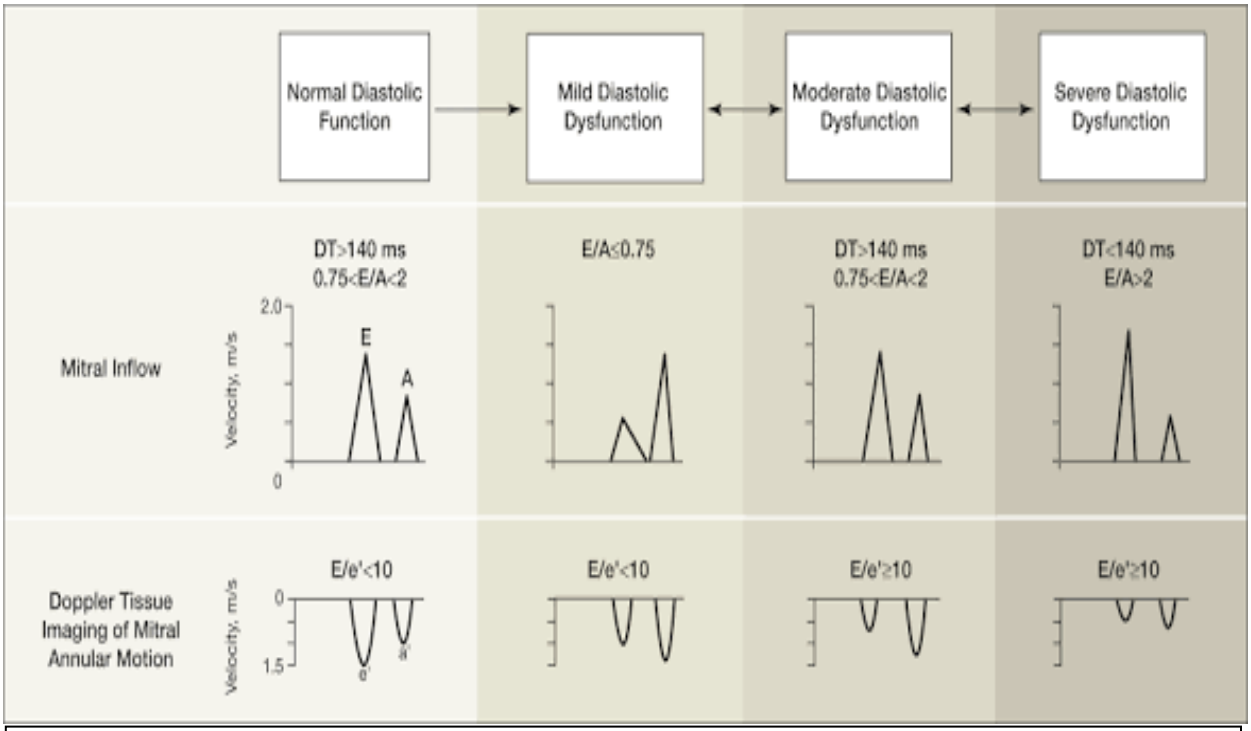


FIGURE 2: MITRAL INFLOW RATIOS , TISSUE DOPPLER IMAGING RATIOS, DECELERATION TIME IN VARIOUS DEGREES OF DIASTOLIC DYSFUNCTION

OBSERAVATION

DISTRIBUTION OF CASE AND CONTROL GROUP

Among the 50 patients in the case group 30 were male and 20 female. In the control arm among 50 patients 29 were male and 21 female were present.

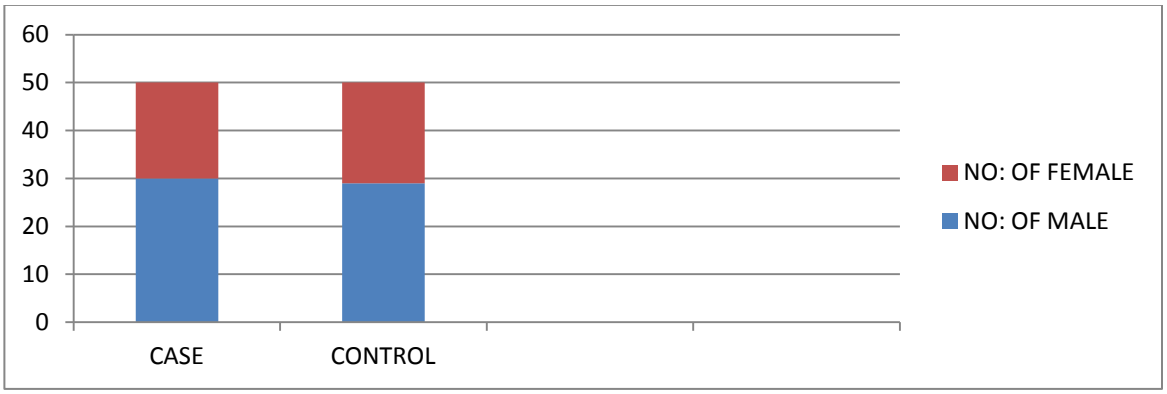


TABLE 1:

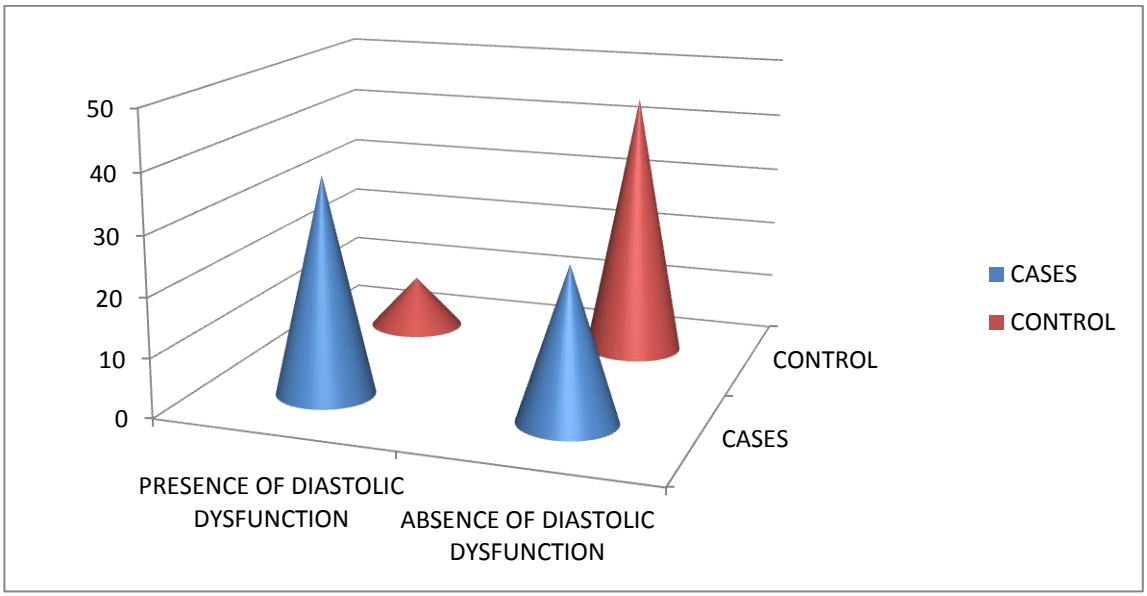
SEX	CASES	CONTROL
MALE	30	29
FEMALE	20	21

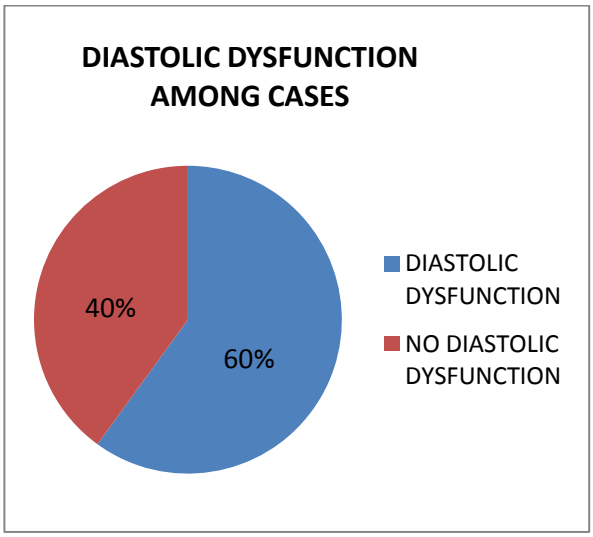
DIASTOLIC DYSFUNCTION IN CASE AND CONTROL

