ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN ADULT NIGERIANS WITH NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS

A Dissertation Submitted to the National Post Graduate Medical College of Nigeria in Partial Fulfillment of the Requirement for the Fellowship of the College

BY

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MBBS PORT HARCOURT 1989

NOVEMBER, 2005.
DECLARATION

It is hereby declared by me that this work is original unless otherwise acknowledged. The work has not been presented to any other college for Fellowship nor, has it been submitted elsewhere for publication.

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The study reported in this dissertation: Echocardiographic Assessment of Left Ventricular function in Adult Nigerians with Newly Diagnosed Type 2 Diabetes Mellitus was done by the candidate, DR. BONAS B. HARRY of the Department of Medicine University of Port Harcourt Teaching Hospital (UPTH) Port Harcourt, under our supervision.

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<td>A M-mode amplitude in cm</td>
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<td>AO</td>
<td>Aortic diameter in cm</td>
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<td>BMI</td>
<td>Body mass index in kg/m²</td>
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<td>BSA</td>
<td>Body surface area</td>
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<td>CI</td>
<td>Cardiac index in l/ m²</td>
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<td>CO</td>
<td>Cardiac output in litres.</td>
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<td>CT-Scan</td>
<td>computerized tomographic scan</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>Diastolic Blood pressure in mmHg</td>
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<td>DC</td>
<td>Diabetic cardiomyopathy</td>
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<td>DDM</td>
<td>Duration of diabetes mellitus in years</td>
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<td>DT</td>
<td>Deceleration time in msec.</td>
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<td>FS</td>
<td>Fractional shortening in percentage or fraction</td>
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IDDM  Insulin dependent diabetes mellitus
IVRT  Isovolumic relaxation time in msec.
IVSTD Inter ventricular septal thickness in diastole in cm
LA  Left atrial diameter in cm
LVMI  Left ventricular mass index in g/m²
LV mass  Left ventricular mass in gm.
LV  Left ventricle
LVEDD  Left ventricular posterior wall diameter in diastole.
LVEDV  Left ventricular end diastolic volume in mls.
LVESD  Left ventricular end systolic dimension in cm
LVESV  Left ventricular end systolic volume in mls.
LVPWD  Left ventricular end diastolic diameter in diastole in cm
MHC  Myosin heavy chain
MRI  Magnetic resonance imaging
NDDG  National diabetic data group
NIDDM  Non-insulin dependent diabetes mellitus
PET  Positron emission tomography
RV  Right ventricle
RVEDD  Right ventricular end diastolic dimension in cm
SBP  Systolic blood pressure in mmHg
SHN  Systemic hypertension
SV  Stroke volume in mls.
SVI  Stroke index in mls/kg/ m²
TCH  Total cholesterol
VCF  Mean velocity of Circumferential fibre shortening in circ./sec.
WHO  World Health organization
WT  Weight in Kg
DEDICATION

To my beloved wife Soibi and lovely daughter Ella
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First of all my immense gratitude goes to Dr B.C. Anisiuba consultant cardiologist UNTH Enugu who gladly and graciously ushered me into the real and exciting world of echocardiography and had encouraged and supervised every technical detail of this work even when it appeared as if the work was not going to materialize.

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**ABSTRACT**

From January 2004 to August 2005, a total of 82 (42 male and 40 female) newly diagnosed diabetic subjects who were not more than 3 years in duration, normotensive with normal plasma cholesterol, no urinary microalbuminuria and no ECG evidence of ischaemia after exercise with no other evidence of cardiac dysfunction were recruited out of 420 patients attending medical, cardiac and diabetic clinics. Also recruited were 81 age and sex matched control subjects, who were mainly drawn from patients relatives and hospital community. The control subjects were screened to meet the inclusion criteria.

The study populations were investigated non-invasively with M-mode, Two-dimensional and pulsed Doppler echocardiographic techniques and their systolic and diastolic indices were determined.
Diabetic subjects showed significant alteration in their left ventricular geometry with increased LV mass, $134.9 \pm 35.5$ gm for diabetics and $109.2 \pm 25.7$ gm for control, $P<.0001$. Also IVSTD, LVPWD were significantly increased in diabetic subjects, $.825 \pm .12$ cm and $.849 \pm .11$ cm against $.721 \pm .10$ cm and $.783 \pm .10$ cm for normal control subjects respectively, $P<.0001$ across.

Systolic parameters were significantly depressed in diabetic subjects by 16.8%, 6.2% and 13.6% for EF, FS and VCF respectively when compared to normal control. The 13.6% depression of VCF is noteworthy since it is less subjected to vagaries of loading conditions than EF and FS.

The prevalence of impaired relaxation as evidenced by E:A ratio $<1$ with prolonged IVRT and DT was 40.2% and majority of them were women implicating F:M ratio of 1.2 :1.

In the assessment of diastolic dysfunction there was little or no correlation between Em/Am ratio by M-mode and E:A ratio by Doppler means, $r = .005$ for diabetic and $r = .134$ for control $P>.05$. Therefore E:A ratio by Doppler is more sensitive.

The major determinants of diastolic dysfunction as shown by multiple regression analysis were age $\beta = - .293$, $P<.01$ and IVRT $\beta = -.627$, $P<.0001$ for the diabetics. Age $\beta = -.432$, $P<.01$ and IVRT $\beta = -.378$, $P<.01$ for normal control subjects.
Therefore, diabetes mellitus causes left ventricular dysfunction in newly diagnosed diabetic subjects.
**INTRODUCTION**

Diabetes Mellitus (DM) constitutes the single most important endocrine problem in Africa. Details of the incidence and the devastating effects of this condition in developing countries are emerging daily from most major centres in the continent.\(^1\)\(^-\)\(^3\) The prevalence of DM in developing countries including those of Africa varies from place to place and also from rural to urban centres.\(^3\)\(^,\)\(^4\)\(^,\)\(^5\) Mclarty et al showed a prevalence of 1.7% in an urban setting and 0.9% in a rural African Community.\(^5\) In Nigeria Akinkugbe found a national prevalence rate of 2.2%.\(^6\)\(^,\)\(^7\) Oli had earlier shown a preponderance of 4% in urban dwellers as against 2% of rural inhabitants.\(^8\)

As at 1992 Nigeria’s population was put at a little more that 80 million,\(^9\) today, thirteen years later the projection of Nigeria’s population is put around 150 million. From the foregoing, one only needs to take a cursory look at the prevalence rate vis-a-vis the phenomenal population growth to appreciate the enormity of the disease burden in Nigeria.

Epidemiological studies have established that the type 2 DM is the commonest variety. It constitute about 80 to 90% of the entire diabetes population world wide.\(^10\)\(^,\)\(^11\) The disease is chronic and progressive, the metabolic derangement associated with it is responsible for the secondary pathophysiological changes in multiple organ system (multi-organ complications) that imposes tremendous disease and financial burden on the individual and the health care delivery system. While the acute complications consist of those dare
emergencies like hypo and hyperglycaemic comas\textsuperscript{12,13} which rapidly progress to death if urgent interventional measures are not taken to abbreviate their full clinical course, the chronic complications are the most agonisingly debilitating and could involve all organ systems in the body.\textsuperscript{14,15} Thus retinopathy, neuropathy and nephropathy among others are as a result of microvascular complication (microangiopathy). While stroke, the spectrum of ischaemic heart disease, peripheral artery disease (PAD) etc could be the terminal outcome of macrovascular complication (macroangiopathy).

Cardiovascular complications, which form the focus of this study, are the commonest complication and indeed the leading cause of death in diabetic patients. It has been reported to account for almost 80\% of all deaths from DM in the Western world,\textsuperscript{16} while cardiovascular complications were found to be 54.4\% in a developing country like SriLanka.\textsuperscript{17} About three fourth of these deaths result from coronary artery disease.\textsuperscript{16,18,19} That diabetes is a potent risk factor for congestive heart failure has been established for decades, but the knowledge of the pathophysiology and treatment of heart failure in diabetes are limited.\textsuperscript{20} On the other hand the prevalence of diabetes in different surveys and clinical trials of heart failure ranges from 10 to > 30\%.\textsuperscript{21}

There is significant evidence from the community data of the Framingham Heart study which have shown increased incidence of congestive heart failure in diabetic patients irrespective of coronary heart disease and hypertension.\textsuperscript{22} The relative impact of diabetes in developing heart failure was found to be greater in women.\textsuperscript{23,24,25} In the studies of left ventricular dysfunction (SOLVD)
Trials and Registry, diabetes was found to be an independent risk factor for mortality in both symptomatic and asymptomatic heart failure patients. Despite similar left ventricular systolic function, patients with diabetes have more florid heart failure symptoms, use more diuretics, and have an adverse prognosis compared to those without diabetes. One explanation for this observed discrepancy is diastolic dysfunction of the left ventricle.\textsuperscript{20,26} In overt heart failure diastolic dysfunction often coexist with systolic dysfunction.\textsuperscript{20,27} However, diastolic dysfunction is a frequent finding in many studies of cardiac function in type 2 diabetic subjects without symptoms and signs of heart disease.\textsuperscript{28} Diastolic dysfunction independent of ischaemic heart disease and hypertension has been explained by the concept of diabetic cardiomyopathy.\textsuperscript{29}

Several studies have pointed to the fact that there exist distinct morphological changes in the diabetic heart.\textsuperscript{29} These anatomical studies have clearly shown that diabetic cardiomyopathy is characterized by alterations in the microvasculature and interstitium. In the initial stages of the disease interstitial changes with preserved myocytes and microvascular morphology may predominate and cause the observed reduction in myocardial compliance.\textsuperscript{30} With disease progression salient findings include left ventricular hypertrophy with perivascular, interstitial and replacement fibrosis and accumulation of periodic acid Schiff (PAS) – positive materials. Arteriolar or capillary involvement typical of diabetic microangiopathy including increased thickening of myocardial capillary basement membrane and micro aneurysms occur later in association with more severe myocardial dysfunction.\textsuperscript{31}
The above described pathological alterations are associated with a wide range of myocardial dysfunction states ranging from asymptomatic diastolic dysfunction to overt systolic heart failure. Impaired or diminished left ventricular compliance in the presence of normal systolic function is usually the initial step.\textsuperscript{32,33} Diastolic abnormalities occur in 27 to 69% of diabetic patients without symptoms of heart failure and may often predict subsequent progression towards the development of frank heart failure.\textsuperscript{32,34,35} Balogun found diastolic dysfunction of 24.2\% in his study.\textsuperscript{36} Systolic function indices are most times found to be within normal limits in diabetics, but are often found to be reduced when compared to normal control.\textsuperscript{37,38}

Even in the absence of frank systolic dysfunction in resting conditions, several studies have shown lower ejection fraction and fractional shortening in response to dynamic exercise as well as reduced exercise capacity\textsuperscript{38-42} suggesting a decreased functional reserve in many asymptomatic patients with diabetes.

Most of the available data have demonstrated left ventricular dysfunctions (both diastolic and systolic) in Type 1 diabetes mellitus. In contrast, little information is available in Nigerian patients with Type 2 diabetes mellitus with regard to age weight, level of DM control and presence of microangiopathy all of which may affect left ventricular functions particularly diastolic. It is known that some degree of left ventricular abnormality exists even in subjects with impaired glucose tolerance\textsuperscript{43} when compared with normal control. There is dearth of data, which could possibly establish clearly the critical point in the
natural temporal course of diabetes mellitus where significant, left ventricular and indeed cardiac dysfunctions begin, particularly in Nigerian subjects. This forms the major thrust of this study. The finding no matter the strength or weakness of validity is hoped might add a layer or two to the accretion of functional working knowledge that could help in the longitudinal follow up of patients, early application of preventive measures to those at risk, abbreviation or arrest of the disease progression and early treatment of Type 2 diabetes mellitus.

Left ventricular systolic and diastolic indices were initially assessed using cardiac catheterisation.\textsuperscript{43-45} Subsequently, first pass and gated Radionuclide ventriculography, rapid cine-CT scan and magnetic resonance imaging have all been used to assess these parameters directly with even greater accuracy. The disadvantage of cardiac catheterisation is in its invasive nature, which cannot be justified, in longitudinal studies of asymptomatic patient.\textsuperscript{46}

Radionuclide techniques though non-invasive offer good balance of accuracy, ease of use, portability and cost effectiveness, expose the patient to ionizing radiation\textsuperscript{47,48} and it is not available in the country. Rapid Cine-CT scan and magnetic resonance imaging both of which can give extremely precise determination of left ventricular mass, volume, ejection fraction and other parameters\textsuperscript{49,50,51} are very expensive bulky and not readily available in Nigeria.

Echocardiography, which can accurately and serially measure indices of left ventricular systolic and diastolic function non-invasively is particularly
attractive for the evaluation of the effects of Type 2 diabetes mellitus on the heart.\textsuperscript{38,52,53,54,55}

Doppler echocardiography is a validated, simple reliable and safe technique for non-invasive assessment of left ventricular diastolic function.

In the present study, the author carried out a case control study using M-mode, two-dimensional and Doppler echocardiographic techniques to evaluate left ventricular function in adult Nigerian subjects with Type 2 diabetes mellitus with the view to determining whether abnormal left ventricular function is present at an early stage of the disease diagnosis in Nigerians; the pattern and prevalence of the left ventricular dysfunction if any; and whether the left ventricular dysfunction has any sex predilection.
AIMS AND OBJECTIVES

General
To determine the role of hyperglycaemia in the pathogenesis of Diabetic Heart Dysfunction.

Specifics
(1) To determine whether abnormal left ventricular function is present at an early stage of Type 2 DM in Nigerians.
(2) To determine the pattern and prevalence of the left ventricular dysfunction.
(3) To determine whether the left ventricular dysfunction has any sex predilection.
Definition

Diabetes Mellitus (DM) comprises a group of common disorders that share characteristic of chronic hyperglycemia which result from relative or absolute deficiency of insulin production and/or secretion, decreased peripheral utilization of insulin (insulin resistance) and increased hepatic production of glucose.\textsuperscript{56-60} The above mechanisms may operate singly or in variable combinations. Classically DM is associated with symptoms of excessive thirst, increased urine volume and if severe enough, weight loss. On the other hand, it may remain asymptomatic and presents with its complications.

Disease and Financial Burden

The disease and financial burden arising from chronic complications of DM can be enormous and can task the health care delivery system. Thus in the United States of America (USA), DM is the leading cause of end stage renal disease, non traumatic lower extremity amputation and adult blindness\textsuperscript{59,61} all of which add to the increasing toll of disability. As a result, its economic impact on available resources is tremendous. In 1992 the estimated cost of diabetes in the USA alone was between $85bn and $92bn, two thirds of which resulted from lost productivity, from admissions to hospital and absence from work, disability, diminished work effectiveness and premature deaths.\textsuperscript{61} During the course of literature search, no available data were found with respect to the economic impact of DM in Nigerians but it is most likely to be very high.
**Prevalence**

As at 1994, more than 100 million people were affected worldwide and this prevalence figure is expected to more than double to 239 million people by the year 2010. Data emanating from Canada and the USA suggest that a vast majority, more than 90% of diabetics are of type 2 variety. About 6% of the United States population has proven cases of DM. This figure represents almost 16 million individuals. The incidence is increasing every year.

Approximately 1,700 new cases of diabetes mellitus are diagnosed every day with 625,000 new cases annually. Twenty five percent of cases of new onset type 2 diabetes mellitus occur among people below age 20. The prevalence varies with sex, age race and geography.

The incidence is 1.5% from 20–39 year age range. Approximately 20% of those more than 64 years age range have diabetes mellitus. The incidence is similar in both men and women through most age range but greater in men than women in those above 60 years. Diabetes mellitus is common among racial minority in the USA for example all aboriginal populations in America, East Indians, American Blacks and other minor racial groups have disproportionate increase in prevalence of diabetes mellitus.

Worldwide, the Scandinavian countries have the highest rate of occurrence of Type 1 DM. Finland has an incidence of 35 new cases in every 100,000 people per year. Japan and China, both of which belong to the Pacific Rim, have 1 to 3 per 100,000 populations every year of type 1 diabetes mellitus. Northern Europe and the USA have an intermediate rate of occurrence, about 8 – 17 per
100,000. A national survey done in Australia involving 11,247 participants found a national prevalence of 7.4% and is as a result of doubling effect since 1981.\textsuperscript{65}

In Africa prevalence also varies. A public survey done in 1995 in Gaborone City Botswana showed a prevalence rate of 1.5%.\textsuperscript{66} In Malawi, hospital based studies had in two centres in 1973 and 1986 showed a prevalence average of 2%.\textsuperscript{67,68} As already stated, in Nigeria, the national prevalence is 2.2%. Although in a related work some workers found an urban gradient of 4% with a rural rate of 2%. These figures may have increased given the upward trend observed worldwide attributable to the phenomenon of “epidemiological transition,”\textsuperscript{69–71} changing life style to more Westernized type.