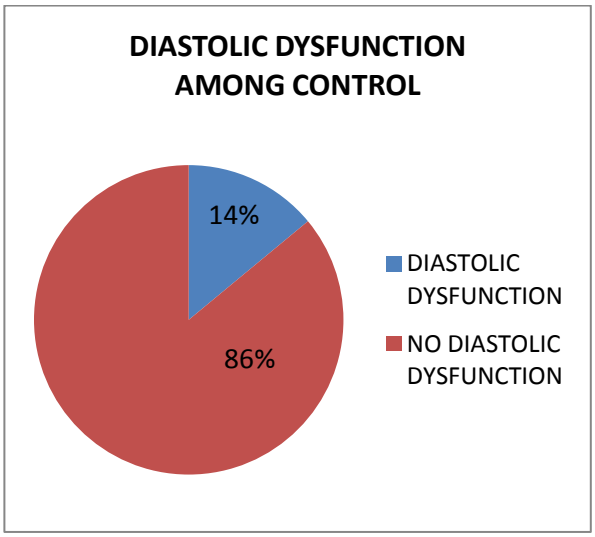
TABLE 2:

PARAMETER	CASES	CONTROL
DIASTOLIC DYSFUNCTION	30	7
NO DIASTOLIC DYSFUNCTION	20	43
PERCENTAGE	60%	14%

DISTRIBUTION OF DIASTOLIC DYSFUNCTION IN CASE AND CONTROL GROUP







RELATIONSHIP OF DIASTOLIC DYSFUNCTION WITH AGE OF PATIENTS

The study population was categorized as age < 45 yrs and > 45 yrs and tabulated as follows

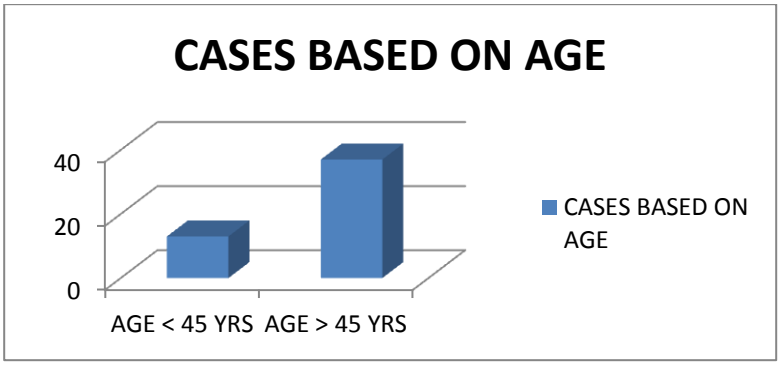
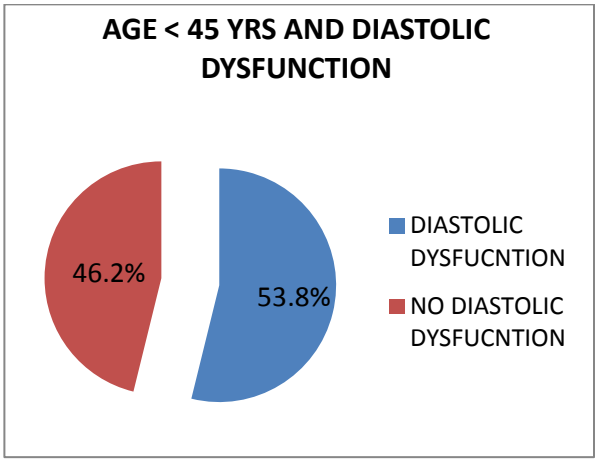
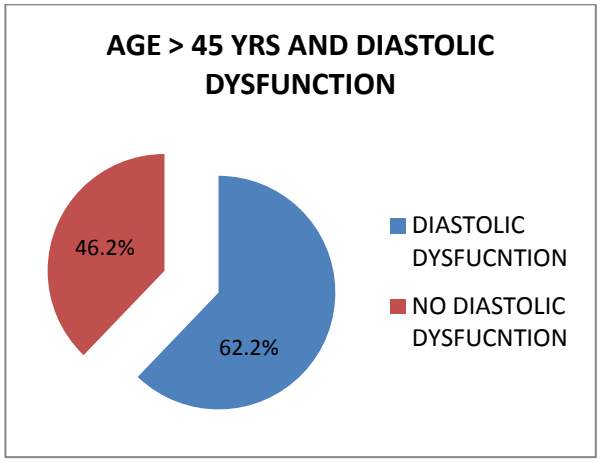


TABLE 3:

PARAMETER	AGE < 45 YRS	AGE > 45 YRS	TOTAL
DIASTOLIC DYSFUNCTION	7	23	30
NO DIASTOLIC DYSFUNCTION	6	14	20
TOTAL	13	37	50
PERCENTAGE WITH DIASTOLIC DYSFUNCTION	53.8%	62.16%	60%

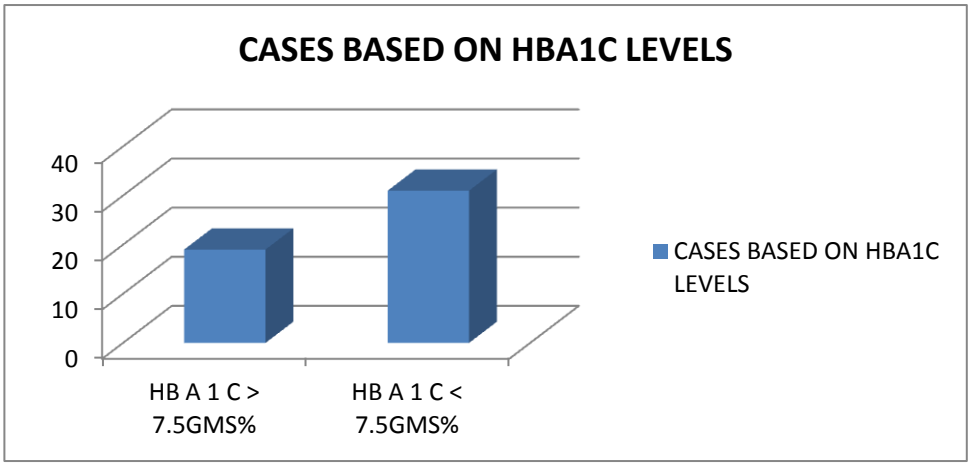


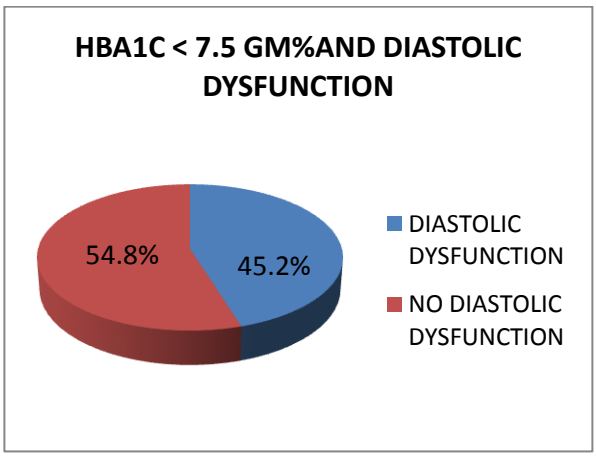


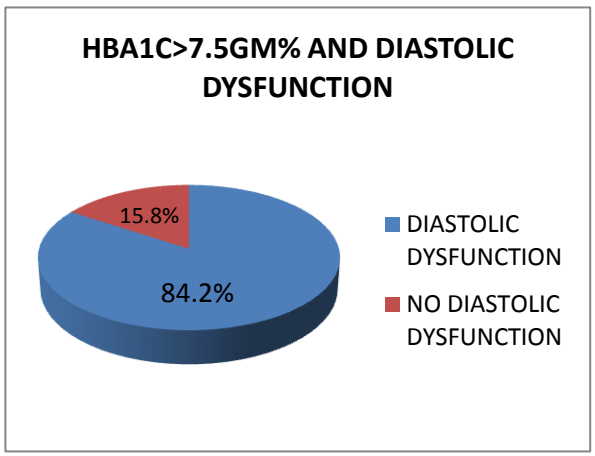
RELATIONSHIP OF DIASTOLIC DYSFUNCTION WITH HBA1C LEVELS OF PATIENTS

TABLE 4:

PARAMETER	HBA1C <7.5gm%	HBA1C > 7.5 gm%	TOTAL
DIASTOLIC DYSFUNCTION	14	16	30
NO DIASTOLIC DYSFUNCTION	17	3	20
TOTAL	31	19	50
PERCENTAGE WITH DIASTOLIC DYSFUNCTION	45.2%	84.2%	60%







DURATION OF DIABETES AND DIASTOLIC DYSFUNCTION

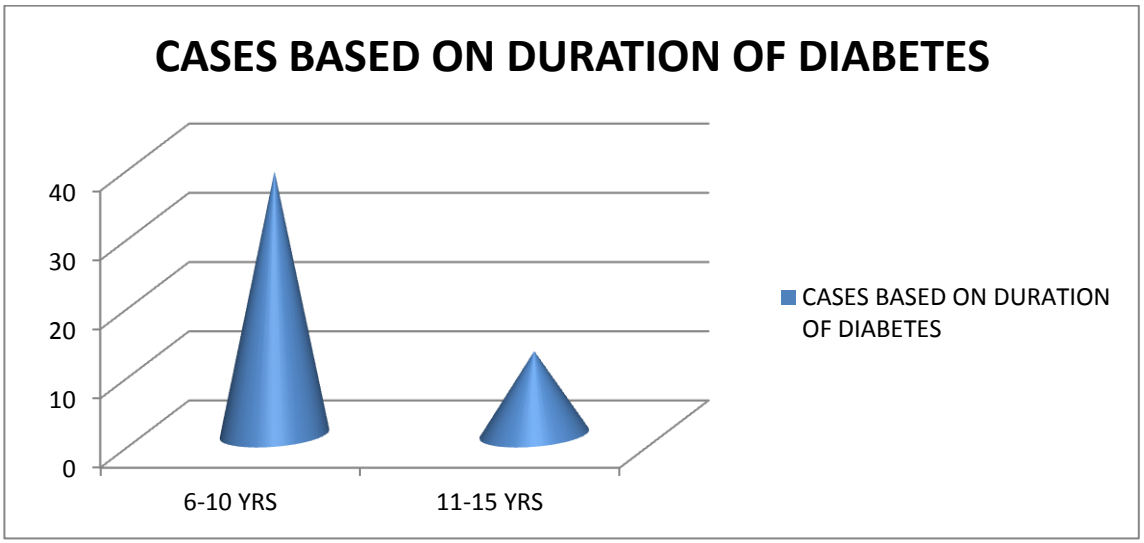
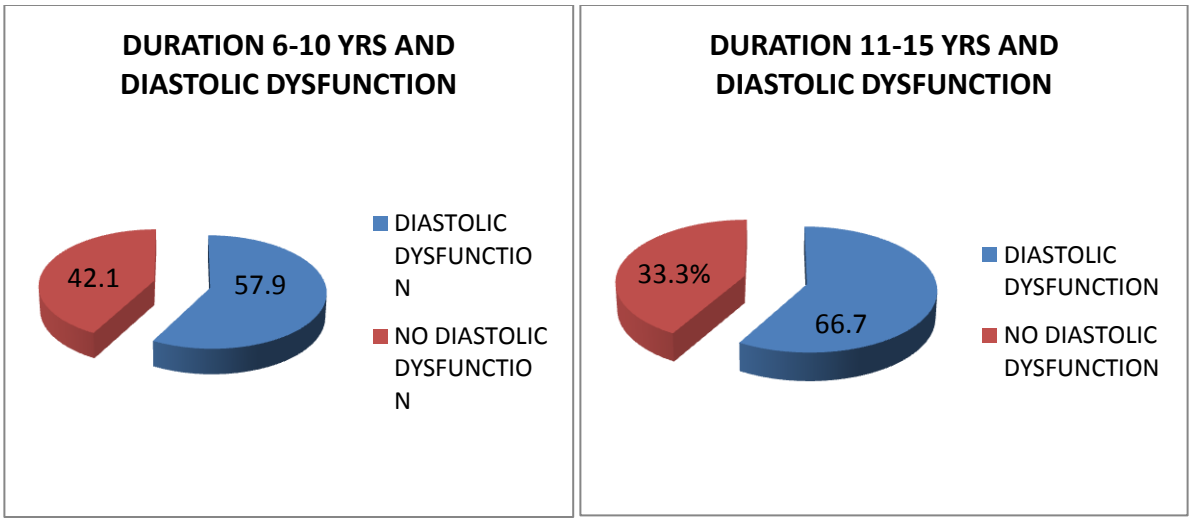


TABLE 5:

PARAMETER	DURATION 6-10 YRS	DURATION 11-15 YRS	TOTAL
DIASTOLIC DYSFUNCTION	22	8	30
NO DIASTOLIC DYSFUNCTION	16	4	20
TOTAL	38	12	50
PERCENTAGE WITH DIASTOLIC DYSFUNCTION	57.9%	66.7%	60%



RETINOPATHY AND DIASTOLIC DYSFUNCTION

In the study all 100 subjects were examined clinically for the presenc of diabetic retinopathy with fundus examination after using mydriatics. They were tabulated as either presence of nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) and no diabetic retinopathy. The results were tabulated