The type 2 diabetes mellitus is usually preceded by a long period of Impaired Glucose Tolerance (IGT), a reversible metabolic state associated with increased prevalence of macrovascular complications. Thus, at the time of diagnosis, long-term complications may have developed in almost 25% of subjects.\textsuperscript{72} Susceptibility to type 2 diabetes mellitus requires an intricate interplay between genetics (most likely polygenic) and environment (acquired factors). Pathogenesis involves intervening sequences in insulin resistance and beta-cell failure.\textsuperscript{72,73} Cardiovascular disease (CVD) is the commonest complication of type 2 diabetes mellitus in the developed world. It accounts for between 66 to 80 percent of deaths in the developed world.\textsuperscript{74} As documented earlier SriLanka a developing country has 54.4% of all diabetes mellitus complications as CVD.
The cardiovascular complications involve the myocytes, the neural, coronary and interstitial structures of the heart through myriads of mechanisms including, glucotoxicity, lypotoxicity, amyliintoxicicy, insulintoxicicy, angiotensintoxicicy, redox stress and accelerated atheroscleropathy and consequent macroangiopathy and mirocangiopathy. All these ultimately result in the impairment of left ventricular (LV) functions.\textsuperscript{75}

\textbf{Concordance Rate in Twin Studies}

Type 2 diabetes mellitus is highly concordant among monozygous twins and less so in dizygotic twins. Most studies show a concordance rate ranging from 34 – 100\% and 16 – 40\% among monozygous and dizygous twins respectively.\textsuperscript{76,77} These twin studies indicate that genetic factors play a major role in the aetiology of type 2 diabetes mellitus. In contrast, they also support a role for non-genetic factors, since the concordance rate may be less than 100\% in some cases.
Classification and Diagnosis

The National Diabetes Data Group (NDDG) in 1979 formally recognized two broad categories of diabetes mellitus—Insulin Dependent Diabetes Mellitus (IDDM) type 1 and Non Insulin Dependent Diabetes Mellitus (NIDDM) type 2. The Type 1 diabetes mellitus is further subdivided into type 1A diabetes mellitus, which results from autoimmune beta cell destruction with consequent insulin deficiency, evidenced by immunological markers i.e., islet cell autoantibodies (ICAs). Sufferers are ketosis prone. Type 1B diabetes mellitus, also characterized by insulin deficiency as well as tendency to develop ketosis but lacks immunological markers indicative of autoimmune origin. Although only a minority of patients with type 1 diabetes mellitus falls into this category, of those who do, most are Africans or Asians. This type of diabetes mellitus is strongly inherited and is not HLA associated.

Immunological Markers for type 1A diabetes mellitus include

i) Autoantibodies (ICAs) to glutamic acid decarboxylase (GAD), a biosynthetic enzyme for production of neurotransmitters, Gamma Amino Butyric Acid (GABA).

ii) ICA to phogrin—insulin secretory granule protein

iii) ICAs to insulin, ganglioside and carboxyl peptidase H.

On the other hand, type 2 diabetes mellitus has variable degrees of Beta-islet cell dysfunction with impaired insulin secretion, insulin resistance (IR) and increased hepatic glucose production. Beta-cell dysfunction in type 2 diabetes mellitus is characterized by a gradual but progressive decline from near-absent first-phase glucose-induced insulin secretion to impaired second-
phase insulin secretion, glucose potentiation and disproportionate hyperproinsulinaemia with impaired basal or steady state insulin secretion. Patients with the clinical disease and fasting hyperglycemia are at the end – stage of this process. The remarkable finding in this condition is that hyperglycaemia seems to compensate for the impaired glucose potentiation and second-phase defect so that, at the intermediate stages of final B-cell failure (fasting plasma glucose<200mg/dl), non-glucose secretagogues are able to produce an insulin response that is absolutely normal in both magnitude and timing. This response is to such diverse signals as glucagon – like peptide-1, secretin, the B-adrenergic agonist isoproterenol, tolbutamide, arginine etc.

The NDDG also recognized gestational DM, Impaired Glucose Tolerance (IGT) – comprising asymptomatic diabetes mellitus, latent and chemical DM and other types of secondary DM. The NDDG diagnostic criteria were based on measures of blood glucose; a fasting blood sugar (FBS) 7.8mmol/L (140mg/dL) or Random blood sugar (RBS) 11.1mmol/L (200mg/dL). They further proposed that a FBS < 5.5mmol/L excludes DM and random values between 5.6 and 11.0mmol/L requires an oral glucose tolerance test for diagnosis. Values less than 7.8mmol/L show no glucose intolerance and between 7.8 – 11.0mmol/L depict impaired glucose tolerance. Demonstration of a plasma glucose concentration in excess of these values on a single occasion in a symptomatic individual confirms the diagnosis while more than 2 separate occasions are required for asymptomatic individuals. This was adopted by WHO Expert
Committee on diabetes mellitus\textsuperscript{82} in 1980. They further subdivided type 2 diabetes mellitus into obese and non-obese.

In 1985,\textsuperscript{83} WHO added a contentious group - Malnutrition related diabetes mellitus, for which there was a lot of argument pertaining to its existence. Over the last decade however it has become clear that fasting cut off of 7.8mmol/L does not detect all individuals who go to demonstrate a 2 hour post load value of 11.1mmol/L or over, the latter being the most rigorously validated diagnostic limit for diabetes. In the mid 1990s, both the American Diabetes Association (ADA) and WHO convened expert groups to consider these issues.

The ADA published its report in 1997,\textsuperscript{84} accepting a lower value of \( \geq 7.0\text{mmol/L} \) than the value of \( \geq 7.8\text{mmol/L} \). They also stated that Oral Glucose Tolerance Test (OGTT) was no longer necessary for routine clinical purposes. A new category of Impaired Fasting Glucose (IFG) was identified; recognizing individuals whose fasting glucose concentration is raised (\( \geq 6.1\text{mmol/L} \)) but is below the diagnostic threshold. Like IGT, IFG is a risk factor for cardiovascular and future diabetes mellitus.\textsuperscript{85} A re-analysis of data from >25,000 OGTTTS performed in epidemiological surveys across Europe showed that the ADA (fasting) and WHO (2hour glucose load) criteria did not identify the same group of patients. Other studies reached similar conclusion.\textsuperscript{86} Differences were greatest in the lean elderly who are more likely to have a normal fasting plasma glucose concentration with an inability to tolerate glucose in response to oral glucose challenge\textsuperscript{87} and in obese middle aged individuals who are more likely to have a raised fasting glucose concentration but a normal response to the OGTT.
The ADA had recognized this potential for diagnostic discrepancy but had argued that the fasting glucose was the more satisfactory test for routine clinical use in view of its simplicity, higher reproducibility, better patient and physician acceptability and lower cost. The WHO provisional report, published in 1998, accepted the reduction of a fasting cut off value to $\geq 7.0\text{mmol/L}$ but retained the use of OGTT to establish the diagnosis in patients with random blood glucose between 5.5-11.1\text{mmol/L}.

The period of consultation ended with the publication in 1999 of the definitive report (All glucose values refer to venous plasma in \text{mmol/L}). It states: in the absence of classical symptoms (thirst, polyuria and unexplained weight loss) a random plasma glucose in the recommended first test, values < 5.5 \text{mmol/L} excludes DM, $\geq 11.1\text{mmol/L}$ diagnoses diabetes mellitus. Between 5.1 – 11.0\text{mmol/L}, requires at least 2 diagnostic fasting glucose results at different occasions. Values between 6.1–6.9\text{mmol/L} diagnoses IFG and such subjects are subjected to OGTT to make a definitive diagnosis. A 2 hour glucose load $\geq 11.1\text{mmol/L}$ establishes the diagnosis, while a value < 7.8\text{mmol/L} proves no IGT and between 7.8 to 11.0\text{mmol/L} contends with IGT.

The diagnosis of diabetes is sometimes made when a patient presents with severe metabolic decompensation and grossly elevated blood glucose concentration (particularly true of type 1) or by demonstration of unequivocal hyperglycaemia in the presence of common symptoms (urinary frequency and thirst). However an insidious presentation, particularly of type 2 diabetes is common and it is such patients (who in WHO terms are more likely to have
glucose values in the uncertain range) that clear diagnostic guidelines are required. For recruiting patients in this study, a fasting plasma glucose ≥ 7.0mmol/L (126mg/dl) or a random plasma glucose ≥ 11.1mmol/L (200mg/dl) established the diagnosis.

**Table 1: Criteria for the Diagnosis of Diabetes Mellitus**

<table>
<thead>
<tr>
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<th>Criteria</th>
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<tr>
<td>1</td>
<td>Symptoms of diabetes plus random blood glucose concentration &gt;11.1mmol/L (200mg/dL) (^a) OR</td>
</tr>
<tr>
<td>2</td>
<td>Fasting plasma glucose &gt; 7.0mmol/L (126mg/L) (^b) OR</td>
</tr>
<tr>
<td>3</td>
<td>Two-hour plasma glucose ≥11.0mmol/L (200mg/dL) (^c) during an oral glucose tolerance test</td>
</tr>
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**NB:** In the absence of unequivocal hyperglycaemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on another day.

a) Random is defined as without regard to time since the last meal.

b) Fasting is defined as no caloric intake for at least 8 hours.

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

Source: Adapted from American Diabetes Association 2000.
**Pathogenesis of Type 2 Diabetes Mellitus**

The pathophysiological mechanisms of developing type 2 DM may be hinged on the process of amyloidogenesis and beta-cell loss, lipotoxicity, thrifty gene expression, Redox stress, environmental factors and increased hepatic glucose production.

**Amyloidogenesis and Beta-Cell Loss**

Before now the prevalent view was that for hyperglycaemia to develop and therefore type 2 diabetes mellitus, there would be a significant beta-cell loss. From recent evidence a significant beta cell loss does not seem likely especially at the early phase of clinical hyperglycaemia. This conclusion is supported by autopsy studies suggesting that at death perhaps $\leq 20 – 50\%$ of B-cell have been lost after many years of disease process.\textsuperscript{90,91} The mechanism of this loss is not fully elucidated. However, emerging evidence has implicated the process of amyloid depositions in the pancreatic islet gland or amyloidogenesis to be partly responsible. Findings reported of pancreas at pathology shows lack of inflammation normal appearing alpha and delta cells, and normal B-cells. There is significant deposit of amyloid, which seems to be replacing the B-cells.

The magnitude of the replacement of B-cell by amyloid deposits during life is unknown as are its onset and rate of development. Vechere et al\textsuperscript{92} and other groups through animal experiments have found that the major precipitating factor is high fat diet. It is also revealed that the amyloidogenic processes impair B-cell function before B-cell death occurs and replaced by amyloid. It has also been pointed out that the loss of B-cell function is disproportionately
more important than the B-cell loss.\textsuperscript{93} It is also known that the amyloid fibril formation begins during impaired glucose tolerance and this process is responsible for beta-cell failure and consequent abnormal insulin secretion.

Amylin or the islet-cell amyloid polypeptide (IAPP) the major constituent of amyloid protein deposits is stained in the failing or dysfunctional B-islet cells.\textsuperscript{94} Further more intermediate sized amyloid particles have been found to be toxic to B-cells through the induction of apoptosis by membrane disruption.\textsuperscript{95} Amylin is known to stimulate the elevation of free fatty acid (FFA) through the process of lypolysis.\textsuperscript{96} In a permanently elevated state of FFA such as found in obesity, the FFA is utilized in preference to glucose by muscles leading to a decrease in glucose up-take by the muscle cells. The increased level of circulating glucose as a result of poor utilization by muscle cells leads to hyperinsulaemia or insulin resistance which is a key phase in Type 2 DM and metabolic syndrome. The process of lypolysis by amylin also increases the redox stresses which have been found to be toxic to cells including β-cells by its action of lipolysis and increased FFA. Free Fatty Acids are a substrate for increased redox stress, cytotoxicity and intimal remodeling associated with accelerated atheroscleropathy.

There are amylin binding sites in renal cortex and amylin activates the Renin Angiotensin Aldoesteron System (RAAS) with elevation of renin angiotensin and consequently aldosterone and there adverse effects.\textsuperscript{97} Be these as they may, the lipocentric view which holds the elevation of FFA as a prime initiator or a player of dominant role in B-cell dysfunction and insulin resistance has been
challenged by Poitout and Robertson\textsuperscript{98} who recently pointed out that glucotoxicity is a prerequisite for lipotoxicity. The duo posited that chronic hyperglycaemia independent of hyperlipidaemia is toxic to B-cell functions whereas chronic hyperlipidaemia is deleterious only in the presence of hyperglycaemia. They further concluded that in the course of time both glucotoxicity and lipotoxicity contribute to the progressive deterioration of glucose homeostasis and B-cell dysfunction. Seldom do either of these two toxicities exists alone in the post prandial clinical setting of prediabetic and type 2 diabetes mellitus; both of which contribute to the redox stress associated with B-cell damage.

\textbf{Diabetes and the Genes}

It is established that Type 2 diabetes mellitus has a strong genetic component. Although the major genes that predispose to this disorder have remained elusive to date. However, some insights to the genetic linkage of type 2 diabetes mellitus to other disease conditions like the metabolic syndrome (MS) have been provided by the discovery of the Peroxisome Proliferator activator receptors (PPARs): The PPARs are ligand activated transcription factors belonging to the nuclear receptor super family, which also includes the steroid and thyroid hormone receptors. In fact the PPARs and the retinoid X receptors were the so-called orphan receptors before their natural ligands were identified. There are currently three known sub types alpha, delta and gamma. As transcription factors PPARs regulate the expression of numerous genes through which they affect glycaemic control, lipid metabolism, vascular-tone and inflammation\textsuperscript{99,100,101,102}
Activated PPAR – alpha stimulates the expression of genes involved in fatty acids and lipoprotein metabolism. When PPAR- alpha is activated by one of its ligands, for instance normolipidaemic fibric acids, there is a decrease in triglyceride concentration, increase in HDL – Cholesterol, increase in insulin sensitivity with consequent decrease in insulin resistance. It also decreases thrombosis and vascular inflammation. Activation of the isoform of PPAR-gamma also improves insulin sensitivity and decreases blood pressure in addition to FFA and inflammation. These lead to inhibition of atherogenesis, improvement of endothelial function and reduction of adverse cardiovascular events. The thiazolidinedione group of insulin-sensitizing drugs are PPAR-gamma ligands, and these have been found to have beneficial effects on serum lipids in diabetic patients and have also been shown to inhibit the progression of atherosclerosis in animal models.103,104

The Thrifty Gene Hypothesis

States that individuals living in an environment with an unstable food supply could increase their probability of survival if they could maximize storage of surplus energy, for instance as abdominal fat. Exposing this energy-storing genotype to the abundance of food typical of Western societies, and epidemiological transition as found in a subset of Nigeria’s affluent population is detrimental, causing insulin resistance, and subsequently, type 2 diabetes mellitus.99,105

The PPAR-gamma had been shown to be a master controller of the thrifty “gene response” leading to efficient energy storage – thus putting PPAR in a position
of a double edged-sword. Other potential thrifty genes include those that regulate lipolysis or code for β-adrenergic receptor, the hormone sensitive lipase, and lipoprotein lipase. Therefore, it can be said that one, type 2 diabetes mellitus develops as a consequence of a collision between thrifty genes and hostile affluent environment. Secondly the deactivation of PPARs modulation activity has been found to be one of the underlying mechanisms of developing type 2 diabetes mellitus and the metabolic syndrome.

Furthermore, some forms of type 2 diabetes mellitus are characterized by monogenetic defects with mild hyperglycaemia at onset, usually in women before the age of 25 years, these group were formally referred to as maturity onset diabetes of the young (MODY). The defect mainly result to impaired insulin secretion and not impaired insulin action. They are inherited in an autosomal dominant pattern. The most common form is formerly MODY3 in which there is mutation in chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. The second form is associated with mutations in the glucokinase gene on chromosome 7p. Glucokinase is known as glucose sensor and converts glucose to glucose–6-phosphate, this in turn stimulates insulin secretion by the B-cells. Because of the defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. The third form has a mutation in the HNF-4α gene on chromosome 20q which is a transcription factor involved in the regulation of HNF-4α expressions. The second and third conditions were formerly known as MODY2 and MODY1 respectively.
some subsets of type 2 DM Syndromes that have their genetic mutation and
defect at the level of insulin receptors. They are Acanthosis nigrican,
Leprauchaunism and Mendenhall syndromes.