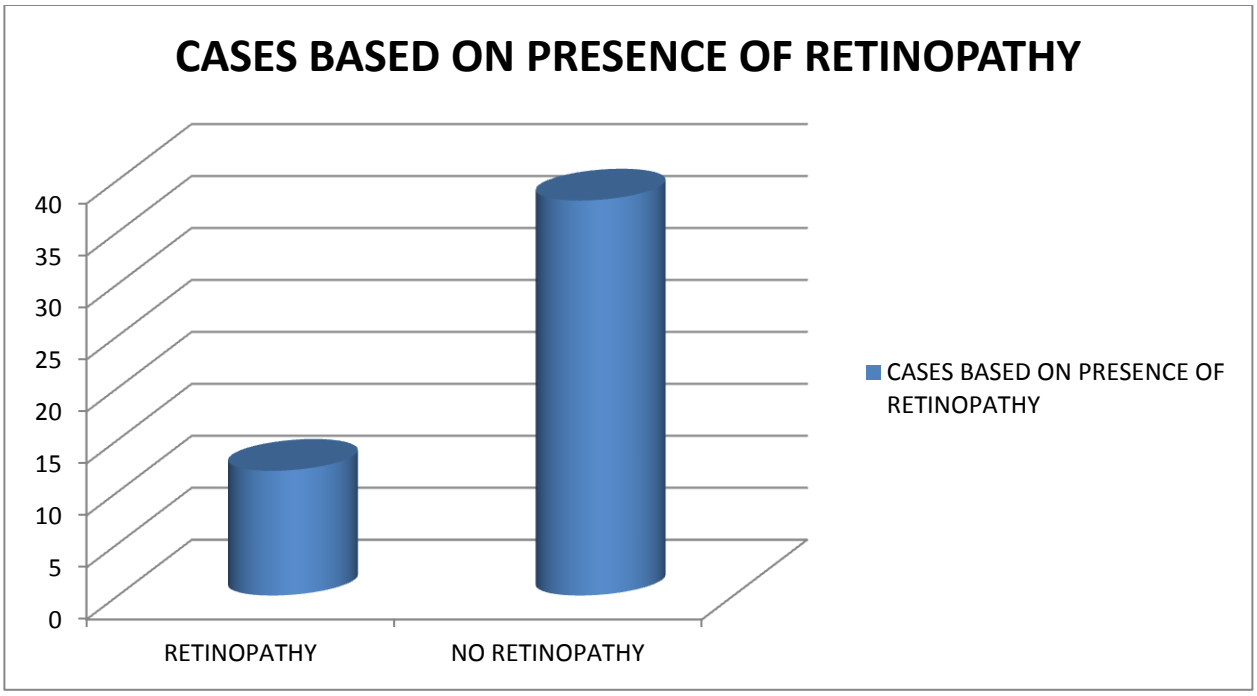
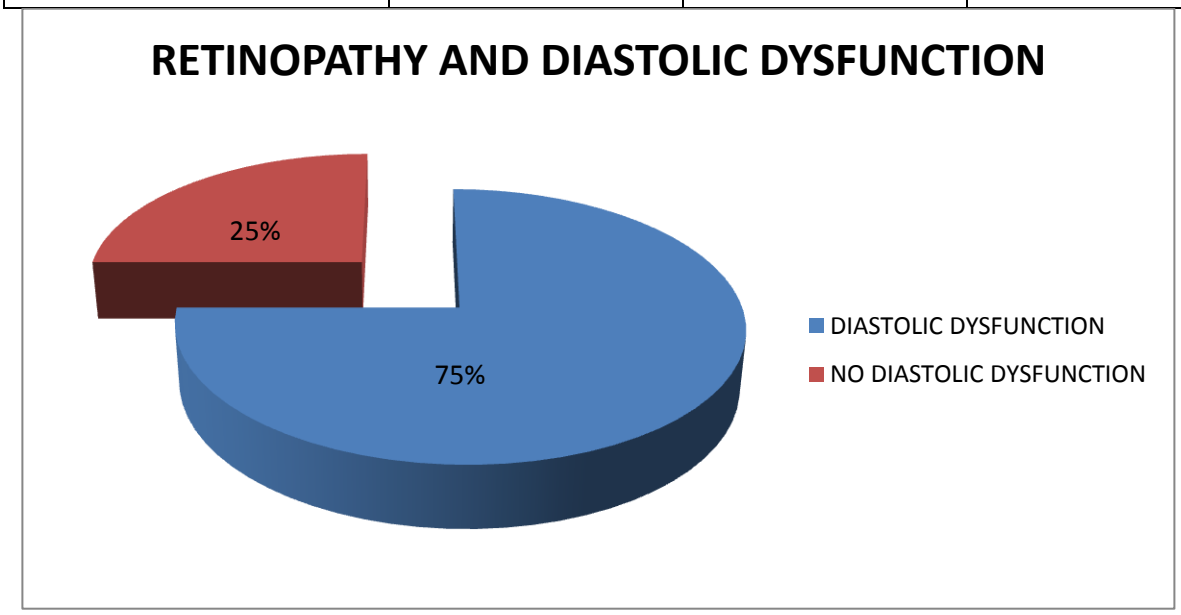


TABLE 6:

PARAMETER	RETINOPATHY	NO RETINOPATHY	TOTAL
DIASTOLIC DYSFUNCTION	9	21	30
NO DIASTOLIC DYSFUNCTION	3	17	20
TOTAL	12	38	50
PERCENTAGE WITH DIASTOLIC DYSFUNCTION	75%	55.26%	60%



AUTONOMIC NEUROPATHY AND DIASTOLIC DYSFUNCTION

In the study presence of cardiac autonomic neuropathy was defined when patient had orthostatic hypotension, which was defined as the fall in Systolic BP > 30mm of Hg or a Diastolic BP fall of more than 10 mm hg on standing for more than 3 minutes. For this the systolic and diastolic blood pressure was measured in all patients while sitting, immediately on standing and 3 minutes after standing. A sustained fall in SBP/DBP after 3 minutes is taken as positive and petients were computed as having autonomic neuropathy and not having autonomic neuropathy

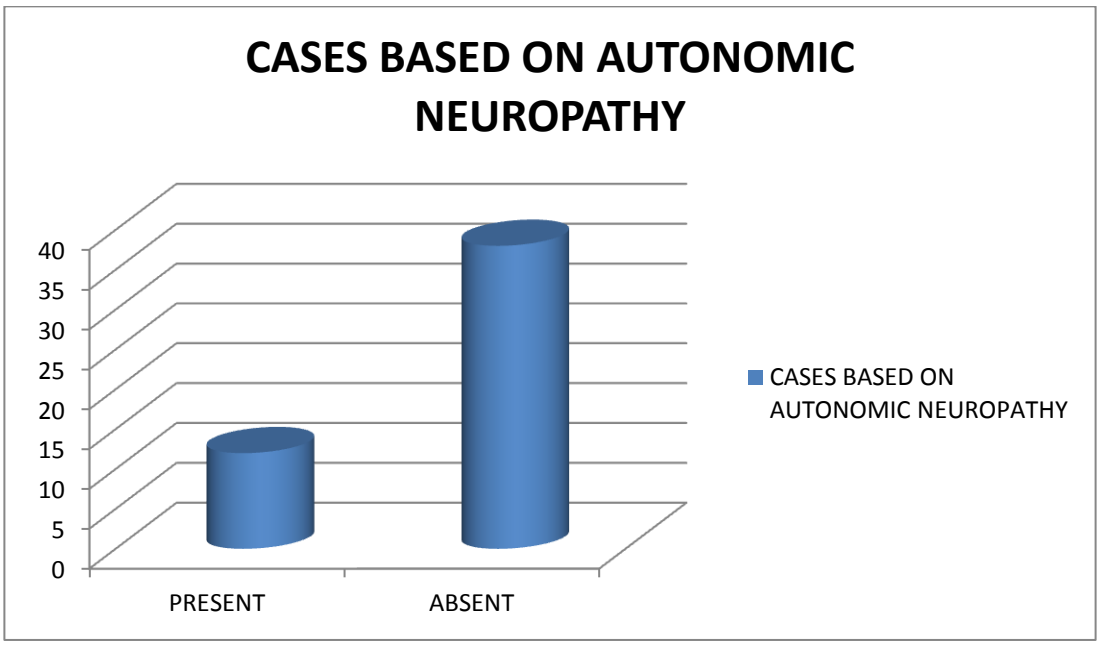
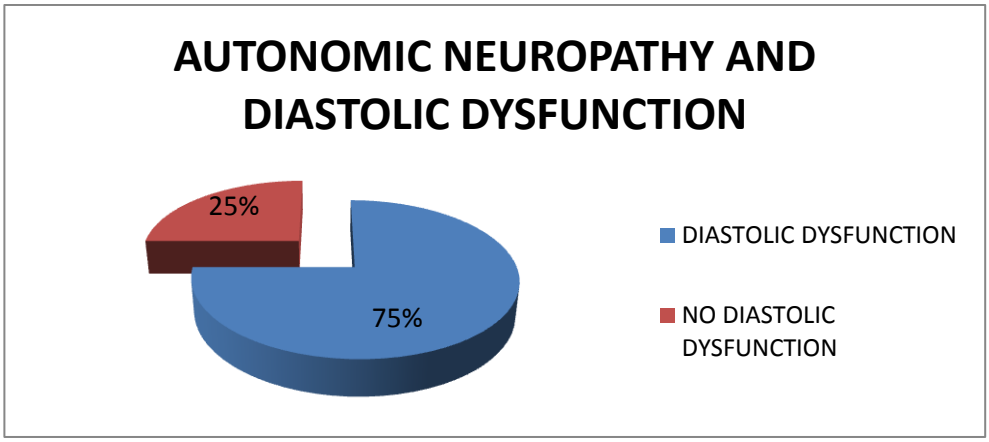


TABLE 7:

PARAMETER	AUTONOMIC NEUROPATHY	NO AUTONOMIC NEUROPATHY	TOTAL
DIASTOLIC DYSFUNCTION	9	21	30
NO DIASTOLIC DYSFUNCTION	3	17	20
TOTAL	12	38	50
PERCENTAGE WITH DIASTOLIC DYSFUNCTION	75%	55.26%	60%



STATISTICAL ANALYSIS:

All the variables and their data were analysed for percentage, mean, standard deviation,'t' test and chi square test. Those variables which were not distributed in normal distribution were transformed for the analysis. The 't'-test was used to study the quantitative data while chi square test was used to study the qualitative data. A 'P' value of <0.05 is considered as statistically significant.

TABLE 8: MEAN AND SANDARD DEVIATION OF THE VARIABLES UNDER STUDY

Sl no	VARIABLES	CASE MALE (MEAN+/-SD)	CASE FEMALE (MEAN+/-SD)	CONTROL MALE (MEAN+/-SD)	CONTROL FEMALE (MEAN+/-SD)
1.	AGE IN YEARS	52+/-12	48+/-11	51+/-9	50+/-9
2.	DURATION OF DIABETES IN YEARS	12+/-5	11+/-3	-	-
3.	BODY MASS INDEX(KG/M2)	27.4+/-2	26.2+/-2.4	23+/-1.5	24+/-1.2
4.	WAIST HIP RATIO	0.95+/-0.15	0.83+/-0.17	0.75+/-0.17	0.75+/-0.14
5.	TOTAL CHOLESTROL	221+/-24	231+/-23	140+/-12	145+/-13
6.	TRIGLYCERIDES	206+/-26.7	197+/-25.4	130+/-10	128+/-12
7.	LDL –CHOLESTROL	145+/-17.8	149+/-13	95+/-13	103+/-9
8.	HDL-CHOLESTROL	40+/-7	38+/-6	45+/-3	44+/-2
Sl no	VARIABLES	CASE MALE (MEAN+/-SD)	CASE FEMALE (MEAN+/-SD)	CONTROL MALE (MEAN+/-SD)	CONTROL FEMALE (MEAN+/-SD)
9.	BLOOD SUGAR LEVEL	136+/-20.1	134+/-19	90+/-6	85+/-8
10.	HBA1C %	8.2+/-2.80	8.1+/-1.5	-	-
11.	E/A RATIO	0.80+/-0.12	0.79+/-0.13	1.20+/-0.2	1.18+/-0.10
12.	IVRT(ms)	80+/-12	81+/-9	94+/-15	96+/-12
13.	DT(ms)	175+/-21	179+/-18	160+/-24	153+/-25

14.	EJECTION FRACTION%	55+/-3	54+/-2	59+/-5	58+/-3
15.	DIASTOLIC DYSFUNCTION	19(63.33%)	11(55%)	4(13.79%)	3(14.2%)

INDEX

HBA1C-GLYCATED HEMOGLOBIN;

LDL-LOW DENSITY LIPOPROTEIN;

HDL- HIGH DENSITY LIPOPROTEIN

E-EARLY DIASTOLIC VELOCITY (CM/S)

A-ATRIAL WAVE (CM/S)

IVRT-ISOVOLUMETRIC RELAXATION TIME

DT-DECELERATION TIME

TABLE 9: RELATIONSHIP OF DIASTOLIC DYSFUNCTION WITH THE DEPENDENT VARIABLES AND CORRESPONDING 'P' VALUES

SL NO	VARIABLES	DD PRESENT	DD ABSENT	TOTAL %	'P' VALUE
1.	AGE <45 YEARS(n=13)	7(53.8%)	6	23%	<0.05
2.	AGE>45 YEARS(n=37)	23(62.16%)	14	76.6%	<0.02
3.	HBA1C<7.5%	14(45.16%)	17	46.67%	<0.05
4.	HBA1C>7.5%	16(84.21)	3	53.3%	<0.02

5.	DURATION OF DIABETES 6-10 YRS	22(57.89%)	16	73.33%	<0.02
6.	DURATION OF DIABETES 11-16YRS	8(66.66%)	4	26.66%	<0.05
7.	RETINOPATHY PRESENT	9(75%)	3	30%	<0.02
8.	AUTONOMIC NEUROPATHY PRESENT	9(75%)	3	30%	<0.02

DD- DIASTOLIC DYSFUNCTION

DISCUSSION

Table 1 shows that there were total of 50 patients in cases under study and total of 50 matched controls. Of the cases 30 were male and 20 were female. Of the control group 29 were male and 21 were female.

Table 2 shows that

i) Of the total 50 patients in the cases arm 30 had diastolic dysfunction which is 60% prevalence.

ii) On the control arm a total of 7 had diastolic dysfunction which equals to 14%.

Table 3 shows that

i) A total of 13 patients were of age <45 years of which 7 had diastolic dysfunction. This equals 53.8% prevalence.

ii) The remaining 37 patients were in the age group >45 years. A total of 23 patients in this category had diastolic dysfunction which equals 62.16%.

Table 4 shows that

i) 31 patients in cases arm had HBA1c less than 7.5 gm% and 19 had HBA1c greater than7.5gm%.

ii) 14 patients with HBA1c less than 7.5 gm% had diastolic dysfunction with a prevalence of 45.2%.

iii) 16 patients with HBA1c greater than 7.5 gm% had diastolic dysfunction with an prevalence of 84.2%.

Table 5 shows that

i) 38 patients had diabetes mellitus for 6-10 years and 12 had duration between11-15 years.

ii) 22 patients with duration 6-10 years had diastolic dysfunction with an prevalence of 57.9%.

iii) 8 patients with duration of diabetes 11-15 years had diastolic dysfunction with an prevalence of 66.67%

Table 6 shows that a total of 12 patients had diabetic retinopathy while the remaining 38 did not show features of diabetic retinopathy. Of the 12 patients 9 had diastolic dysfunction with a prevalence of 75%.

Table 7 shows that a total of 12 patients had autonomic dysfunction and remaining 38 patients did not have autonomic dysfunction. Of the 12 patients with autonomic dysfunction 9 had diastolic dysfunction with an incidence of 75%.

Table 8 shows that

i) The mean body mass index, waist hip ratio, total cholesterol, LDL cholesterol, in cases was high when compared to controls.

ii) The mean HDL cholesterol was lower in cases than in the control group.

iii) The mean E/A ratio was lower in the cases that in the control group.

iv) 19 males in cases arm had diastolic dysfunction with an incidence of 63.3%. 11 females in cases arm had diastolic dysfunction with an incidence of 55%. This was statistically significant with a 'p'-value of <0.02.

v) 4 males and 3 females in the control arm had diastolic dysfunction with an incidence of 13.79% and 14.2%.

Table 9 shows that

i) The incidence of diastolic dysfunction is more in age >45 years with the Statistical 'p' value of <0.02.

ii) The incidence of diastolic dysfunction is more in the HBA1c > 7.5 gm% with a statistical 'p' value of <0.02

iii) The incidence of diastolic dysfunction occurs more often after a 5 years duration with an incidence in 6-10 years of 73.33% of total and a stastical ‘p’ value of <0.02.

iv) The incidence of diastolic dysfunction 75 % when the patient develops diabetic retinopathy.

v) The incidence of diastolic dysfunction 75 % when the patient develops diabetic autonomic neuropathy.

CONCLUSION

Diabetes Mellitus causes serious morbidities one of which is cardiovascular. The occurrence of coronary artery disease and systolic dysfunction are well known. However the **prevalence of a diastolic dysfunction** even in asymptomatic patients independent of a CAD is a relatively new observation. It is also obvious that, diastolic dysfunction **correlates** well with **diabetes duration, micro vascular abnormalities obesity index, lipid profile and HbA1c**. Diastolic dysfunction, being a **marker of Diabetic Cardiomyopathy**, may be useful as the **predictor of heart failure with preserved ejection fraction** and **mortality** in the medium to long term. At present the treatment options for a diastolic heart failure with normal systolic function are very limited. It is prudent to **screen** for diastolic dysfunction through the markers of insulin resistance for an early identification and treatment of the determinants so as to **prevent the progression** to full blown heart failure. All these determinants and diabetes in itself stem from the common patho-physiology of insulin resistance. Recently trials have shown a **cardio-protective effect for metformin**, probably because it increases insulin sensitivity. Studies are needed further to crystallize our knowledge, to understand the pathophysiology of Diabetic cardiomyopathy which at present looks very complex and also to ensure better management so as to reduce the morbidity and mortality associated with Diastolic Dysfunction.