**Increased Hepatic Glucose Production**
The liver maintains plasma glucose during periods of fasting through
gluconeogenesis and glycogenelosis using substrates derived from skeletal
muscle and fat (Alanine, Lactate, glycerol and fatty acids). Insulin promotes
the storage of glucose as hepatic glycogen and suppresses gluconeogenesis. In
type 2 diabetes mellitus insulin resistance in the liver arises from the failure of
hyperinsulinaemia to suppress gluconeogenesis which results in fasting
hyperglycaemia and decreased glucose storage by the liver in the postprandial
state. Increased hepatic glucose production occurs early in the course of
diabetes, though after the onset of insulin secretory abornmalities and insulin
resistance in the skeletal muscle.$^{111,112}$

**Environment and Type 2 Diabetes Mellitus**
Acquired causes of type 2 diabetes Mellitus and the metabolic syndrome
include, overweight, physical inactivity and high carbohydrate diets, in some
individual in which carbohydrate intake makes up more than 60% of the total
caloric intake.

**Type 2 Diabetes Mellitus and Metabolic Syndrome**
Type 2 diabetes Mellitus is now considered as part of metabolic syndrome (MS)
and as such has been given the status of “cardiovascular disease risk
equivalent”; that is patients with type 2 diabetes Mellitus are considered to
have an increased risk, equivalent to those who have established heart disease.\textsuperscript{113,114}

Metabolic syndrome is the term used to define a patient who presents with 3 or more of the underlisted 5 risk factors.

\textbf{Table 2: Diagnostic Criteria for Metabolic Syndrome}

<table>
<thead>
<tr>
<th></th>
<th>Abdominal Obesity (Waist circumference $\geq 102$cm (40in) in men, $\geq 88$cm [35in] in women.</th>
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<tbody>
<tr>
<td>2</td>
<td>Hypertriglyceridaemia ($\geq 150$mg/dl)</td>
</tr>
<tr>
<td>3</td>
<td>Low HDL-C ($&lt;40$mg/dl in men, $&lt;50$mg/dl in women)</td>
</tr>
<tr>
<td>4</td>
<td>High blood pressure ($\geq \frac{130}{85}$ mmHg).</td>
</tr>
<tr>
<td>5</td>
<td>High fasting glucose (IGT [blood sugar $&gt; 100$mg/dl and $&lt;126$mg/dl] without diabetes.</td>
</tr>
</tbody>
</table>

\textbf{NB:} The presence of three or more of the above criteria qualifies a patient as having metabolic syndrome (MS)


The other factors that may or may not be present include glucose intolerance, prothrombotic and pro-inflammatory states. Obesity is closely related to type 2 diabetes mellitus.\textsuperscript{115,116} In obesity an insulin resistance state develops following the deactivation of nuclear peroxisome activator receptors (PPARs) as the initiating phase to the unfolding of the cascades of the other metabolic
abnormalities found in the MS.\textsuperscript{115,116} Hyperinsulaemia appears to be compensatory to the increased level of circulating glucose.

People who develop type 2 diabetes mellitus commonly pass through the phases of excessive adipogenesis (obesity), PPARs modulation deactivation, insulin resistance, hyperinsulinaemia, pancreatic B-cell stress and damage leading to progressive decrease of insulin secretion\textsuperscript{99,115} impaired postpandrial and fasting glucose levels. The fall in insulin secretion leading to hyperglycaemia occurs as a late phenomenon, and in fact separates the patients with MS from those with or without overt Type 2 diabetes mellitus.

In summary, therefore when PPARs are deactivated the metabolic adverse effects occur through two pathways:-

1. With preserved pancreatic B-cell function and insulin hypersecretion which can compensate for insulin resistance. This pathway leads to macrovascular complication of MS.
2. With massive damage of pancreatic B-cell leading to decreased insulin secretion and subsequent hyperglycaemia (eg overt type 2 DM). this pathway leads to both macro and microvascular complications all of which are cardiovascular risk factors.\textsuperscript{107,116}
**DIABETES AND THE HEART**

*Abnormal Energy Balance of Diabetic Heart; a cause of CVD*

The major function of the LV is to receive and pump out oxygenated blood to the body to meet up with the metabolic requirements. The heart fails when it is unable to pump blood commensurate with these requirements and can only do so in the presence of elevated filling pressure. This essentially results from diminished or poor cardiac output. There are four major variables that determine the cardiac output preload, after load, contractility and heart rate. These variables make it difficult to measure the LV function accurately. Linden gave the average cardiac output (CO) in normal subjects at rest as 5 litres per minute and this can increase up to 500% during exercise. This is because the heart has great versatility and reserve.

Diabetes affects the heart in four major ways:

1. Earlier and more severe coronary artery disease.
2. Autonomic neuropathy
3. Specific diabetic cardiomyopathy

These adverse processes disrupt the energy generating pathways of the heart which have been in certain equilibrium when insulin secretion was normal irrespective of other structural and metabolic alterations. This ultimately leads to abnormal energy metabolism, abnormal energy kinetics and improper functioning of the myocardium. The energy of metabolism is derived from carbohydrates, fat and protein, the heart like other tissues utilises the continuous supply of these substances of energy. Diabetes is known to
interfere with some of the metabolic pathways of these substances.\textsuperscript{118} Whereas the mitochondrial fatty acid oxidation is the chief energy source for the normal postnatal heart, the relative contribution of glucose utilization pathways is significant, allowing the plasticity necessary for steady ATP production in the context of diverse physiologic and dietary conditions.\textsuperscript{119} Because of the importance of insulin in the regulation of myocardial metabolism, chronic insulin deficiency or resistance results in a marked reduction in cardiac glucose utilization such that the heart relies almost exclusively on fatty acids to generate energy.\textsuperscript{119}

Although in this adverse situation the myocardium tends to use more free fatty acids for energy. Its utilization is inefficient. Thus high rate of fatty acids utilization in the diabetic could lead to functional derangements related to accumulation of metabolic lipid intermediates, mitochondrial and peroxisomal generation of reactive oxygen species or excess oxygen consumption–a precursor of potent damaging redox potential.\textsuperscript{119,120} The diabetes induced shift in cardiac energy preference is associated with activation of the peroxisomal proliferation activator receptors activity and gene regulatory system. PPARs as already discussed transcript for diverse genes involved in cellular fatty acid utilization pathways including transport, esterification and oxidation among other things.\textsuperscript{119,120}

The metabolism of protein is also affected as shown by Manchester.\textsuperscript{121} The diabetic heart muscle loses protein with out-pouring of amino acids into the blood stream. The phenomenon of the out-pouring of amino acids has been
used to explain why some patients with diabetes mellitus do not present with significant increase in left ventricular mass or hypertrophy when compared to normals in some studies. In the diabetic heart the disturbance of ATP synthesis which is needed for contractility and maintenance of tonic balance across the sarcolemmal and mitochondrial membranes has been implicated as part of the mechanisms responsible for cardiac dysfunction.

**The Concept of Diabetic Cardiomyopathy (DC) and Specific Ultrastructural Features**

The Framingham Heart study and indeed other rigorously determined studies have clearly shown that a subset of diabetes population go into congestive heart failure without evidence of coronary heart disease or hypertension both of which are independent risk factors for heart failure, often associated with diabetes.\textsuperscript{22,122} These observations gave rise to the concept of specific heart muscle disease known as diabetic cardiomyopathy (DC).

The initial clues to the anatomical and pathophysiological changes in diabetic heart came from the works of Regan et al in the hearts of diabetic dogs.\textsuperscript{123} This was followed by the investigation of other workers in the hearts of diabetic rats.\textsuperscript{124} Besides the experimental findings in animals, numerous studies in humans have explored the association of diabetes with histopathological abnormalities. Endothelial proliferation and subendothelial hyaline thickening with PAS positive material in the vessel wall have been described in patients with diabetes with or without congestive heart failure.\textsuperscript{125,126} Capillary basement
membrane thickening and capillary microaneurysms have also been observed in the hearts of diabetics.\textsuperscript{126, 127}

In the study by Zoneriach et al\textsuperscript{128} conducted in young normotensive type 1 diabetes small vessel disease was reported in 72\% of diabetic patients while the lesion was present only in 12\% of non-diabetic subjects. Interstitial accumulation of advanced-glycated end products (AGEs), which include collagen, elastin and other connective tissue proteins, as well as fibrosis in the myocardium have been reported in biopsy or post mortem studies of human diabetic hearts.\textsuperscript{129, 130, 131, 132, 133} AGEs are formed as a result of the non-enzymatic damaging protein glycation due to an excess of glucose (hyperglycaemia) present in both type 1 diabetes mellitus, prediabetic and type II diabetes mellitus.

AGEs are initially formed through the process of glucose nucleophillic addition reaction with proteins forming a schiff base followed by an Amadori compound, which undergoes further reactions, rearrangements, dehydrations and cleavage resulting in brown insoluble, cross-linked complexes–AGEs. This process is thought to liberate H\textsubscript{2}O\textsubscript{2} – one of the reactive oxygen species. These highly cross linked proteins especially collagen, cause stiffening within the vessel which results in decreased compliance of the arterial vessel wall and implicated as an important player in the development of diastolic dysfunction in diabetic cardiomyopathy.
Furthermore, there are advanced fructosylation end products (AFEs), which actually have greater affinity binding to proteins than glucose and follow similar pattern of reactive oxygen specie formation\textsuperscript{134,135} and impaired compliance of the diabetic heart.\textsuperscript{136,137} The multiligand immunoglobulin super family cell surface receptors; the receptors for advanced glycation end products (RAGE) is up regulated by the presence of AGEs and result in the signal transduction of nuclear factor kappa B (NF KappaB) which then results in the chronically active inflammatory state found in type 2 DM.\textsuperscript{138,139}

The mechanisms of collagen accumulation in the diabetic myocardium seems to be due to impaired degradation rather than enhanced synthesis of glycated proteins.\textsuperscript{140} The interstitial abnormalities could explain an increase in end-diastolic stiffness as well as LV mass and contribute to the diastolic dysfunction.\textsuperscript{133} In the less advanced form of tissue abnormality, the interstitial changes seem to predominate for some time and are associated with preserved cell morphology that is consistent with normal systolic function. The accumulation of collagen in the extracellular matrix is said to be responsible for the abnormal acoustic properties (enhanced echogenicity) of the myocardium observed in diabetics and has been suggested as a diagnostic tool. Echocardiographic myocardial texture and ultrasonic myocardial video densitometric analysis showed increased myocardial echodensity, possibly related to collagen deposition both in symptomatic and asymptomatic diabetic patients with normal rest function.\textsuperscript{141} Increased myocardial echo-density suggestive of increased collagen deposition despite normal septal and posterior wall thickness has been observed by some other investigators.\textsuperscript{142}
The coexistence of diabetes and hypertension has been considered as a major factor in the expression of the abnormalities in human diabetic myocardium. This concept initially suggested in diabetic rats’ studies was illustrated in the human study of Van Hoeven et al.\textsuperscript{132} They demonstrated in hearts obtained at autopsy, that interstitial and replacement fibrosis and myocytolitic necrosis were substantially more prominent in heart of hypertensive – diabetics than in patients with isolated diabetes or hypertension. From this observation emerged the concept that this association, which is very frequent in this population, is very likely to have synergistic relationship as a cause of LV dysfunction. This probably forms the basis for the positive effects of the antihypertensive therapy in diabetic patients observed in the UKPDS\textsuperscript{143} and HOT\textsuperscript{144} studies.

**Pathophysiology of Diabetic Cardiomyopathy**

The pathophysiologic mechanism of DC remains largely unknown. However several working hypothesis have been investigated. Amongst them is the shift in myosine isoenzyme content in favour of the V3 isoform.\textsuperscript{145} Calcium homeostasis also appears defective. While calcium transport by the sarcolemmal and sarcoplasmic reticular calcium pumps are minimally affected by diabetes, significant impairment occurs in Na\textsuperscript+ -Ca\textsuperscript{2+} exchange activity. This defect limits the ability of the diabetic heart to extrude calcium, contributing to an elevation in Ca\textsuperscript{2+} cytosolic concentration.

A decrease in Na\textsuperscript+ K\textsuperscript+ - ATPase (the ultimate consequence of the disturbance of ATP production in the energy imbalance occasioned by inefficient use of excess FFA in preference to glucose) which is known to increase calcium ions
secondary to a rise in Na⁺ may also promote the accumulation of Ca²⁺ by diabetic cells. These defects are related to earlier mentioned aberrations of glucose and/or lipid metabolisms which involve membrane change such as phosphotidyle ethanolamine, N-methylation and protein phosphorylation which in turn determine myocyte metabolic dysfunction. Other toxic by products of the abnormal energy metabolism includes acylcarnitine and coenzyme derivatives. The abnormally high rise in these intermediate metabolites could further heighten the disturbance in calcium homeostasis and eventually, leading to cardiac dysfunction. Therefore it is partly in this context, that lowering of raised plasma triglyceride (TG) and FFA has validated clinical relevance. This could decrease the hearts reliance on FFA and overcome the FFA inhibition of myocardial glucose utilization.

Increased levels of citrate, produced by free fatty acid oxidation, inhibit phosphofructokinase, leading to decreased glycolysis and promoting glycogen synthesis. Impaired glucose oxidation also leads to lactic acid accumulation, which further promotes the degradation of FFAs. Reduced myocardial blood flow has been clearly related to diabetes mellitus, independently of frank epicardial coronary disease and is linked to impaired endothelial function. Acute hyperglycaemia may further impair endothelial derived nitric oxide (eNO) mediated vasodilation. Infact the inability to increase myocardial blood flow appears independently related to long-term glucose control, indicating that hyperglycaemia by itself is of considerable importance for the impaired vascular function.
Hyperglycaemia, by increasing the production of endothelial factors such as endothelin\textsuperscript{151}, will also adversely affect the evolution of cardiovascular disease. In the long-term, impaired coronary flow reserve in the presence of the above-described metabolic alterations, might well determine and aggravate a cardiomyopathic process. Diabetes related changes to troponin T, the contractile regulatory protein of thin filaments\textsuperscript{152} have all been implicated in DC. Genetics and dysautonomia have been shown to be contributory to the development of DC.

Clinical and experimental investigations have suggested that increased sympathetic activity, activated cardiac rennin angiotensin system, myocardial ischaemia/functional hypoxia and elevated levels of glucose for prolonged period, due to insulin deficiency result in oxidative stress.\textsuperscript{153} This concept seems to be a unifying one and has special implication in the drug management of diabetics with angiotensin converting enzyme inhibitors etc.

Finally, diabetic patients with mitochondrial tRNA mutation (mitochondrial diabetes) are known to develop cardiomyopathy at an early stage. Through the study of Momiyama et al\textsuperscript{154}, this defect has been shown to lead to rapid progression to cardiomyopathy, initially presenting as hypetrophic cardiomyopathy with definite ECG and echocardiographic evidence and later changing to dilated cardiomyopathy with systolic dysfunction. This may be the case in some patients with diabetes mellitus who rapidly progressed to end stage heart disease.
**DIABETES AND OTHER CARDIOVASCULAR RISK FACTORS: TRACING THE LINK**

There is an interesting interplay between diabetes itself, cardiovascular diseases and various cardiovascular risk factors, and this has been extrapolated to events in early foetal life. This is tacitly explained by the phenomenon of 'PROGRAMMING' - a process where permanent alterations on structure, physiology and metabolism result from stimuli or damage during the critical periods of early development. It is well known in animals as proven by different investigators at different times.\textsuperscript{155,156,157} For example if a new born rat is put on a low-protein diet for only three weeks, its ability to produce insulin is permanently impaired.\textsuperscript{158} The underlying factor in this case must have been permanent impairment of function of the beta cells of the pancreas which produce insulin. Programming occurs because different systems and organs of the body develop in foetal life and infancy during critical and sometimes brief periods. Adverse effects around these periods may result in failure of maturation of the affected organs and subsequently hypofunctioning of the organ.\textsuperscript{159}

Through geographical studies, Barker and Osmond\textsuperscript{160} showed that the phenomenon of programming may be associated with cardiovascular diseases in human. The variations in death rates from coronary heart disease between different areas of England and Wales could not actually be explained by differences in adult lifestyle such as smoking and body build. Through the various follow-up studies, CVD was linked to maternal physique, nutritional state and health of mothers, birth weight of babies and adverse early
environmental influences.\textsuperscript{160-162} Therefore adverse intrauterine conditions result in low birth weight and poor maturation of most organs and consequently malfunctioning of these vital organs in adult life.