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ANNEXURE 1

A Study of Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function

PROFORMA

Name of the patient :

AGE/SEX :

OP NO. :

Complaints :

Date :

History of Presenting illness:

Past history

Duration of Diabetes :

H/O Systemic hypertension :

H/O Coronary Artery Heart Disease :

H/O Valvular Heart disease :

Personal history:

On General examination

Anthropometric examination

Height:

Weight :

BMI

High waist circumference

Waist Hip Ratio(WHR)

Vitals

CVS :

RS :

P/A :

CNS :

FUNDUS EXAMINATION:

Investigations

Fasting Blood sugar(mg%) :

Postprandial blood sugar(mg%) :

Lipid profile :

Total cholesterol :

Triglycerides :

LDL :

HDL :

Electrocardiogram :

Echocardiography :

ANNEXURE 2

MASTER CHART FOR CASES

SL no	Name	Age/ Sex	Diabetes-Duration(YRS)	H/O CAD/ SHT/ VHD	FBS (MG%)	HB A1C	BMI Kg/m2	WHR	FUNDUS	AUTONOMIC NEUROPATHY	TC TGL LDL HDL (MG%)	ECG	ECHO E/A IVRT DT E/e'
1.	Arivoli	52/ M	7	Nil	156	8 %	22.9	0.8	NO-DR	NO	TC-180 TGL-130 LDL-110 HDL-45	Wnl	E/A-0.6 IVRT-124msec DT-240 msec
2.	Abdullah	53/ M	6	Nil	148	8.2%	23.5	0.8	NO-DR	NO	TC-190 TGL-133 LDL-135 HDL-40	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
3.	Alagammal	51/ F	8	Nil	135	7.2%	26.1	1.3	NO-DR	NO	TC-240 TGL-180 LDL-160 HDL-34	Wnl	E/A-0.5 IVRT-140msec DT-250 msec
4.	Bharath	56/ M	9	Nil	170	7.1%	22.3	0.8	NO-DR	NO	TC-185 TGL-146 LDL-140 HDL-39	Wnl	E/A-0.7 IVRT-114msec DT-230 msec
5.	Bhagyalakshmi	49/ F	6	Nil	160	6.5%	25.6	1.2	BDR	YES	TC-225 TGL-202 LDL-175 HDL-36	Wnl	E/A-0.9 IVRT-104msec DT-223 msec
6.	**Bharani**	62/ M	12	Nil	143	8.5%	23	0.8	BDR	YES	TC-198 TGL-157 LDL-139 HDL-38	Wnl	E/A-1.5 IVRT-80msec DT-210 msec **E/e'-18**
7.	Buvaneswari	48/ F	6	Nil	129	6.9%	22	0.7	NO-DR	NO	TC-180 TGL-150 LDL137 HDL-40	Wnl	E/A-0.6 IVRT-124msec DT-240 msec
8.	**Bruntha**	64/ M	13	Nil	162	8%	25.5	1.1	BDR	YES	TC-222 TGL-180 LDL-150 HDL-30	Wnl	E/A-1.6 IVRT-80msec DT-210 msec E/e'-17
9.	Chellamal	50/ F	7	Nil	134	7.2%	23	0.9	NO-DR	NO	TC-170 TGL-140 LDL-150 HDL-36	Wnl	E/A-0.7 IVRT-114msec DT-230 msec
10.	**Chellaiah**	64/ M	13	Nil	156	8.5%	27.2	1.4	BDR	YES	TC-250 TGL-190 LDL-176 HDL-32	Wnl	E/A-1.8 IVRT-80msec DT-210 msec E/e'-19
11.	Durai	56/ M	6	Nil	176	8.2%	27.3	1.7	NO-DR	NO	TC-198 TGL-145 LDL-120 HDL-40	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
12.	**David**	58/ M	15	Nil	134	8%	28	1.6	BDR	YES	TC-270 TGL-180 LDL-150 HDL-30	Wnl	E/A-1.6 IVRT-80msec DT-210 msec E/e'-18
13.	Dinakar	42/ M	6	Nil	156	8.3%	22	0.8	B-DR	YES	TC-197 TGL-130 LDL-143 HDL-40	Wnl	E/A-0.9 IVRT-104msec DT-223 msec
14.	Dinesh	54/ M	8	Nil	140	7.2%	21	0.7	NO-DR	NO	TC-240 TGL-190 LDL-170 HDL-32	Wnl	E/A-0.6 IVRT-124msec DT-240 msec
15.	**Dhanam**	60/ F	14	Nil	179	8.4%	26	1.2	BDR	YES	TC-247 TGL-180 LDL-140 HDL-30	Wnl	E/A-1.9 IVRT-80msec DT-210 msec E/e'-20
16.	Ibrahim	45/ M	6	Nil	180	6.5%	23	0.8	NO-DR	NO	TC-235 TGL-232 LDL-195 HDL-34	Wnl	E/A-0.9 IVRT-104msec DT-223 msec
17.	Elumalai	50/ M	9	Nil	128	7%	22	0.8	NO-DR	NO	TC-190 TGL-150 LDL-145 HDL-34	Wnl	E/A-0.7 IVRT-114msec DT-230 msec
18.	Elavarasi	43/	7	Nil	138	7.4%	23.1	0.9	NO-DR	NO	TC-170	Wnl	E/A-0.8

		F									TGL-130 LDL119 HDL-41		IVRT-106msec DT-225 msec
19.	Ganesan	56/ M	8	Nil	129	7.6%	23	0.8	NO-DR	NO	TC-190 TGL-130 LDL-140 HDL-38	Wnl	E/A-0.5 IVRT-140msec DT-250 msec
20.	Ganthimathi	39/ F	6	Nil	137	7.1%	24.4	1.1	BDR	YES	TC-230 TGL-160 LDL-136 HDL-36	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
21.	**Gunaselan**	63/ M	12	Nil	143	6.5%	25.5	1	N0-DR	NO	TC-250 TGL-165 LDL-140 HDL-34	Wnl	E/A-1.7 IVRT-80msec DT-210 msec E/e'-19
22.	Gayathri	45/ F	7	Nil	167	7.7%	23.2	1	NO-DR	NO	TC-220 TGL-140 LDL-120 HDL-30	Wnl	E/A-0.6 IVRT-124msec DT-240 msec
23.	Kavitha	40/ F	7	Nil	149	7.3%	22.2	0.7	NO-DR	NO	TC-198 TGL-130 LDL-146 HDL-37	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
24.	Kathiravan	45/ M	8	Nil	152	8%	28	1.7	NO-DR	NO	TC-210 TGL-170 LDL-150 HDL-32	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
25.	Kumar	55/ M	8	Nil	170	6.7%	25.1	1.1	NO-DR	NO	TC-238 TGL-165 LDL-145 HDL-35	Wnl	E/A-0.7 IVRT-114msec DT-230 msec
26.	Krishnan	60/ M	10	Nil	175	7.6%	27.3	1.6	NO-DR	NO	TC-225 TGL-152 LDL-165 HDL-36	Wnl	E/A-0.5 IVRT-140msec DT-250 msec
27.	Krishnaveni	62/ F	7	Nil	141	7.8%	21	0.7	BDR	YES	TC-197 TGL-160 LDL-155 HDL-37	Wnl	E/A-0.6 IVRT-124msec DT-240 msec
28.	Krishnakumar	43/ M	7	Nil	156	6.4%	22.2	0.8	NO-DR	NO	TC-176 TGL-120 LDL 100 HDL-39	Wnl	E/A-0.5 IVRT-140msec DT-250 msec
29.	Lalitha	42/ F	8	Nil	159	7.9%	22.6	0.7	NO-DR	NO	TC-180 TGL-130 LDL-120 HDL-35	Wnl	E/A-0.9 IVRT-104msec DT-223 msec
30.	Logesh	37/ M	6	Nil	176	8%	27.9	1.7	NO-DR	NO	TC-210 TGL-170 LDL-146 HDL-36	Wnl	E/A-0.7 IVRT-114msec DT-230 msec
31.	Loorth mary	48/ F	6	Nil	157	7.9%	21	0.7	NO-DR	NO	TC-235 TGL-155 LDL-130 HDL-37	Wnl	Normal disastolic function
32.	Mohammed	56/ M	7	Nil	139	7.6%	22.2	0.8	NO-DR	NO	TC-210 TGL-156 LDL-110 HDL-36	Wnl	Normal diastolic function
33.	Manikam	59/ M	6	Nil	130	7.4%	22.5	0.7	NO-DR	NO	TC-178 TGL-110 LDL-125 HDL-32	Wnl	Normal diastolic function
34.	Moorthy	57/ M	9	Nil	164	7.3%	23.1	0.7	BDR	YES	TC-210 TGL-140 LDL-120 HDL-35	Wnl	Normal diastolic function
35.	Mary	62/ M	8	Nil	174	6.8%	21.6	0.7	NO-DR	NO	TC-180 TGL-134 LDL-145 HDL-40	Wnl	Normal diastolic function
36.	Naseer	43/ M	7	Nil	178	6.6%	23.3	0.8	NO-DR	NO	TC-240 TGL-180 LDL-160 HDL-34	Wnl	Normal diastolic function
37.	Navin	56/ M	12	Nil	157	6.4%	21.7	0.7	NO-DR	NO	TC-185 TGL-146 LDL-140 HDL-39	Wnl	Normal diastolic function
38.	Petchiammal	43/ F	6	Nil	159	6.9%	26.1	1.5	NO-DR	NO	TC-215 TGL-192 LDL-165 HDL-36	Wnl	Normal diastolic function
39.	Perumalamal	54/ F	10	Nil	145	7.1%	22	0.7	BDR	YES	TC-178 TGL-147	Wnl	Normal diastolic

											LDL-120 HDL-34		function
40	Perumal	54/ M	9	Nil	149	7.3%	27.1	1.6	NO-DR	NO	TC-175 TGL-120 LDL 138 HDL-34	Wnl	Normal diastolic function
41.	Peratchi	55/ F	11	Nil	139	7.9%	23.9	1.1	NO-DR	NO	TC-176 TGL-120 LDL-130 HDL-35	Wnl	Normal diastolic function
42.	Pushpam	56/ F	12	Nil	140	7%	22	0.7	NO-DR	NO	TC-196 TGL-146 LDL-125 HDL-30	Wnl	Normal diastolic function
43.	Kathar Moideen	42/	7	Nil	147	6.5%	27.9	1.7	NO-DR	NO	TC-220 TGL-170 LDL-140 HDL-34	Wnl	Normal diastolic function
44.	Rathinam	55/M	12	Nil	147	7.3%	26	1.2	NO-DR	NO	TC-185 TGL-146 LDL-140 HDL-39	Wnl	Normal diastolic function
45.	Revathy	49/F	6	Nil	143	6.4%	26.3	1.6	NO-DR	NO	TC-225 TGL-202 LDL-175 HDL-36	Wnl	Normal diastolic function
46.	Rasathi	60/F	13	Nil	168	6.3%	22.7	0.7	NO-DR	NO	TC-178 TGL-150 LDL-139 HDL-38	Wnl	Normal diastolic function
47.	Sheik	57/M	7	Nil	156	6.6%	22.6	0.7	NO-DR	NO	TC-180 TGL-130 LDL134 HDL-35	Wnl	Normal diastolic function
48.	Sathik	52/ M	8	Nil	154	6.1%	21.9	0.7	BDR	YES	TC-180 TGL-130 LDL-110 HDL-45	Wnl	Normal diastolic function
49.	Salim	56/M	10	Nil	165	7.2%	27.3	1.6	NO-DR	NO	TC-190 TGL-133 LDL-135 HDL-40	Wnl	Normal diastolic function
50	Selvi	50/M	6	Nil	187	7.7%	21.1	0.7	NO-DR	NO	TC-240 TGL-180 LDL-160 HDL-34	Wnl	Normal diastolic function

MASTER CHART FOR CONTROL

Sl no	Name	Age/ Sex	Diabe Tes Dura Tion	Cad/ sht	Fbs Mg%	Hb a1c	BMI	WHR	FUN DUS	AUTO NOMIC NEURO PATHY	LIPID PROFI LE	ECG	ECHO
1.	SHUNMUGAM	45M	Nil	Nil	92	6.4	22.9	0.8	NAD	Nil	TC-180 TGL-130 LDL-110 HDL-45	Wnl	Normal diastolic function
2.	MAYANDI	55M	Nil	Nil	95	6.3	23.5	0.8	NAD	Nil	TC-190 TGL-133 LDL-135 HDL-40	Wnl	Normal diastolic function
3.	MASANAM	57M	Nil	Nil	86	5.6	23.1	0.8	NAD	Nil	TC-170 TGL-120 LDL-140 HDL-39	Wnl	E/A-0.5 IVRT-140msec DT-250 msec
4.	PARAMSIVAM	52M	Nil	Nil	90	5.7	22.3	0.8	NAD	Nil	TC-185 TGL-146 LDL-140 HDL-40	Wnl	Normal diastolic function
5.	MOHAMED	61M	Nil	Nil	79	5.4	24.6	1.0	NAD	Nil	TC-185 TGL-140 LDL-135 HDL-36	Wnl	Normal diastolic function
6.	JEBAKANI	47F	Nil	Nil	88	6.1	23	0.8	NAD	Nil	TC-198 TGL-145 LDL-130 HDL-38	Wnl	Normal diastolic function
7.	MURUGAN	52M	Nil	Nil	94	6.3	22	0.7	NAD	Nil	TC-180 TGL-150	Wnl	Normal diastolic

											LDL137 HDL-40		function
8.	SHAKILA	58F	Nil	Nil	99	6.2	23	0.8	NAD	Nil	TC-165 TGL-132 LDL-115 HDL-40	Wnl	Normal diastolic function
9.	RAJESWARI	63F	Nil	Nil	87	5.9	22	0.8	NAD	Nil	TC-190 TGL-150 LDL-125 HDL-34	Wnl	Normal diastolic function
10.	SOURIAMMAL	45F	Nil	Nil	85	6.0	23.1	0.8	NAD	Nil	TC-170 TGL-130 LDL120 HDL-42	Wnl	Normal diastolic function
11.	DURAI	43M	Nil	Nil	93	6.4	23	0.8	NAD	Nil	TC-190 TGL-130 LDL-110 HDL-38	Wnl	Normal diastolic function
12.	GURUSAMY	59M	Nil	Nil	97	6.3	24.4	0.9	NAD	Nil	TC-160 TGL-100 LDL-106 HDL-47	Wnl	Normal diastolic function
13.	MARIA THERASA	60F	Nil	Nil	94	5.6	25.5	1.0	NAD	Nil	TC-250 TGL-165 LDL-140 HDL-34	Wnl	Normal diastolic function
14.	KARUPASAMY	65M	Nil	Nil	91	5.7	23.2	0.8	NAD	Nil	TC-205 TGL-140 LDL-120 HDL-35	Wnl	Normal diastolic function
15.	FATHIMA BEEVI	59F	Nil	Nil	86	5.4	22.2	0.7	NAD	Nil	TC-198 TGL-130 LDL-146 HDL-38	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
16.	SARASWATHY	51F	Nil	Nil	90	6.1	25	1.1	NAD	Nil	TC-210 TGL-170 LDL-150 HDL-32	Wnl	Normal diastolic function
17.	SARAVANAN	46M	Nil	Nil	79	6.3	24.1	1.0	NAD	Nil	TC-238 TGL-165 LDL-145 HDL-35	Wnl	Normal diastolic function
18.	GANESAN	40M	Nil	Nil	88	6.2	27.3	1.2	NAD	Nil	TC-235 TGL-152 LDL-150 HDL-36	Wnl	Normal diastolic function
19.	AMBIGAI	54F	Nil	Nil	94	5.9	21	0.7	NAD	Nil	TC-197 TGL-160 LDL-155 HDL-37	Wnl	Normal diastolic function
20.	RAHMATH KHAN	49M	Nil	Nil	99	6.0	22.2	0.8	NAD	Nil	TC-156 TGL-110 LDL 90 HDL-39	Wnl	Normal diastolic function
21.	SUNDARAM	65M	Nil	Nil	87	5.4	22.6	0.8	NAD	Nil	TC-180 TGL-130 LDL-120 HDL-40	Wnl	Normal diastolic function
22.	ABDUL KATHER	67M	Nil	Nil	85	6.1	26.9	1.2	NAD	Nil	TC-250 TGL-170 LDL-166 HDL-36	Wnl	Normal diastolic function
23.	PETER	56M	Nil	Nil	93	6.3	21	0.8	NAD	Nil	TC-170 TGL-155 LDL-130 HDL-37	Wnl	E/A-0.9 IVRT-104msec DT-223 msec
24.	SUDALAI	59M	Nil	Nil	94	6.2	22.2	0.8	NAD	Nil	TC-178 TGL-147 LDL-120 HDL-34	Wnl	Normal diastolic function
25.	PONNI	43F	Nil	Nil	91	5.9	22.5	0.8	NAD	Nil	TC-175 TGL-120 LDL 138 HDL-34	Wnl	Normal diastolic function
26.	LAXSHMANAN	47M	Nil	Nil	86	6.0	23.1	0.9	NAD	Nil	TC-176 TGL-120 LDL-130 HDL-35	Wnl	Normal diastolic function
27.	ESAKIAMMAL	61F	Nil	Nil	90	6.4	21.6	0.7	NAD	Nil	TC-196	Wnl	Normal