Various CVD risk factors such as hypertension, impaired glucose tolerance, Type 2DM, dyslipidaemia and abnormal fibrinogen and factor VII concentrations have been linked to either low birth weight or low weight at infancy. Hypertension is associated with low birth weight but not independently with weight at one year.\textsuperscript{163,164} Raised plasma fibrinogen concentrations are associated with low weight at one year but not independently with low birth height.\textsuperscript{160} Serum concentration of cholesterol are related to methods of infant feeding, which do not influence either blood pressure or plasma fibrinogen concentrations.\textsuperscript{165}

The development of hypertension may not entirely depend on effects initiated in utero (leading to low birth weight), but may be slowly amplified over the lifetime of the individual.\textsuperscript{164} Folkow\textsuperscript{166} first proposed the existence of these two components - initiation and amplification in the aetiology of essential hypertension. The mechanism underlying them is a matter of speculation. Initiation could depend on changes in foeto-placental blood flow or increasing activity of trophins leading to changes in blood vessel structure\textsuperscript{133}, associated with foetal growth retardation. Reduced compliance increases blood pressure, increases pulse pressure, makes vessel walls less compliant. Such a feed back could amplify an initially raised blood pressure from infancy to old age.
Hales et al\textsuperscript{167} showed that the percentage of adults with impaired glucose tolerance or non-insulin dependent diabetes mellitus fell with increasing birth weight and weight at one year. He stated that the weight at one year is not actually related to fatness of the baby but to the length or height of the baby. This was confirmed by other studies carried out at different times by Phipps et al\textsuperscript{168} and Robinson et al\textsuperscript{169}. Hales et al\textsuperscript{167}, noted the link between reduced early somatic growth and impaired glucose/insulin metabolism in adult life, through the measurement of 32-33 split pro-insulin in plasma. This is a precursor of insulin but is not thought to be biologically active in the concentration in which it is found in plasma. Higher plasma concentrations are thought to indicate impaired pancreatic beta-cell activity.

The beta cell compliment of the pancreas is established largely before the age of one year. High levels of 32-33 split pro-insulin were found among men who had low infant weight, especially if they subsequently become obese. An interpretation therefore, is that men with low rates of early growth failed to develop an optimal functioning endocrine pancreas. The precise mechanism of suboptimal pancreatic function (according to Hales et al), is not clear but may be related to impaired blood supply, modification of genes controlling metabolism or some other mechanisms.

Observations among groups of adults have shown some to have both hypertension and Type 2DM.\textsuperscript{170} They also have abnormal lipid metabolism, with high triglyceride and low high density lipoprotein cholesterols, and are also insulin resistant.\textsuperscript{166} They were collectively referred to as syndrome X, by
It has been shown that this syndrome is associated with thinness at birth.\textsuperscript{162} A recent study in which 103 men and women were given insulin tolerance tests confirmed that thinness at birth is associated with insulin resistance or insulin deficiency later in life.\textsuperscript{171} Thus, reduced foetal growth may be associated with both insulin deficiency and resistance to insulin in later life. The insulin resistance syndrome as earlier mentioned therefore forms the pathological bases for Type 2 diabetes itself and its relationship with other CVD risk factors such as hypertension, dyslipidaemia, obesity and other multiple factors of which IRS also has a causal relationship.

There is a linear association between raised blood cholesterol, low density lipoprotein (LDL) and CVD risk and there is evidence that reduction of cholesterol levels in those with hypercholesterolaemia reduces the CV risks.\textsuperscript{172} For many years there has been controversy on the relationship between raised triglyceride levels and cardiovascular risk, with studies that support a relationship being refuted by others which suggest the contrary. Plasma triglyceride levels are a known predictive factor for vascular disease at least in Paris Prospective study\textsuperscript{173} and WHO multinational\textsuperscript{174} study. Its predictive value is quite inconclusive as shown by various studies in Africa.\textsuperscript{175,176} Insulin is involved in both triglyceride synthesis and removal and triglyceride levels reflect the balance between the two. In many populations, linear correlation between insulin and triglyceride levels have been described and it has been suggested that in states of insulin resistance, often associated with obesity, high insulin levels result in high triglyceride levels.\textsuperscript{175}
Hypertension is an important risk factor for CVD\textsuperscript{176,177} and there is abundant evidence that reduction in blood pressure reduces the incidence of stroke.\textsuperscript{178} Hypertension has been shown to accelerate the course and severity of diabetic micro and macroangiopathy\textsuperscript{179,180} The exact mechanism by which diabetes causes elevated blood pressure is not known. One possible explanation is the effect of hyperinsulinaemia on the homeostasis of hormones that regulate blood pressure.\textsuperscript{181,182} It has been shown that accelerated hyperinsulinaemia increases the circulatory concentration of rennin-angiotensin and noradrenalin, as well as systolic blood pressure.\textsuperscript{182-185,186} Another possible factor for hypertension in diabetic subjects is that insulin may promote sodium retention. Hyperinsulinaemia predisposes to hypertension due to its anti-natriuretic effect, with increased reabsorption of sodium and water at the proximal renal tubules.\textsuperscript{185,186}

Obesity in patients with diabetes has been associated with increased insulin resistance which may be associated with hypertension and increased lipid levels.\textsuperscript{187,188} Thus, obese individuals with diabetes run higher risks of renal disease and cardiovascular complications.\textsuperscript{189} Weight reduction has been strongly recommended for obese diabetic patients.\textsuperscript{190} As with diabetes mellitus, it is not obesity per se but rather abdominal obesity that constitutes the strongest adiposity risk factor.\textsuperscript{191,192} In a number of small studies, high insulin levels have also been associated with some other cardiovascular risk factors such as plasminogen activator inhibitor\textsuperscript{193}, microalbuminuria\textsuperscript{194} and cigarette smoking.\textsuperscript{195} Although no single mechanism has been established for the pathogenic role of insulin in the atherosclerotic process, several possibilities
exist for instance, insulin might contribute to the pathogenesis of hypertension by activating the sympathoadrenal axis through modulation of cation transport and hypertrophy of vascular smooth muscle cells. Hyperinsulinaemia might also produce dyslipidaemia by increasing catecholamine levels and by increased synthesis of very - low - density lipoprotein cholesterol. All of these abnormalities are important risk factors for atherosclerosis.\textsuperscript{196} Insulin resistance is commonly associated with a cluster of risk factors for atherosclerosis and coronary artery disease as shown below.

**Summary sketch of the Relationship Between Insulin Resistance**

**Syndrome and other Cardiovascular Risk Factors**

- Obesity
- Hyperinsulinaemia
- Hypertriglyceridaemia
- Hypertension
- High dense LDL
- Low HDL
- Hypercoagulability
- Atherosclerosis
- Endothelial dysfunction

Lastly, there is now compelling evidence that many cardiovascular risk factors either singly or in combination are associated with high circulating insulin levels. High insulin levels in the presence of normal or slightly elevated blood glucose levels signify a state of insulin resistance. In some cases direct measurements of insulin levels have confirmed this relationship. It seems reasonable to hypothesize, therefore, that a primary defect of insulin resistance occurs and that the associated high insulin levels may be causally related to
some of the cardiovascular risk factors and either – may also be associated with the development of atherosclerosis.

(I) **ECHOCARDIOGRAPHY AND LEFT VENTRICULAR DYSFUNCTION**

(1) **Definitions**

The term echocardiography refers to the transmission of pulsed-reflected ultrasound through the heart, with detection of the returning echoes, detailing the position and movement of the cardiac acoustic interface\(^{197,198}\). Ultrasound is sound whose frequency is above the upper threshold of human hearing that is greater than 20,000 cycles per second (or 20 kilohertz). Very high frequency sound in the range of 2 to 10 megahertz (million cycles per second) is used in echocardiography. In adults 2 to 5MHZ frequencies are used, while in children they are usually higher, ranging from 3.5 to 10 MHZ.

Three inter-related modalities of echocardiography in common use now are M-mode, two-dimensional and Doppler echocardiography. M-mode echocardiography uses a narrow ultrasound beam to depict one-dimensional image of the heart. Two-dimensional echocardiography records a spatially correct image of the heart while Doppler echocardiography tracks the velocity of blood flow through the heart and great vessels.

(II) **Principles of Echocardiography**

M-mode and two-dimensional echocardiography are based on the same fundamental principles. Both utilize one or more crystals of a piezo-electric material (a device which interconverts electrical and mechanical energy) which acts both as a transmitter and a receiver of ultrasound. The returning echoes
are then processed and displayed either as an m-(motion) mode or as a two-dimensional echocardiogram.

The Doppler echocardiography utilizes the principle that moving objects alter the frequency of any sound they reflect to recognize blood flow and to characterize its pattern. 197-199

(III) Types of Echocardiography

1. **M-mode echocardiographic equipment** uses a transducer containing one crystal which emits a single ultrasound beam of 1000 to 2000 pulses per second. This produces a very narrow “ice-pick” image of the cardiac structures. The depth of the echo is displayed on the vertical axis, and time on the horizontal axis. The recording thus appears as a continuous graph of the depth of the structures with respect to time. The spatial resolution (the ability to differentiate and recognize structures that are close together) is very high, about 1 to 2cm along the axis of the sound beam. The temporal resolution is also very high. This makes it possible to obtain high-resolution images of rapidly moving structures such as valve opening, closing, fluttering and subtle wall motion abnormalities.

M-mode echocardiography is useful in measuring left ventricular wall thickness and internal dimensions. It is superior to electrocardiograph in detecting left ventricular hypertrophy. 200 Left ventricular internal dimensions can be used to assess the systolic function of the left ventricle by calculating the fractional shortening. Left ventricular mass is also derived from M-mode measurements.
The main disadvantages of M-mode echocardiography are that: it provides only a one-dimensional view of the heart; the cardiac structures are displayed in an unfamiliar format that bears no resemblance to the cardiac anatomy and it is limited in its ability to provide information regarding the spatial orientation of the cardiac structure. Two-dimensional echocardiography was introduced to overcome these disadvantages.

2. **Two Dimensional echocardiographic equipment** uses a transducer containing one or more crystals that are mechanically rotated or electronically fired in a sequential manner. The transducer transmits and receives 120 discrete ultrasound beams through a 60 to 90° sector in order to produce a fan-shaped image of the heart in a cross section. Since it utilizes multiple ultrasound beams, processing of a two-dimensional image takes a longer time than an M-mode image. The sampling rate is thus lower (30 to 60 times per second as against 1000 times per second with M-mode). There is therefore, a substantial decrease in resolution.

A cross-sectional image of the heart is depicted with two-dimensional echocardiography. Thus, direct and accurate visualization of the entire heart, intracardiac structures and great vessels is possible. Global left ventricular function can be assessed by this technique. Left ventricular systolic and diastolic volumes are calculated using the Simpson’s rule \(^{201,202}\). Stroke volume and cardiac output can be derived from these values. The major limitation of two-dimensional echocardiography is its inability to image blood cells and provide data about velocity, direction, timing and spatial profile of
blood flow. To correct this limitation, Doppler echocardiography was introduced.

3. **Doppler Echocardiography** is based on a physical principle known as the ‘Doppler Effect’. This was first described in 1842 by an Austrian mathematician and physicist, Johann Christian Doppler.\(^{203,204}\) Doppler effect is the change in the frequency of sound waves when the source of sound is moving in relation to the receiver. If the source of sound is moving towards the receiver, the frequency would be increasing but if the source of sound is moving away from the receiver, the frequency would be decreasing. Doppler echocardiography is, therefore, based on the frequency shift between the transmitted and the returning ultrasound. When a transmitted ultrasound meets a moving target such as a column of blood, the frequency of the returning echo is different; higher if the target is moving towards the transducer. This difference in frequency—the Doppler shift—is within the audible range and can be displayed as audible signals or as visual signals called spectral trace, on an oscilloscope.

There are several types of Doppler studies, all of which can be performed using a single probe: Pulsed Doppler Echocardiography uses a single crystal to study the patterns of blood flow, including the detection of abnormal flows, shunts and cardiac output; continuous wave Doppler with two separate adjacent crystals, one that continuously transmits sound and the other, which continuously receives reflected sound. In continuous wave Doppler, one has no way of knowing where the individual target might be with relation to the
transducer. In addition one cannot determine whether there is more than one moving targets. There is no range definition with continuous wave Doppler. To overcome this problem pulsed wave Doppler which is range gated Doppler system was introduced. This allows specific areas of the heart to be interrogated.\textsuperscript{205-209}

The major drawback of pulsed wave Doppler is that the velocity one can measure is limited beyond which there will be “aliasing”.\textsuperscript{209,210} The upper limit of frequency that can be detected with a given pulsed system is known as the “Nyquist” limit or number. This limit is defined as one half the pulse repetition frequency. These two modalities add the possibility of studying pressure gradients across valves from flow and valve area observations. Doppler echocardiography can thus detect diastolic dysfunction, which results from left ventricular filling abnormalities, a possible consequence of DM. Transmitral Doppler recordings are now actually the most frequently used methods for evaluating left ventricular diastolic filling.\textsuperscript{211}

The main limitation of Pulsed Doppler echocardiography is that determination of diastolic function by this technique is imprecise: it permits only an indirect measure of diastolic function in relation to left ventricular filling, since it cannot assess all the factors influencing left ventricular diastolic filling directly. Combined alterations of influencing factors may actually “pseudonormalize” the transmitral flow pattern, thus complicating the evaluation of diastolic filling, especially with the presence of both prolonged relaxation and other maldaptive filling abnormalities.\textsuperscript{212} The Doppler examination of pulmonary venous flow is performed to differentiate the normal
pattern of LV filling from pseudonormalization. Also accurate Doppler measurements are impossible in patients with atrial fibrillations.

**Colour Flow Mapping** is a technique that was developed about two decades ago. This technique allows the visualization of intracardiac blood flow superimposed on a two-dimensional echocardiographic display. Using the BART convention, flow towards the transducer is depicted as red, flow away from transducer as blue. Green is added in a mosaic pattern to represent turbulent flow. Colour-coded Doppler is very useful in the detection and mapping of regurgitant and shunt lesions, while facilitating the evaluation of congenital heart disease.

4. **Newer Developments in Echocardiography**

Other echocardiography modalities have come into use to a varying extent in the recent past, especially within the last decade. These include:

(a) **Transoesophageal Echocardiography:** This is of great use in patients in whom the examination from the usual transthoracic approach is technically difficult or impossible. It allows better examination of structures such as the left atrium, assessing prosthetic valves, aortic dissection, vegetations and intracardiac masses. It has a major application now in cardiac surgery, both during and after surgery.