											TGL-146 LDL-125 HDL-30		diastolic function
28.	LATHA	46F	Nil	Nil	79	6.3	23.3	0.8	NAD	Nil	TC-220 TGL-170 LDL-140 HDL-34	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
29.	RAMESH	57M	Nil	Nil	88	6.0	21.7	0.7	NAD	Nil	TC-185 TGL-146 LDL-140 HDL-39	Wnl	Normal diastolic function
30.	PARAMESWARI	49F	Nil	Nil	94	6.4	26.1	1.1	NAD	Nil	TC-225 TGL-202 LDL-175 HDL-36	Wnl	Normal diastolic function
31.	MUNIAMMAL	59F	Nil	Nil	97	6.3	22	0.7	NAD	Nil	TC-178 TGL-150 LDL-139 HDL-38	Wnl	Normal diastolic function
32.	PALANIAPPAN	44M	Nil	Nil	88	5.6	27.1	1.2	NAD	Nil	TC-180 TGL-130 LDL134 HDL-35	Wnl	Normal diastolic function
33.	JENIFER	41F	Nil	Nil	94	5.7	23.9	0.9	NAD	Nil	TC-180 TGL-130 LDL-110 HDL-45	Wnl	Normal diastolic function
34.	POOLPANDI	54M	Nil	Nil	99	5.4	22	0.8	NAD	Nil	TC-170 TGL-130 LDL-115 HDL-40	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
35.	MUTHIAH	56M	Nil	Nil	87	6.1	26.9	1.2	NAD	Nil	TC-240 TGL-180 LDL-160 HDL-34	Wnl	Normal diastolic function
36.	ANTHONIAMMAL	63F	Nil	Nil	85	6.3	26	1.1	NAD	Nil	TC-220 TGL-170 LDL-150 HDL-30	Wnl	Normal diastolic function
37.	BALASUBRAMANIAN	60M	Nil	Nil	93	6.2	25.3	1.1	NAD	Nil	TC-220 TGL-160 LDL-110 HDL-34	Wnl	Normal diastolic function
38.	PRABHU	43M	Nil	Nil	97	5.9	22.7	0.8	NAD	Nil	TC-185 TGL-146 LDL-140 HDL-39	Wnl	E/A-0.8 IVRT-106msec DT-225 msec
39.	KARUPPAIH	47M	Nil	Nil	94	6.0	22.6	0.7	NAD	Nil	TC-150 TGL-100 LDL-85 HDL-36	Wnl	Normal diastolic function
40.	PREMA	50F	Nil	Nil	91	5.4	21.9	0.7	NAD	Nil	TC-170 TGL-140 LDL-130 HDL-38	Wnl	Normal diastolic function
41.	MARIAMMAL	64F	Nil	Nil	86	6.2	27.3	1.3	NAD	Nil	TC-180 TGL-130 LDL 115 HDL-35	Wnl	Normal diastolic function
42.	RAJA	57M	Nil	Nil	90	5.9	21.1	0.7	NAD	Nil	TC-180 TGL-130 LDL-110 HDL-45	Wnl	Normal diastolic function
43.	RUKMANI	45F	Nil	Nil	79	6.0	22.7	0.7	NAD	Nil	TC-190 TGL-130 LDL-110 HDL-40	Wnl	Normal diastolic function
44.	JUDITH	56F	Nil	Nil	88	5.4	26.3	1.2	NAD	Nil	TC-240 TGL-180 LDL-160 HDL-34	Wnl	Normal diastolic function
45.	ESAKIAPPAN	51M	Nil	Nil	94	6.1	23.1	0.8	NAD	Nil	TC-175 TGL-120 LDL 138 HDL-34	Wnl	Normal diastolic function
46.	PIRAMU	60F	Nil	Nil	91	6.3	22	0.7	NAD	Nil	TC-176 TGL-120 LDL-130	Wnl	E/A-0.8 IVRT-106msec DT-225 msec

											HDL-35		
47.	KARTHIKEYAN	45M	Nil	Nil	82	6.2	26.2	1.2	NAD	Nil	TC-196 TGL-146 LDL-125 HDL-30	Wnl	Normal diastolic function
48.	PONAPPAN	48M	Nil	Nil	90	5.9	23.9	1.0	NAD	Nil	TC-220 TGL-170 LDL-140 HDL-34	Wnl	Normal diastolic function
49.	GURUVAMMAL	63F	Nil	Nil	76	6.0	23	0.8	NAD	Nil	TC-185 TGL-146 LDL-140 HDL-39	Wnl	Normal diastolic function
50.	IBRAHIM	47M	Nil	Nil	98	6.4	24.1	1.0	NAD	Nil	TC-225 TGL-202 LDL-175 HDL36	Wnl	Normal diastolic function

ANNEXURE 3 : KEY TO MASTER CHART

Sl no	Parameter	Normal values
1.	FBS- FASTING BLOOD SUGAR	<100 mg/dl
2.	HBA1C- GLYCATED HEMOGLOBIN	<6.5 %
3.	BODY MASS INDEX	18.5-22.5
4.	WAIST HIP RATIO	Male-<0.9 Female < 0.8
5.	TOTAL CHOLESTEROL	<200 mg/dl Desirable 200–239 mg/dl Borderline high 240 mg/dl High
6.	TRIGLYCERIDE	<150 mg/dl
7.	LDL- CHOLESTEROL	<70 mg/dl Therapeutic option for very high risk patients <100 g/dl Optimal 100–129 mg/dl Near optimal/above optimal 130–159 mg/dl Borderline high 160–189 mg/dl High 190 mg/dl Very high
8.	HDL- CHOLESTEROL	<40 (<1.03) Low 60 (1.55) High
9.	ELECTROCARDIOGRAM INTERVALS RATE/PR SEGMENT/AXIS/QRS SEGMENT/QT SEGMENT/ST-T CHANGES	75-100/mt/80-120 msec/Normal axis 80-120 msec/320-400 msec/No st-t changes
10.	E/A RATIO	>/= 1.5
11.	DECELERATION TIME	160-240 msec
12.	ISO VOLUMETRIC RELAXATION TIME	60-100 msec

ANNEXURE 4

ABBREVIATIONS

1. DbCM – Diabetic Cardiomyopathy
2. ROS – Reactive Oxygen species
3. PKC – Protein Kinase C
4. NFkB – Nuclear Factor kappa B
5. T2DM – Type 2 Diabetes Mellitus
6. AGEs – Advanced Glycation End products
7. RAS – Renin Angiotensin System
8. AGT II – Angiotensin II
9. CAN – Cardiac Autonomic Neuropathy
10. PDR – Proliferative Diabetic Retinopathy
11. NPDR – Non Proliferative Diabetic Retinopathy
12. LVEF – Left Ventricular Ejection Fraction
13. IVRT – Iso Volumetric Relaxation Time
14. DT – Deceleration Time
15. CAD – Coronary Artery Disease
16. ACS – Acute Coronary Syndrome
17. DNA – Deoxy ribo Nucleic Acid