(b) **Intravascular Ultrasound:** The ultrasonic transducer is placed in a small catheter so that a vessel can be imaged through the lumen. This
can evaluate atherosclerosis from within the arteries, and the heart from within the cardiac chambers, using a rotation transducer, rotating ultrasonic mirror, or phased array multielement systems. 221-222

(c) **Contrast Echocardiography:** This makes use of the fact that ultrasound is an extremely sensitive detector of intravascular bubbles. The injection of almost any liquid into the intravascular spaces will introduce many microbubbles that appear as a cloud of echoes on the echocardiogram. Thus the injection into the blood stream of a marker such as saline, agitated or sonicated, angiographic contrast agents, sonicated albumen, indocyanine or some of the patients own blood, may be used as a substitute for the Doppler examination for certain types of flow and shunt visualization. This technique has potential for numerous clinical uses. 223-224

(d) **Stress Echocardiography:** This aids the overall management of patients with suspected coronary artery disease and acute myocardial infarction since stunned or hibernating myocardium can be unmasked, even before patient reports chest pain or ST segment changes are seen in the electrocardiogram. Global or regional changes in left ventricular function can also be assessed. Dobutamine and dipyridamole are commonly used as the biochemical stress agent. 225, 226

(e) **Digital Echocardiography:** This is the digital acquisition, formatting, analysis, storage and review of ultrasound data. The technique was initially developed to reduce some of the practical difficulties
encountered during the performance of stress echocardiography. The most common format used for the observation of cardiac wall motion is ‘quad screen’ format where four synchronized image loops are displayed simultaneously on the screen. 227, 228

\textbf{(f) Doppler Tissue Imaging:} This is a unique and recent application of the Doppler principle to tissue imaging instead of blood. By adjusting gain and reject settings, the Doppler technique is used to record the motion of the myocardium rather than the blood within it. To accomplish this, two important differences must be recognized. First, because the velocity of the tissue is much lower than that of blood flow, the machine must be adjusted to record a much lower range of velocities. Second, because the tissue is much stronger reflector of the Doppler signal compared to blood, additional adjustments are required to avoid over saturation. 229

One potential important derivation of this technique involves strain rate imaging. Strain is a measure of the deformation that occurs when force is applied to tissue. Therefore strain rate is simply its temporal derivative. One obvious drawback about this technique is that the incident angle between the beam and the direction of target motion varies from region to region. This limits the ability of the technique to provide absolute velocity information. By and large instantaneous velocity at two points within the myocardium can be measured and strain and strain rate determined. 230
(g) **Colour Doppler M-Mode Imaging:** Colour Doppler M-Mode imaging is a technique in which pulsed Doppler interrogation is done along a single line of interrogation, analogous to M-mode echocardiography. Unlike M-mode echocardiography, in which the location and intensity of a reflective spectral signal are recorded, the Doppler velocity shift is recorded and then subsequently colour encoded and superimposed on the traditional M-mode image.\(^{231}\) This provides high temporal resolution data regarding the timing and direction of flow events. Since this is pulsed Doppler technique velocity resolution is limited as is the case with routine colour Doppler imaging; however this limitation is compensated for by the ability of the technique to provide high level of spatial and temporal resolution because of the single line interrogation. This technique is used to evaluate characteristics of mitral valve inflow; to determine the width of an aortic insufficiency jet and duration of mitral regurgitation. It can also be used to determine the velocity of propagation (\(V_P\)) of Left Ventricular Inflow.\(^{232}\)

(h) **Tissue Characterization:** Tissue characterization refers to the ultrasound determination of myocardial texture. It uses dedicated, specifically designed ultrasound units that evaluate the complete returning radio frequency signal for cyclical changes in image intensity (backscatter) and “signature”.\(^{233}\) This is so because in the normally contracting myocardium, there is cyclical variation in the intensity of the signal being reflected from the myocardium such that the reflected intensities are lower in systole and greater in diastole. This technique is
a sensitive indicator of both myocardial infarction and ischaemia because with ischaemia and infarction the normal pattern of systolic thickening is lost and with it the magnitude of cyclic variation in backscatter is diminished.\textsuperscript{234,235}

\textbf{(i) Epicardial Imaging:} This technique is anchored on the fact that the fidelity of image intensity is greatest when the amount of intervening tissue is minimal. For this reason the application of an ultrasound probe directly to the cardiac structures provides a high resolution, non-obstructive view of cardiac structures. In epicardial imaging, use is made of specially designed probes capable of eliminating near field distortions. Due to its close contact with the beating heart or vasculature the probes are usually sterilized or placed in a sterile insulating sheath before use. The probes engineered to maximize near-field quality with remarkable high-resolution, high-fidelity images of cardiac structures. The technique was popular before the advent and widespread use of intra-operative transoephageal echocardiography, then it was used to evaluate atheromas in the course of the ascending aorta and arch in an effort to identify the most appropriate site for either cannular insertion or vein grafting. Epicardial imaging still remains a substitute to intra-operative transoephageal echocardiography.\textsuperscript{236}

\textbf{(j) Intracardiac Echocardiography:} This is a recently developed catheter based transducer imaging technique. This technology involves a single-plane high frequency transducer (typically 10 MHz) on the tip of a
steerable intravascular catheter, typically 9 to 13 French in size. The catheter can be steered in both directions laterally and can be retroflexed and anteflexed. The 64-element, single plane transducer at the tip of the catheter is capable of high-resolution, two dimensional imaging as well as colour flow and Doppler spectral imaging.\textsuperscript{237} With this technique visualization of right atrium including fossa ovali is possible with high-resolution. The left atrium and the base of the heart are visualized as part of left ventricular function assessment. Its best application is in complex procedure such as percutaneous atrial septal defect closure, pulmonary vein isolation for treatment of atrial fibrillation and atrial septostomy.\textsuperscript{238}

\begin{itemize}
\item[(l)] **Automated Boundary Detection:** This is recently developed technique, which uses ultrasonic backscatter technology to characterize tissue properties. It incorporates a border detection algorithm for delineating the endocardial blood interface. The system automatically detects the blood and tissue borders, which can be displayed on a two-dimensional sector image. It is of use in calculating blood area changes in the cardiac cycle, and subsequently diastolic function indices.

\item[(m)] **Three Dimensional Echocardiography:** Reconstructed three-dimensional images of the heart using multiple two-dimensional images are now actually in use. A technique orients a two-dimensional transducer in a three-dimensional space using spark gap sensors. Another technique creates 3-D images of the heart using gated,
reconstructed 2-D examinations. Chamber dimensions can, with this technique, be estimated with greater accuracy than is possible using cross-sectional methods. Valves can be seen and assessed with great accuracy.\textsuperscript{239,240}

**Safety of Echocardiography**

Echocardiography is safe for patients as there are to date no appreciable side effects associated with it. The popularity and success of echocardiography as an investigative tool are hinged on safety and risk free nature of ultrasound. Most of their applications with the exception of a few are done non-invasively. This has also improved on its acceptability. Ultrasonic examination of many parts of the body, including such potentially sensitive tissues as a developing fetus and the eye, have been performed on millions of patients worldwide with out documentation of a single serious adverse event.\textsuperscript{241-250} However, the biologic effects of ultrasound depend on the total energy applied to a given region. Both the intensity of the ultrasound beam and the duration of exposure are important factors in the consideration of possible side effects.

Biologic effects of ultrasounds are generally discussed in terms of power and energy generated or transmitted by the equipment. Thus, the amount of acoustic energy (capacity to do work or to produce a biologic effect) is measured in joules.\textsuperscript{250} A joule is the amount of heat generated by the ultrasonic energy. A joule is an equivalent of 0.239 calories. While a calorie is the amount of energy required to raise, the temperature of 1g of water to 1\textdegree C. Acoustic power is the amount of acoustic energy per-unit time. For example the power is 1-
watt (1W) if 1 joule of energy is produced per second. However in biologic tissues the unit of power is usually in milli-watts range (0.001W). This range of power is extremely innocuous. Measurement of power in biologic tissue is done in relation to cross sectional area and this brings us to the term intensity. Intensity is power density or concentration of power within an area usually expressed as watts per meter squared (W/M$^2$) or milli-watts per centimeter squared (m W/cm$^2$).

When the continuous wave Doppler mode is in use power is expressed as average intensity frequently called the spatial average intensity (SA). This is obtained by dividing the total power emitted by the transducer by the surface area of the face of the transducer. Spatial peak intensity of the transducer (SP) can also be measured by using a small thermocouple temperature sensor to detect minuscule rises in temperature in certain areas of the sound field. For M-mode echocardiography use is made of the “duty factor” (DF) – which represents the fraction of time during which the transducer emits ultrasound and the pulse repetition frequency (PRF) must be known to calculate power and intensity. Power and intensity on pulsed wave Doppler and 2 D-echocardiography are also calculated in similar ways.

The evidence available at present indicates that the brief pulses of ultrasound waves used in echocardiography are not likely to cause any cumulative damage. Cavitation is another physical effect of ultrasound. This is apparently produced by gaseous cavitation formed during the negative phase of the sound wave cycle. This has not been proven to occur readily invivo for
lack of sensitive device to detect it. Since blood and tissue are of high viscosity, it is highly unlikely that such an effect could occur in biologic tissue. But when microbubbles are introduced during contrast studies, the ultrasound causes the bubbles to increase cyclically and decrease its diameters. The resultant vibration may cause the bubble to absorb more energy which may be released as heat. Other biological effects caused by ultrasound are:- oscillatory, and sheer forces, radiation, pressure and streaming effects, all have been found to be of no adverse consequence.

A few reports have suggested that some changes might occur at the chromosomal level that affect fetal behaviour and movement. These observation caused considerable concern for individuals using Doppler devices in obstetrics. However, several investigators have had difficulties duplicating these studies. Thus there is still no confirmation of deleterious effects produced by ultrasound in experimental animals using dosage parameters of current clinical applications. All findings thus far indicate that diagnostic ultrasound, particularly that used in echocardiography, is an extremely safe tool with no known deleterious effects, even with the introduction of newer techniques such as Doppler, transesophageal, epicardial and contrast examinations and use of more powerful instruments.

**Cardiovascular Function studies**

The important role of echocardiography as a valid means of evaluating cardiac function has been well demonstrated by various investigators in Nigeria. Since Falase outlined its revelance in the Nigerian contemporary clinic setting in
1976, reports of echo related and indeed other cardiovascular function works have been published. Ladipo\textsuperscript{257} et al in 1980 clearly demonstrated that echo findings can be reproducible in his work of serial measurements of LV dimensions in patients with valvular heart disease and normal subjects. This study is akin to the study of Wise\textsuperscript{258} who evaluated patients with mitral stenosis using diastolic posterior wall motion indices (LVDS). He found that the mitral valve area correlated more closely with LVDS than with left atrial index derived from the posterior aortic wall motion. He then concluded that the result of his study will be useful in predicting the severity of mitral stenosis. While Ladipo’s work was on identifying intra-observer variability Wise’s was to validate an index of measurement. Wise also in addition to evaluating native valve stenosis evaluated mitral prosthetic valves.

Odia\textsuperscript{259} and Falase in 1983 worked on the structural alterations of left ventricular geometry in adult Nigerian hypertensives with valvular heart disease. They determined LV muscle size with ECG and correlated their findings with that of echocardiographic measurements. They found that the \( SV_1 + RV_5 \) or \( RV_6 \) was most sensitive criterion for detecting LVH with 80% positivity in the mitral /aortic incompetent group and 71.1% positivity in the hypertensive patients. A similar study done by Katibi\textsuperscript{260} and Adenle arrived at identical conclusions though their patients were purely hypertensives without other cardiac abnormality. However, in a related work Sybolt\textsuperscript{261} and colleagues used criteria such as \( SV_1 \) and \( SV_4 \) and terminal P-wave duration in \( V_1 \) as independent variables in the prediction of LVH and found their predictive value higher than that of Sokolov and Lyon and the Cornell voltage criteria.
Recently, Ike\textsuperscript{262} and Onwubere published their work in which they related diastolic dysfunction and level of blood pressure in blacks using Doppler flow modality. They concluded that diastolic dysfunction was significantly and progressively higher in the hypertensive group when compared to the normotensive control group. They further recommended that a population based study was necessary to determine diastolic dysfunction and other confounding variables in our environment. Earlier Lawal\textsuperscript{263} and Falase had published similar article on hypertensives attending medical clinic at UCH Ibadan. At the foreign scene, Koren\textsuperscript{200} and Levy\textsuperscript{264} had in seperate works pointed out the implication of increase in LV mass and geometry to morbidity and mortality in uncomplicated essential hypertension. While Anderson\textsuperscript{265} et al did their work on diabetic hypertensive patients using strain rate Doppler modality to arrive at similar conclusions of depressed systolic and diastolic functions. The technique used by Anderson et al was Doppler tissue imaging (DTI) which is proven to be more accurate as it is less dependent on loading conditions.

Babalola\textsuperscript{38} and Ajayi in their study of microvascular complications in Nigerians with hypertension associated with DM showed (among depressed systolic function), worse exercise tolerance in their patients with diabetes and hypertension than with those with either condition alone. Also in a similar work, Okokhere, Obasohan and Balogun, though purely an exercise stress study arrived at identical conclusion.\textsuperscript{39} One related work by Kosakova\textsuperscript{266} et al done with dobutamine stress also demonstrated reduced LV functional reserve
in hypertensive patients who otherwise had normal rest cardiovascular function.

Balogun in a series of published articles has given scholarly insight into mechanisms of heart dysfunctions. In his review article published in 1999 he described the mechanism of heart failure. This was followed by another in 2001 in which the mechanistic sequence of diastolic dysfunction of the heart was described indepth. In a similar review, Zile, Dirk and Brutsaert gave an extensive discourse on the diagnosis, prognosis and measurements of diastolic function in diastolic heart failure. Also in a related work on Nigerian hypertensive heart failure patients Balogun and colleagues demonstrated the nature of diastolic function in this subset of patients. In another related work Oyatti and Danbauchi looked at the structure and functions of the hearts of the hypertensive heart failure patients in Zaria and found a prevalence of 69.4% of diastolic dysfunction. Their finding of 69.4% diastolic dysfunction was in consonance with findings elsewhere. Balogun et al also evaluated diastolic function in young type 1 diabetic Caucasian subjects and found diastolic dysfunction prevalence of 24.2%. Whereas in related studies Paillole, Dibonito and Poirier et al in separate studies arrived at prevalence rate between 30 to 69%.

**Diabetes Mellitus And Systolic Dysfunction**

Systolic dysfunctions have been observed in DM patients using the findings in ejection phase indices in several studies. Although some studies did not demonstrate any significant differences when compared with normal control in
the ejection phase indices. Others did\textsuperscript{37,38}. Elevated LV mass, wall thickness and relative wall thickness have all been shown to be a predictor of cardiovascular morbidity and mortality independent of hypertension and obesity\textsuperscript{200,264,271}. The various ultrastructural alterations associated with these have been noted earlier in the diabetes and the heart discourse.

The composition of the myosin heavy chains (MHC) determines the rate of energy liberation by myosin i.e. the myosin ATPase activity. Replacement of fast (alpha, V\textsubscript{1}) MHC by slow (beta, V\textsubscript{3}) myosin isoform reduces the rate of cross-bridge cycling (contractility) but prolongs ejection and reduces energy costs of contraction and thereby enhances myocardial efficiency. This synthesis of myosin with abnormally low intrinsic ATPase activity such as Beta-V\textsubscript{3} as found in DM could explain many of the functional changes in failing heart muscle such as depression of fractional shortening (FS), ejection fraction (EF) and mean velocity of circumferential fibre shortening (VCF) which ultimately reflect in the depression of force-velocity curve. However, it has been proposed that such a biochemical abnormality might actually be beneficial in heart failure as an adaptive mechanism designed to maximize the quantity of mechanical energy derivable from each mole of ATP utilized and thus increase the efficiency of cardiac muscle at the expense of slowing the maximum rate at which blood is ejected.\textsuperscript{272} On the other hand there is evidence that in the human with heart failure there is a reduction in the number of cells containing fast alpha MHC\textsuperscript{273} which increases ATPase activity.
The role of Ca\(^{2+}\) in diastolic dysfunction has also been documented previously. Defect in the active accumulation of Ca\(^{2+}\) by the sarcoplasmic reticulum (SR) is mediated by activated ATPase. Relaxation is effected by ATP dependent-uptake of calcium by SR. In systolic heart dysfunction there is less Ca\(^{2+}\) binding to the sarcoplasmic reticulum which means less Ca\(^{2+}\) is made available for regenerative release for the contractile process\(^{274}\) - excitation – contraction coupling. From the foregoing, it is clear that the abnormality of Ca\(^{2+}\) handling by the SR is central to both diastolic and systolic dysfunction. Other causes include the effect of abnormal energy balance and autonomic dysfunction in DM earlier mentioned.

Babalola and Ajayi found significant depression of fractional shortening in diabetics 19±3\% when compared to normal healthy controls 23±4\%\(^{38}\) in their study. Conversely, Dibonito\(^{275}\) et al in their study showed normal improved FS in diabetics when compared to normal control group (i.e. 37 ± 6 to 38 ± 8).\(^{275}\) His subjects were diabetics of short duration.

In the Framingham Heart study the FS of the left ventricle was found to be reduced in men but not in women.\(^{22}\) In keeping with these observations are the findings in the strong heart study in which Devereux et al determined whether DM affects LV structure and function independent of body mass index and blood pressure. They showed that stress corrected LV midwall shortening which is a better index of contractility than FS and EF was found to be 5\% lower in diabetic adults when compared to normal control.\(^{276}\) Also in the same study a clear and consistent result showed that stiffness of the systemic
arterial tree, estimated by the ratio of pulse pressure to stroke volume, is higher in diabetic subjects than non-diabetic subjects\textsuperscript{276}. An association between DM and elevated arterial stiffness has been documented previously. One possible mechanism responsible is the non-enzymatic production of irreversible advanced glycosylated end products that has been commonly observed in arteries of diabetics.\textsuperscript{277} This could add to after load, which will further depress the systolic indices.

**Spectrum of Diastolic Dysfunction**

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole.\textsuperscript{268} These abnormalities can occur in the presence or absence of clinical syndrome of heart failure and with normal or abnormal systolic function\textsuperscript{53,268}. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.\textsuperscript{53,268} There are four described patterns in the spectrum of diastolic function. These include normal, impaired relaxation, pseudonormal and restrictive patterns.\textsuperscript{53}

**Normal Pattern**

In the normal pattern, the E velocity is usually more than the A velocity. Therefore, the E/A ratio is usually more than 1 with 2 SDs from the mean of normal E/A ratio of the study population. The E/A ratio in normal, healthy, young or middle aged subjects is between 1 to 1.73 ± 0.30.\textsuperscript{53} While IVRT is between 80 – 110 msec. DT is from 180 – 240 msec. In the normal pattern of pulmonary venous flow velocity profile, the systolic forward flow velocity is
higher than the diastolic forward flow velocity. While there will be a pulmonary venous A velocity of less than 0.2m/s.

**Impaired Relaxation Pattern**

In this pattern, the mitral E velocity is decreased with increased mitral A velocity leading to the reversal of E/A ratio < 1. There will be shortened total diastolic filling period, IVRT is prolonged with an increase in DT of the E wave. The pulmonary venous flow velocity curve will show decreased diastolic forward flow velocity and increased systolic forward flow velocity. The pulmonary A wave velocity may not change or increased.

**Pseudonormal Pattern**

In the progress of cardiac disease LV compliance is reduced and left atrial pressure (LAP) increases. This results in the increase in E wave velocity and a decrease in the mitral A wave velocity. The E/A ratio will appear normal within the range of 1.0 – 2.0. There will be apparent reduction of IVRT which becomes prolonged when measured on valsava manoeuver. DT will be reduced to between 150 – 200 msec. The pulmonary diastolic forward flow velocity will be increased and the systolic forward flow velocity will be reduced. While the pulmonary A wave velocity will be increased and widened with time.

**Restrictive Pattern**

As cardiac disease worsens ventricular compliance further decreases with increase in LAP. The mitral E velocity and E/A ratio increase further with marked decreases in DT and IVRT. The value for E/A ratio is > 2.0. The DT is
< 150 msec. The pulmonary forward diastolic flow velocity will be markedly increased while the systolic forward flow velocity will be diminished. The pulmonary A wave velocity and size will be markedly increased.

The Clinical, Therapeutic and Prognostic Importance of Diastolic Dysfunction in Diabetics

Detection of left ventricular dysfunctions early enough in diabetics is of clinical therapeutic and prognostic importance because it would allow application of early preventive strategy that would avoid or delay development of heart failure. Furthermore longitudinal or serial assessment of the various functional parameters will engender follow up. The full clinical implication of early development of the observed diastolic dysfunction is not fully understood. However, Coughlin et al observed that the risk of developing heart failure in their study (the Washington DC Dilated cardiomyopathy study) was grossly increased in diabetic patients. Similar conclusion was arrived at by Kannel and his group from evidence in the Framingham study in which they posited that diabetic males had more than twice the incidence rate of heart failure compared to their non-diabetic cohorts, while women showed a five fold increased risk. Apart from that, diastolic abnormalities which have been shown to occur in 24.2 to 69% of asymptomatic patients have been thought of as an indicator of subsequent progression towards the development of frank heart failure. Some studies have demonstrated a marked reduction in functional reserve through dynamic exercise even in the asymptomatic patients with adequate function at rest.
The state of stable sub-clinical cardiomyopathy as might be evidenced by the presence of diastolic abnormalities may be converted to clinically important heart failure in the context of uncontrolled systemic hypertension and or the presence of myocardial Ischaemia. Diabetic patients experiencing myocardial infarction have poorer prognosis compared to non-diabetics even though infarct size may not be larger. It has been shown that a meticulous metabolic control in diabetic patients may definitely delay the occurrence of cardiovascular complication and improve the prognosis once they have occurred. In terms of therapeutics, the established use of ACE-inhibitors and B-blockers in patients with heart failure also applies to diabetic patients.

Recent data have suggested that the beneficial effects of ACE-inhibitors in heart failure patients are even greater in diabetic patients. The observed benefits of ACE-inhibitors in diabetic patients are likely due to a variety of mechanisms other than those attributable to decrease in systemic blood pressure but are probably related to specific vasculoprotective and renoprotective effects of ACE inhibitors, mediated by a decrease in angiotensin II levels and an increase in bradykinnins. The introduction of current (β-blockers) with alpha-1 blocking properties which have been shown to improve insulin sensitivity and glucose metabolism should be suitable for diabetic patients. In the light of most recent trials of the vasodilating (β-blockers) in heart failure, their use in diabetic patients is advocated.
Risk stratification in terms of drug management is also important. The thiazolidinedione (TZD) group of drugs (e.g. Roziglitazone, pioglitazone) used with beneficial effects in diabetic patients have been found to exacerbate heart failure and pulmonary oedema and should be avoided in patients with left ventricular dysfunction or chronic renal insufficiency. The TZDs cause intravascular volume expansion by approximately 7%, through perhaps a mechanism of “vascular leak syndrome”. The TZDs increase plasma concentration of vascular permeability factors such as vascular endothelin growth factors – implying a role for these factors in TZD induced oedema.\textsuperscript{284,285}

Finally only diastolic dysfunction is considered here because it is insidious and an early marker of impending heart failure. The diabetic cardiomyopathic process initially manifests as a diminished left ventricular relaxation and compliance in the presence of normal systolic function\textsuperscript{21-34}, whereas frank systolic dysfunction usually appears in patients with longstanding disease who have advanced microvascular complications or coexistent hypertension.\textsuperscript{34,286}

\textbf{Factors Affecting LV Diastolic Dysfunction in Diabetics}

The proposal for the existence of primary myocardial disease, diabetic cardiomyopathy became inevitable as evidence accumulated unequivocally for its presence in myocardial dysfunctions in the absence of ischaemic, valvular or hypertensive heart disease.\textsuperscript{22,125,133,287} After Rubler\textsuperscript{121} made the initial observation in human autopsy studies in 1972, abnormalities in both systolic and diastolic performance of the heart in diabetic subjects have been demonstrated in both animal and human studies.\textsuperscript{133,283,288,289} Diastolic
dysfunction has been described as an early sign of this diabetic heart muscle disease preceding the systolic damage.

Diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force. Diastolic dysfunction occurs when these processes are prolonged, slowed or incomplete. If diastolic function is truly normal, it must remain normal both at rest and during the stress of variable heart rate, stroke volume, end-diastolic volume and blood pressure. Diastole is traditionally divided into four phases i.e. Isovolumic relaxation, early diastolic filling, diastasis and atrial contraction. The last three phases are collectively referred to as filling phase. In all the phases many factors determine the LV filling with varying degrees of importance.

These factors are myocardial relaxation, atrial contraction, viscoelastic properties, diastolic restoring forces pericardial restraint, ventricular interaction, coronary artery tugor, loading conditions, atrial and ventricular non uniformity and cardiac conduction system. These factors overlap in time. Their final combined effect is on the transmitral pressure gradient, which actually determines left ventricular filling. Diastole is delineated by the time interval between closure of the aortic valve and the opening of the mitral valve. As earlier stated, diastolic dysfunction refers to a condition in which abnormalities in mechanical pump function of the heart are present in diastole. The causes of diastolic dysfunction may be subdivided into a decrease in passive myocardial diastolic compliance and an impairment in active Isovolumic left ventricular relaxation time (IVRT).
The Isovolumic relaxation time (IVRT) is composed of a rapid left ventricular pressure fall due to relaxation of elastic recoil. The relaxation is the process during early diastole by which the heart returns to a precontractile configuration. It is an energy requiring process where calcium ions are removed against a concentration gradient allowing dissociation of the contractile complex.\textsuperscript{53,268} Relaxation can be asynchronous or incomplete for various reasons some of which include: myocardial ischaemia, bundle branch block, increased left ventricular after-load as in systemic hypertension, contractile dysfunction and left ventricular hypertrophy all of which could be found in type 2DM.

The impaired rate of relaxation slows the rate of left ventricular pressure fall and prolongs the time constant of isovolumic left ventricular pressure fall (TAU).\textsuperscript{291} Impaired relaxation results in a small left ventricular volume at a given left ventricular pressure and thus an increase of filling pressure is required to maintain left ventricular diastolic volume. The filling phase is composed of continuing relaxation and elastic recoil, myocardial stiffness ventricular interaction and pericardial restraint. The constituents of the filling phase have already been enumerated.

Left ventricular compliance is a passive function, which indicates the distensibility of the chamber during filling of the left ventricle.\textsuperscript{292} In the LV diastolic pressure – volume relationship, (which is curvilinear,\textsuperscript{293}) slope becomes steeper with decreasing LV compliance such that with any given
filling volume, there is a larger increase in diastolic pressure. LV compliance is primarily determined by myocardial characteristics and load. Myocardial characteristics are altered in the presence of myocardial hypertrophy, Ischaemia, fibrosis or amyloid infiltration. Increase in ventricular volume can decrease compliance. Other variables which influence LV compliance are ventricular interaction or interdependence, pericardial restraint and coronary vascular turgor or engorgement leading to an upward shift in the LV diastolic pressure volume curve.

Abnormalities in diastolic function may occur in the presence or absence of clinical syndrome of heart failure and with normal or abnormal systolic function. The several studies have shown that 30 – 40% of patients with clinical symptoms of congestive heart failure have normal systolic function (diastolic heart failure) with less than 10% occurring in patients below the age of 50 years and more than 70% in those older than 80 years.\textsuperscript{294-296} Whereas diastolic dysfunction describes an abnormal mechanical property diastolic heart failure describes a syndrome with features of congestion – exertional dyspnoea, alveolar oedema at chest-Xray, raised jugular venous pressure etc.

**Prevalence of Diastolic Dysfunction in Diabetes Mellitus**

Numerous studies have shown that impairment of the LV diastolic function may be detected in patients with diabetes. Diastolic LV abnormalities were initially disclosed by cardiac catheterization.\textsuperscript{296} Regan et al in 1977\textsuperscript{140} and D'Elia et al 1979\textsuperscript{297} demonstrated in normotensive, diabetic patients without coronary artery disease and without clinical evidence of heart failure,
increased LV endiastolic pressure, decreased LV-end diastolic volume with normal ejection fraction. Since then, other investigators have demonstrated abnormalities of LV diastolic function using several non invasive methods.

In the study of Paillole et al\textsuperscript{35} 16 type 1 diabetics (36 \pm 8) years old free of microangiopathy, hypertension and or coronary artery disease and with disease duration of 10 years were compared to 16 healthy control subjects. A significant reduction in mitral E wave, E/A ratio and an increase in IVRT was observed in diabetic patients; up to 69\% of diabetics had abnormalities of the diastolic parameters. Di Bonito et al\textsuperscript{275} reached similar conclusions in a case control study using Doppler echocardiography E/A ratio. They observed diastolic dysfunction in 16 normotensive type 2 diabetic patients, free of microvascular complications with a disease duration of less than 4 years and even less than 1 year. Their findings suggest that abnormal diastolic function can occur in diabetics of short duration.

In the study carried out by Berkova et al\textsuperscript{298} significant differences of diastolic parameters were observed between his group of young diabetics and a group of healthy age matched control. Detailed analysis of their findings showed that the 20-32 year old men with diabetes correlated with findings in healthy men of 50 years in other studies.\textsuperscript{47,299} These findings suggest that relaxation properties deteriorate in diabetes more rapidly than healthy subjects. Balogun et al\textsuperscript{36}, in his study of 33 young normotensive IDDM patients without microalbuminuria, which were matched with 20 normotensive non diabetic controls for age, sex and body surface area. The E/A ratio and E\textsubscript{1}/A\textsubscript{1}, ratios were found to be significantly lower in the diabetic group when compared with
normal controls (P<0.001, P<0.01 respectively). In fact 8 IDDM patients, 24.2% had a peak early to late filling ratio (E/A) of ≤1.1. They concluded that DM patients without obvious heart disease may have diastolic dysfunction and that this may likely reflect changes in myocardial relaxation and may be early marker to diastolic cardiomyopathy.

Poirier et al. performed a study using conventional assessment of transmitral Doppler flow velocity as well as measurements of pulmonary venous flow and transmitral flow after Valsalva maneuver. The latter method decreased filling pressures and consequently unmasked the underlying impaired relaxation. The main finding of this work is a very high prevalence of diastolic dysfunction in men with well controlled type 2 diabetes with no clinically detectable heart disease. Among the 46 patients studied, 60% had diastolic filling abnormalities, 32% had impaired relaxation and 28% had a pseudonormalized filling pattern. The introduction of valsaver maneuver was used to delineate those with pseudonormal pattern of diastolic dysfunction who would have otherwise been counted as normal finding.

**Exercise Capacity, A Measure of Functional Capacity**

The diagnostic utility of the electrocardiogram in the assessment of patients with ischaemic heart disease was first recognized by Feil and Siegel as early as 1928, when ST and T wave changes following exercise were reported in three of four patients with chronic stable angina. Subsequently Master and Oppenheimer developed a standardized exercise protocol to assess functional capacity and haemodynamic response of patients in 1929 since then other
authorities like Bruce\textsuperscript{302-304} etc have standardized protocol for the treadmill exercise testing. Exercise stress tests with either the use of bicycle ergometer or treadmill are valuable in estimating prognosis and determining functional capacity, likelihood and extent of coronary heart disease\textsuperscript{305} and effect of therapy. Others have applied the exercise stress test in evaluation of functional capacity and cardiovascular reserve in other disease conditions.\textsuperscript{38,39}

Exercise stretches the physiological reserve of the cardiovascular system and in doing so evaluates the integrity of the autonomic nervous system\textsuperscript{305} as well. Exercise stress test has been used to detect asymptomatic cases of coronary atherosclerosis and other cardiovascular abnormalities (i.e. systolic and diastolic) even before they become clinically evident.\textsuperscript{306,307} It has also proved to be a useful tool for assessing peripheral artery occlusive disease. In diabetics, (who could present with any of the above mentioned, as complication), exercise capacity is markedly reduced when compared with controls.\textsuperscript{39} In the study done by Okokhere, Obasohan and Balogun in which diabetics, hypertensives and diabetic hypertensives and normal controls were subjected to exercise stress using bicycle ergometer. The diabetics showed impairment in the various indices measured. For instance maximum workloads in watts were reduced in diabetics when compared to normal controls. Also the duration of exercise (DOE) was significantly reduced in diabetics when compared to normal control – thus showing poor exercise tolerance. Even changes in systolic blood pressure (SBP) were reduced in diabetic 55.1\% to 59.6\% of normal control. At peak exercise the heart rate was significantly reduced in diabetic subjects when compared to normal controls by almost 30\%.
The pressure rate product (PRP) which is an index of haemodynamic stress on the LV\textsuperscript{307,308} was higher in the control group when compared to diabetics and other groups because they could raise their heart rates and blood pressures when compared to the disease groups. When PRP was adjusted for the duration of exercise (PRP/DOE), the DM patients showed a higher PRP/DOE value when compared to control subjects indicating greater stress on the myocardium of diabetics.

Also when maximal oxygen consumption (MVO\textsubscript{2}) of the various groups was compared the diabetic subjects showed a significantly lower value when compared to the controls reflecting inefficient oxygen extraction by the exercising muscles including the myocardium. When these various indices were compared between those with DM alone and those with DM and hypertension together, they showed worse trend in those with the latter condition thus supporting the synergistic influence of both conditions as cardiovascular risk factors. Furthermore the study confirmed that concomitant systemic hypertension and DM in Nigerians lead to greater impairment of exercise capacity than either disease alone. The investigators also concluded that this impairment cannot be accounted for by the limitation to raise heart rate\textsuperscript{309} alone, which is basically an autonomic dysfunction but possibly through disturbance of systolic and diastolic functions.

In the study carried out by Babalola and Ajayi in which echocardiographic indices and treadmill exercise capacity and microvascular complications were
evaluated in Nigerian subjects with systolic hypertension associated with DM. Treadmill exercise tolerance time was reduced in diabetics $321 \pm 119$ sec $p < .01$ when compared to healthy controls $490 \pm 156$ sec. This again shows the inability of diabetic subjects to tolerate exercise better when compared to normal controls.\textsuperscript{38} From the foregoing it is obvious that the poor exercise tolerance by diabetic subjects can be explained by a mélange of dysfunctional mechanisms in which disautonomia is only a part.

Indeed some studies have demonstrated that in the absence of systolic dysfunction, the impairment of LV relaxation can influence exercise tolerance.\textsuperscript{310} Therefore impaired LV relaxation was supposed to influence maximal treadmill ergometric performance and explain lower maximal performance observed in patients with type 2 diabetes mellitus.

In 1991, Kitzman and colleagues demonstrated that pulmonary venous pressure and hence LV filling pressure is elevated at rest in patients with isolated diastolic dysfunction.\textsuperscript{310} With exercise, the filling pressure further increases but the LV volume decreases. Even higher filling pressures would be required to fill the left ventricle and maintain normal cardiac output. This situation is associated with venous congestion and subjective feeling of breathlessness and limited exercise tolerance. In DM there is reduced compliance and increased stiffness of the ventricular myocardium due to marked deposition of glycated collagen, ventricular hypertrophy, impaired relaxation because of impaired or abnormal $Ca^{2+}$ flux. All these lead to raised filling pressure.
It is noteworthy that it is not in all cases of ventricular hypertrophy that the deleterious effect is manifest on the heart whether in the long-term or short-term. Myocardial hypertrophy in well trained athletes rather enhances their performance because it is an adaptive mechanism which also involved other aspect of cardiovascular system. This condition returns to normal as soon as training is discontinued. The well trained athlete also has increased cavity dimension, improved LV relaxation, low pulse-rate and maximal MVO$_2$ utilization etc as against what is obtained in diabetic subjects who may present with myocardial hypertrophy and those with hypertrophic cardimyopathy.$^{311,312}$

**The Heart of the Unborn Baby is not spared**

DM also affects the heart of the unborn fetus in a similar way to that of adults. Evidence of previous research has shown that poorly controlled maternal DM can result in fetal hyperinsulaemia with consequent macrosomia, hypoglycaemia and ultimately, asymmetric septal hypertrophy$^{313}$. This is because insulin normally stimulates fetal growth in the third trimester through its regulation of glycogen, fat and protein synthesis$^{314}$; thus hyperinsulaemic fetuses often experience exaggerated weight gain. Similarly the fetal heart rich in insulin receptors$^{315}$ may undergo increased ventricular septal thickening in the presence of high insulin levels in the third trimester, culminating in asymmetric septal hyertrophy. Asymmetric septal hypertrophy found at increased incidence in infants of insulin dependent diabetic mothers often hinders diastolic function as evidenced by decreased cardiac output increased
morbidity including persistent pulmonary hypertension of the newborn and perhaps idiopathic respiratory distress syndrome.\textsuperscript{316}

**MATERIALS AND METHOD**

1. **DEFINITIONS**

   (a) **Diabetes Mellitus**

   In this study, the patients with diabetes mellitus were determined by the criteria as defined by the National Diabetic Data Group\textsuperscript{60} and World Health Organization\textsuperscript{82-83} and later revised by the United States Expert Committee on diagnosis and classification of Diabetes Mellitus\textsuperscript{84} – as a fasting blood glucose greater than 7.0mmol/1 (126mg%) and or 2 hour – postprandial or random blood glucose greater than 11.1 mmol/1 (200mg%)\textsuperscript{88,89}. Only type 2 DM, age 40 – 65 years, with diagnosis of DM and duration of symptoms below 3 years were recruited for this study. The duration of DM was determined from the length of time of first diagnosis to the time of presentation for the study.

   (b) **Left Ventricular Function**

   This was assessed using various echocardiographic modalities.

   - Doppler Echo – for assessing the diastolic dysfunction
   - M-mode and 2D – Echo (Both for assessing systolic function).

   (c) **Place of Study**

   The study was done at the University of Nigeria Teaching Hospital (UNTH) Enugu, which is a 700-bed hospital providing tertiary health
The hospital is designated the Centre of Excellence for cardiovascular diseases in Nigeria, and because of this, it draws its patient population from all over Nigeria. However, a great majority of patients come from Enugu State where the hospital is located; and from the neighbouring Anambra, Ebonyi, Benue, Kogi, Abia, Akwa Ibom Cross-River, Rivers, Delta and Bayelsa States.

(d) Type of Study

It is a case-control hospital-based study.

(e) Subjects

i. Ethical approval: Clearance was obtained from the Ethical Committee of the University of Nigeria Teaching Hospital, Enugu.

ii. Patients: Consent was obtained from the patients after explaining the purpose of the study, the little inconvenience involved and for the fact that they were not expected to pay for the cost of the echocardiography and the absence of any significant side effects.

iii. Control group: Healthy volunteers who were staff of the UNTH, Enugu and patients relations as well as those attending mature programmes in nursing and anaesthesia were selected using the same criteria as for the patients in the study. They were sex and age matched with the study subjects.
**METHODS:**

This study commenced after due approval was given by the Hospital Ethical Committee. Patients were recruited from the Diabetic Cardiology and Medical out-patient clinics as they presented for the first time in the hospital. They were clerked to ascertain the on-set of symptoms and the type of treatment being given (if any). They were also recruited with either fasting blood glucose or 2 hour postprandial blood glucose.

i. **Inclusion Criteria:**

Consecutive Type 2 diabetic patients with diagnosis, duration of symptoms and age as defined above were recruited. They were on diabetic diet with or without oral hypoglycaemic agents for control of blood glucose. There was no history of Ketosis and patients were not on insulin.

ii. **Exclusion Criteria:**


2. Microangiopathy
   a. Retinopathy-as evidenced by fundoscopy
   b. Microalbuminuria-using Micral test Kits\(^{319}\)
   c. Autonomic Neuropathy-using modified autonomic neuropathy disability score\(^{320}\)
3. Hypercholesterolaemia—maximum of 6.2 mmol/L (Defined by the chemical pathology department of the UNTH.)

4. Ischaemic heart disease—assessed by the patients history and resting and exercise electrocardiography.

5. Others: Current or past history of smoking, clinical evidence of valvular heart disease, heart failure, atrial fibrillation and multiple ectopic beats, thyroid diseases and other endocrinopathies.

iii. Sample Size:

Sample size was calculated from the World Health Organization formular for sample size determination in an infinite population using the prevalence of DM as roughly 2% in Nigeria.

\[ n = \frac{Z^2 (pq)}{SE^2} \]

Where:

- \( n \) = Sample size
- \( Z \) = Confidence interval = 1.96
- \( P \) = Prevalence = 2%
- \( q \) = 100-p
- \( SE \) = Standard error in the mean = 5

A minimum number of 82 patients together with 81 volunteers used as control were recruited for this study with a fasting blood sugar. The patients together with the controls (marched for age, sex and BMI) were examined using various echocardiographic modalities:

iv. 2-Dimensional, Motion-mode and Pulsed Doppler Modalities:
Parameters measured included:

**Systolic Functions**
- Ejection fraction
- Fractional Shortening
- Mean Velocity of circumferential fibre shortening
- Stroke index

**Diastolic Function**
- Left atrial emptying index
- Isovolumic relaxation time (IVRT)
- Slope of anterior mitral valve leaflet in early diastole.
- E:A Ratio
- Em : Am Ratio

**APPARATUS**

I  *Prestige Smart system Blood Glucose meter*

II  *Standard Sphygmomanometer with appropriate cuff size*

III  *Three channel ECG Machine the BTL 08 – ECG series.*

IV  *Micral Test kits from Boehringer*

V  *Echocardiographic Equipment:*

The machine used for this study was SONOS 2000 Hewlett Packard echocardiograph machine. It has facilities for M-mode, two-dimensional, pulsed wave Doppler, continuous wave Doppler and colour flow Doppler. It also has facilities for simultaneous electrocardiographic display used in timing
cardiac events, a video-recorder which can also play back either at normal speed or in slow motion and a video print-out which produces hard copies of the picture on paper.

VI Echocardiographic Examination:

The echocardiographic examination was done with the patient lying down on an examination couch, in a left lateral decubitus position, about 60 degrees to the horizontal plane.

M-mode examination was done with the transducer in the usual echocardiographic ‘window’ – between the second and fifth intercostal spaces, and within 2 to 4 cm to the left of the left sternal border. M-mode cursor was placed under two-dimensional echocardiographic guidance. All M-mode measurements were made according to the recommendations of the American Society of Echocardiography.

Two dimensional echocardiographic examinations were done with the transducer in the parasternal echocardiographic window – between the second and fifth intercostal spaces, and within 2-4cm to the left of sternal border – for the parasternal long axis and short axis views; the transducer was placed at the apex for the apical four-chamber view.

The pulsed wave Doppler (transmural) examinations were performed with the transducer at or slightly to the left of the apical impulse. The apical 4 chamber view, optimized to visualize the left ventricular cavity and the maximal excursion of the mitral valve leaflets was used. The cursor was positioned through a plane traversing the left ventricle from apex to the mitral valve annulus, with care taken in obtaining the smallest possible angle between the
direction of diastolic blood flow and the orientation of the ultrasonic beam. The sample volume was positioned in the inflow area of the left ventricle between the mitral leaflet tips, and its position along the cursor line adjusted until the highest early and late peaks of diastolic flow velocity were recorded. Each measurement of the indices was obtained for 5 cardiac cycles and averaged.

1. **M-mode Echocardiographic Measurements:**

   The following M-mode echocardiographic indices were measured.

   - **Aortic Root Dimension at End − Diastole:**
     Two dimensional parastemal long axis view of the heart was obtained. The M-mode cursor was placed at the level of the aortic valve leaflets, perpendicular to the aortic root in order to obtain an M-mode recording of the aorta and left atrium. The aortic dimension was measured at the onset of QRS complex, from the leading edge of the anterior wall echoes of the aorta to the leading edge of the posterior wall of the aorta.

   - **Left Atrial Dimension:**
     This was measured from the same view used for the aortic root dimension. The left atrium was measured at its maximum dimension, from the leading edge of the posterior wall of the aorta to the dominant line representing the posterior wall of left atrium.

   - **Ventricular Septal Wall Thickness at End Diastole:**
     A long axis parasternal view was obtained on two-dimensional
echocardiogram. The M-mode cursor was placed between the mitral valve and papillary muscles, perpendicular to the interventricular septum. The M-mode picture obtained from this was used to measure the ventricular septal wall thickness at the onset of QRS Complex, from the leading edge of the right septal echoes to the leading edge of left septal echoes.

- **Left Ventricular Posterior Wall Thickness at End-Diastole:**
  This was measured at the onset of QRS Complex, from the leading edge of the posterior left ventricular wall echoes, to the leading edge of the epicardial echoes, using the same frozen picture obtained for ventricular septal wall measurement.

- **Left Ventricular End-Diastolic Dimension:**
  Left ventricular end-diastolic dimension was measured at the onset of QRS Complex, from the leading edge of the left side of the septal endocardium to the leading edge of the posterior wall endocardial echoes.

- **Left Ventricular End-Systolic Dimension:**
  This was measured from the leading edge of the peak downward motion of the septal endocardium, to the leading edge of the posterior wall endocardial echoes, using the frozen picture obtained for the septal wall measurement.
Fractional Shortening (FS) of Left Ventricle (%):

FS of the left ventricle was calculated automatically by the echocardiographic equipment using the formula:

\[
\text{FS (\%)} = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd}} \times 100
\]

Where:  
- LVIDd = Left Ventricular End Diastolic Dimension  
- LVIDs = Left Ventricular End Systolic Dimension.

Mean Rate of Circumferential Fibre Shortening

\[
\text{VCF (circ/sec)} = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd} \times \text{E.T}}
\]

Where:  
- LVIDd = Left Ventricular Internal Dimension in Diastole  
- LVIDs = Left Ventricular Internal Dimension in Systole  
- E.T = Ejection Time

Left Ventricular (LV) Mass:

This was determined using the American Society of Echocardiographers (ASE) Left Ventricular Mass (LVM) corrected formula.

\[
\text{LVM (gm)} = 0.80 \left[ 1.04 \left( \text{LVDD} + \text{IVSD} + \text{PWD} \right)^3 - \left( \text{LVDD} \right)^3 - 13.6 \right] + 0.6
\]

Where:  
- LVDD = Left Ventricular End-Diastolic Dimension  
- PWD = Left Ventricular Posterior Wall End-Diastolic Thickness  
- IVSD = End-Diastolic Interventricular
Septal Wall Thickness.

- **E-F Slope**
  Using two dimensional echocardiographic guidance, the M-mode cursor was placed perpendicular to the tip of the mitral valve, and the M-mode tracing was obtained. The slope of the EF was then traced with the machine's in-built caliper and the slope was calculated automatically.

- **(EPSS) E Point to Septal Separation**
  With the same view as in EF Slope, the vertical distance between the E Point of the mitral valve M-mode and the interventricular septum was measured. This represents the E point to septal separation (EPSS).

- **E – Amplitude**
  Using the same echocardiographic view for the EF-Slope and EPSS, the M-mode cursor was placed at the D-point which is the opening point of the mitral valve and was traced to the apex of the E point and the machine caliper automatically calculated the D – E height as the E – amplitude.

- **A – Amplitude**
  Using the same view for the EF-slope, EPSS and E amplitude, the cursor was placed at the C point which represents the closure of the mitral valve; the height from C to A was traced with the caliper and automatically calculated as the A – amplitude.

Their ratio was worked out
I.e. Em: Am ratio.

2. **Two Dimensional Echocardiographic Measurements:**

   - **Left Ventricular End-Diastolic Volume:**
     This was measured from an apical four-chamber view of a two-dimensional frozen echocardiogram images. Using the scroll, the loop traces the ventricular cavity in diastole in slow motion. The in-built calipers of the echocardiographic equipment then calculated the left ventricular end-diastolic volumes automatically using the Simpson’s rule.

   - **Simpson’s Rule Method:**
     
     \[
     \text{LV Volume} = (n - 1) AT + \frac{AnT + Tn^3}{2} + \frac{Tn^3}{6}
     \]

     Where:

     - \( \text{LV} \) = Left ventricular
     - \( n \) = Number of sections
     - \( A \) = Short axis view area
     - \( T \) = Thickness of each section.

   - **Left Ventricular End-Systolic Volume:**
     This was obtained by using the same procedure as for the end-diastolic volume but with the picture frozen at the maximum contraction of the left ventricular cavity.

   - **Left Ventricular Stroke Volume (SV):**
The echocardiographic equipment calculated the left ventricular stroke volume automatically using the formula.

\[ SV = LVEDV - LVESV \]

Where:
- \( LVEDV \) = Left Ventricular End-Diastolic Volume
- \( LVESV \) = Left Ventricular End-Systolic Volume

- **Left Ventricular Ejection Fraction (E.F) (%)**

The echocardiographic equipment using the formula calculated this automatically:

\[ E.F. = \frac{LVEDV - LVESV \times 100}{LVEDV} \]

- **Cardiac Output (CO):**

This was calculated using the formula

\[ C.O. = S.V. \times H.R. \]

Where:
- \( H.R. \) = Heart Rate
- \( S.V. \) = Stroke Volume.

Heart rate was recorded continuously by the echocardiographic equipment using the in-built electrocardiogram.

3. **Pulsed-Wave Doppler (Transmitral) Echocardiographic Measurement**

From the apical four chamber view, the mitral in flow velocity profiles were traced along the instantaneous highest velocity spectra by in-built calipers of the echo machine, which determined peak early diastolic filling velocity (E), peak filling velocity at atrial contraction (A).
- **E:A Ratio:**
  This was calculated from the transmitral Doppler echocardiographic measurements of velocities of early diastolic filling (E) and late diastolic Atrial filling (A) waves, and their ratios were worked out (E:A). E:A ratios from 1 to $1.73 \pm 0.30$ were regarded as normal, but E:A ratios of less than 1 were regarded as diastolic dysfunction.

- **Ejection Time:**
  This was measured by placing the pulse Doppler sample volume just distal to the aortic valve, obtaining a clear trace of the aortic flow and then the time from the onset of systole to the end of systole; was measured.

- **Deceleration Time (DT):**
  With the same apical four chamber view as the transmitral flow velocity measurements, deceleration time was calculated as the time between peak E wave and the upper deceleration slope extrapolated to the baseline.

- **Isovolumic Relaxation Time (IVRT):**
  This was measured from the apical four - chamber view with the aortic valve opened out, by placing the pulsed wave Doppler beam between the mitral and aortic valve leaflets. The time interval between the end of the
aortic velocity envelope and the onset of early filling wave of mitral flow was taken to represent the Isovolumic Relaxation Time.

**STATISTICAL ANALYSIS**

Data analysis was carried out using the statistical package for the social sciences (SPSS) version 11 software run on a compatible personal computer. The parameters for each population group were expressed as mean ± standard deviation of mean (SD) or as percentage (%). Comparisons of means and proportions were carried out using the student t-test and chi-square as the case warranted. Results were regarded as statically significant when P < 0.05. Correlations were determined using Pearson correlation coefficients, simple and multiple regressions, and Analysis of Variance (ANOVA), with consideration to appropriate covariates. Data storage was by Microsoft office word 2003 on windows XP.
FIG. 1 Sonos 2000 Hewlett Packard Echocardiographic Machine Used In The Study
RESULTS

From January 2004 to August 2005, a total of 420 consecutive patients attending the diabetic clinic, medical outpatient clinics and cardiac clinic of the University of Nigeria Teaching Hospital Enugu were screened for the study. Eighty two of them (42 males and 40 females) met the inclusion criteria and were recruited for the study. Eighty one age and sex matched controls mainly drawn from the hospital staff, patients relatives, and those attending mature adult programmes in nursing and anaesthesia, 45 males and 36 females were also recruited in the study. Their ages both in the study population and the control group ranged from 40 to 63 years.

Clinical Parameters

The baseline clinical characteristics of the patient groups and the non diabetic control groups are summarized on table 3. No significant difference was observed in age, body surface area, weight, systolic and diastolic blood pressures among the diabetic and control groups (p>0.05). Significant difference was observed in heart rate, height and body mass index (BMI) between the diabetic population and the control group, (p < 0.01) for height and (p < .001) for BMI, and (p<.0001) for heart rate respectively. There was also significant difference in the fasting blood sugar levels between the diabetic and the control groups (P<0.0001) as well as total cholesterol (p< 0.05) Conversely no significant difference was observed in microalbuminuria amongst the population groups (P>0.05). The diabetic complication score was
also not significant between the groups (P>0.05). There was no significant difference in the ST-segment depression between the diabetics and the control group (P>0.05).

**2D-Echocardiographic Measurements of the Study Populations**

Figures 1, 17-29 display the echocardiogram machine and the various M-mode and two-dimensional echocardiographic views of the heart.

As shown in tables 4 and 5, no significant difference was demonstrated in aortic root dimension and E-point to septal separation (EPSS) across the subjects. However there were various degrees of significant levels observed between the diabetic and the normal control subjects in LA dimension (P<.01) and Aortic valve excursion (P<.05). There were also significant differences between the diabetic group and the control group in the values of EF-slope (p<.001) left ventricular posterior wall in diastole (LVPWD) (P<.001), interventricular septal wall thickness in diastole (IVSTD) (P<.0001) and left ventricular mass (LVMass) (P<.0001). Also there was significant difference in left ventricular mass index across the groups (P<.0001). Except for the EF-slope the diabetics showed increased levels in the indices. There was no significant difference observed in left ventricular end-diastolic dimension (LVEDD) (P>.05) and left ventricular end systolic volume (LVESV) P>.05). There were significant differences between the diabetic subjects and the control subjects in LVESD (P<.0001), LVEDV (P<.0001) and SV (P<.0001). The diabetic subjects showed decreased level in the indices.
Also there were significant differences observed between the diabetic subjects and control subjects in stroke index (SI) P<.0001, cardiac output (CO) P<.05 and cardiac index (CI) P<.05. The diabetic subjects showed significant reduction in SV, SI, CO and CI.

Table 6 shows the ejection phase indices in all the study subjects. Ejection fraction and fractional shortening both of which are important indices of systolic function were significantly reduced in the study subjects (P<.0001). The mean velocity of circumferential fibre shortening (VCF) which is a useful and more sensitive index of contractility than FS and EF was also significantly different among the study groups (P<.0001). It was reduced in the diabetic group.

Figure 25 – 29 show the pulsed-wave Doppler echocardiographic spectral displays of the heart and the corresponding two-dimensional views. Table 7 shows the Doppler echocardiographic indices of diastolic function in the study populations. In the table matrix, the E-velocity was significantly reduced in diabetic subjects when compared to normal control (P<0.05) while the A-velocity was significantly increased in diabetics when compared to the control subjects (P<0.01). Also E/A ratio was significantly reduced in diabetic subjects when compared to normal control subjects (P<0.05). IVRT and DT were increased in diabetic subjects than control subjects (P<.0001) and (P<.0001) respectively.

Figure 23 and 24 show m-mode echocardiographic views of E and A amplitude measurements by M-mode. While table 8 shows the M-mode indices of
diastolic function. The mitral valve A-amplitude (Am) was not significantly different across the study populations (P>0.05) while the mitral valve E-amplitude (Em) and the ratio of Em to Am (Em/Am ratio) were significantly different between the diabetic and control subjects (P<.0001) and (P<.0001) respectively. EF-slope had already been discussed earlier.

**Influence of Gender on Clinical Characteristics and Echocardiographic Indices**

Table 9 shows gender differences in the clinical characteristics of the diabetic subjects. There was no significant difference in age, BSA, heart rate and weight, P values were >.05 in all the above mentioned characteristics across gender. However, there were significant differences between gender in height (P<.01), BMI (P<.01) SPB (P<0.01) and DBP (P<.05). The men were taller while the women were more obese in the diabetic population. Also the men had higher Diastolic and Systolic Blood Pressures.

In the study populations, a total of 33 out of 82 representing 40.2% of the diabetic population had E/A ratio less than 1 (see Figures 17 and 18), while in the control 17.3% of the 81 subjects studied had E/A ratio less than 1. Amongst the diabetic population, 18 out of 33 (54.6%) with E/A ratio <1 were females (see Figure 5). When E/A ratio <1 distribution was analyzed according to duration of diabetes mellitus at presentation as shown in figure 21, 14 (42.4%) of them had their diabetes duration under one year, while 7 (21.2%) and 12 (36.4%) were within 1 to 2 years and 2 to 3 years durations respectively. Figure 4 shows E/A ratio frequency distribution according to
age groups. E/A ratio <1 was found mainly in the 51 – 60 year age group, 21 (63.6%) while 11 (33.3%) was found in the younger (40 – 50 years) age group.

Correlations

The correlation between EM/AM ratio and E/A ratio in the various study populations were very weak r=0.005 and r=0.134, P>0.05 in diabetic and control groups respectively (see Figures 15 and 16).

Multiple Regression Analysis

Tables 11 and 12 show multiple linear regression analysis which sought to determine the independent variables or predictors of Doppler E/A ratio in the diabetic and control populations. In table 11, a multiple linear regression was calculated to predict diabetic subjects E/A ratio based on age, LV Mass, DT, LA, IVRT and LVEDD. A significant regression equation was found F (6,76) = 22,352, P<.0001 with an R² of .648. Also in the control group table 12, a multiple regression was calculated to predict control subjects E/A using the same variables. The result was a significant regression, F (6,73) = 18,837, P<.0001 with R² of .779.
## Table 3: Baseline Clinical Characteristics of Study Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>51.1 ± 6.1</td>
<td>51.0 ± 6.3</td>
<td>.140</td>
<td>.889</td>
<td>NS</td>
</tr>
<tr>
<td>HT (cm)</td>
<td>161.1 ± 19.3</td>
<td>167.3 ± 8.3</td>
<td>-2.643</td>
<td>.009</td>
<td>Significant</td>
</tr>
<tr>
<td>WT (kg)</td>
<td>68.1 ± 9.7</td>
<td>65.4 ± 8.3</td>
<td>1.929</td>
<td>.056</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.79 ± .154</td>
<td>1.78 ± .151</td>
<td>.333</td>
<td>.740</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.83</td>
<td>23.3 ± 2.2</td>
<td>5.072</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>85.0 ± 7.75</td>
<td>74.7 ± 5.3</td>
<td>9.904</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.1 ± 8.93</td>
<td>117.8 ± 8.86</td>
<td>1.554</td>
<td>.122</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76.0 ± 7.0</td>
<td>75.2 ± 7.2</td>
<td>.586</td>
<td>.559</td>
<td>NS</td>
</tr>
<tr>
<td>FBS (g/dL)</td>
<td>171.1 ± 63.4</td>
<td>80.7 ± 18.5</td>
<td>11.58</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>Micro(mg/dL)</td>
<td>1.83 ± 3.83</td>
<td>1.00 ± 3.02</td>
<td>1.513</td>
<td>.132</td>
<td>NS</td>
</tr>
<tr>
<td>TCH(mmol/L)</td>
<td>4.46 ± 0.94</td>
<td>4.16 ± 0.84</td>
<td>2.202</td>
<td>.029</td>
<td>Significant</td>
</tr>
<tr>
<td>ST seg↓(mm)</td>
<td>0.055 ± 0.24</td>
<td>0.04 ± 0.133</td>
<td>0.760</td>
<td>.449</td>
<td>NS</td>
</tr>
<tr>
<td>Neuroscore</td>
<td>0.04 ± 0.110</td>
<td>0.02 ± 0.191</td>
<td>-1.035</td>
<td>.302</td>
<td>NS</td>
</tr>
</tbody>
</table>

**P value (P< .05)**

**NS = Not significant**

FBS = Fasting blood sugar

Micro = Microalbuminuria

TCH = Total cholesterol

ST seg↓ = ST- segment depression

Neuroscore = Neurological score (0-7)
Table 4: 2D-Echocardiographic Measurements of the Left Ventricular Geometry in the study Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO (cm)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>T-value</td>
<td>Significance</td>
<td>Comments</td>
</tr>
<tr>
<td>LA (cm)</td>
<td>3.60 ± .40</td>
<td>3.42 ± .30</td>
<td>3.340</td>
<td>.001</td>
<td>Significant</td>
</tr>
<tr>
<td>EX (cm)</td>
<td>1.90 ± .60</td>
<td>2.03 ± .15</td>
<td>-2.169</td>
<td>.032</td>
<td>Significant</td>
</tr>
<tr>
<td>EPSS (cm)</td>
<td>.600 ± .30</td>
<td>.620 ± .20</td>
<td>-.531</td>
<td>.596</td>
<td>NS</td>
</tr>
<tr>
<td>EF Slope (cm/sec)</td>
<td>8.12 ± 2.42</td>
<td>11.25±2.13</td>
<td>-8.766</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>LVPW (cm)</td>
<td>.849 ± .11</td>
<td>.783 ± .10</td>
<td>3.870</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>IVSTD (cm)</td>
<td>.825±.12</td>
<td>.721±.10</td>
<td>6.114</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>LV Mass (gm)</td>
<td>134.9±35.5</td>
<td>109.2±25.7</td>
<td>5.274</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>LVMASSIN (g/m^2)</td>
<td>75.80±20.43</td>
<td>61.34±14.0</td>
<td>5.235</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.42±.60</td>
<td>4.94±.27</td>
<td>.990</td>
<td>.324</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>3.29±40</td>
<td>2.91±.36</td>
<td>6.363</td>
<td>.000</td>
<td>Significant</td>
</tr>
</tbody>
</table>

P value (P< .05)

NS = Not significant
### Table 5: Volumetric Measurement of the Study Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>77.83 ± 16.20</td>
<td>91.90 ± 10.68</td>
<td>-6.535</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>28.65 ± 7.21</td>
<td>29.90 ± 6.00</td>
<td>-1.191</td>
<td>.236</td>
<td>NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>49.60 ± 11.94</td>
<td>62.00 ± 7.56</td>
<td>-7.922</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>SI (ml/m2)</td>
<td>27.35 ± 5.90</td>
<td>34.92 ± 4.80</td>
<td>-8.967</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>CO (l/sec)</td>
<td>4.21 ± 1.12</td>
<td>4.57 ± 7.60</td>
<td>-2.382</td>
<td>.018</td>
<td>Significant</td>
</tr>
<tr>
<td>CI (l/sec/m²)</td>
<td>2.36 ± .596</td>
<td>2.58 ± .499</td>
<td>-2.530</td>
<td>.012</td>
<td>Significant</td>
</tr>
</tbody>
</table>

**P value (P< 0.05)**

NS = Not significant

### Table 6: Ejection Phase Indices or Systolic Indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS (%)</td>
<td>33.68 ± 8.70</td>
<td>40.47 ± 5.00</td>
<td>-6.136</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63.30 ± 6.84</td>
<td>67.51 ± 4.66</td>
<td>-4.566</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>VCF (circ/sec)</td>
<td>1.24 ± .35</td>
<td>1.44 ± .30</td>
<td>-3.793</td>
<td>.000</td>
<td>Significant</td>
</tr>
</tbody>
</table>

**P value (P< .05)**

NS = Not significant
### Table 7: Doppler Echocardiographic Indices of Diastolic Function in Study Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/sec)</td>
<td>59.50±10.37</td>
<td>62.38±6.35</td>
<td>-2.134</td>
<td>0.034</td>
<td>Significant</td>
</tr>
<tr>
<td>A (cm/sec)</td>
<td>55.72±8.54</td>
<td>52.33±7.32</td>
<td>2.720</td>
<td>.007</td>
<td>Significant</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.09±.25</td>
<td>1.22±.25</td>
<td>-3.186</td>
<td>.002</td>
<td>Significant</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>117.15±17.0</td>
<td>90.1±12.3</td>
<td>11.652</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>208.98±23.44</td>
<td>174.00±14.42</td>
<td>11.457</td>
<td>.000</td>
<td>Significant</td>
</tr>
</tbody>
</table>

**P value (P< .05)**

**NS = Not significant**

### Table 8: M-Mode Echocardiographic Indices of Diastolic Function in the Study Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Subjects</th>
<th>Control Subjects</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Em (cm)</td>
<td>1.70±.20</td>
<td>1.90±.28</td>
<td>-5.550</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>Am (Cm)</td>
<td>1.27±.14</td>
<td>1.25±.10</td>
<td>1.140</td>
<td>.256</td>
<td>NS</td>
</tr>
<tr>
<td>Em/Am ratio</td>
<td>1.34±.17</td>
<td>1.53±.22</td>
<td>-6.047</td>
<td>.000</td>
<td>Significant</td>
</tr>
<tr>
<td>EF slope (cm/sec)</td>
<td>8.12±2.42</td>
<td>11.25±2.13</td>
<td>-8.766</td>
<td>.000</td>
<td>Significant</td>
</tr>
</tbody>
</table>

**P value (P< .05)**

**NS = Not significant**
Table 9: Gender Differences in Clinical Characteristics of Diabetic Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>T-value</th>
<th>Significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>51.21±6.75</td>
<td>50.9±5.28</td>
<td>.234</td>
<td>.816</td>
<td>NS</td>
</tr>
<tr>
<td>HT (cm)</td>
<td>167.05±6.77</td>
<td>154.84±25.37</td>
<td>3.009</td>
<td>.004</td>
<td>Significant</td>
</tr>
<tr>
<td>WT (kg)</td>
<td>68.64±8.45</td>
<td>67.55±1.00</td>
<td>.507</td>
<td>.614</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.82±.14</td>
<td>1.76±.16</td>
<td>1.739</td>
<td>.086</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.67±3.00</td>
<td>26.96±4.28</td>
<td>-2.815</td>
<td>0.006</td>
<td>Significant</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>85.50±7.46</td>
<td>84.47±8.12</td>
<td>.596</td>
<td>.553</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122.70±6.46</td>
<td>117.30±10.31</td>
<td>2.851</td>
<td>.006</td>
<td>Significant</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.45±6.79</td>
<td>74.20±6.87</td>
<td>2.173</td>
<td>.033</td>
<td>Significant</td>
</tr>
<tr>
<td>FBS(mg/dL)</td>
<td>163.7±66.5</td>
<td>178.88±68.3</td>
<td>-1.022</td>
<td>0.310</td>
<td>NS</td>
</tr>
</tbody>
</table>

P value (P< .05)

NS = Not significant
**Table 10.1: Frequency Distribution of E/A Ratio According to Duration of Diabetes Mellitus (DDM)**

<table>
<thead>
<tr>
<th>E/A Ratio</th>
<th>( \leq 1 ) (# and %)</th>
<th>1 – 2 (# and %)</th>
<th>2 – 3 (# and %)</th>
<th>Total Number (# and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>14 (42.4)</td>
<td>7 (21.2)</td>
<td>12 (36.4)</td>
<td>33 (100)</td>
</tr>
<tr>
<td>1 – 1.5</td>
<td>14 (31.8)</td>
<td>21 (47.7)</td>
<td>9 (20.5)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>1 (20)</td>
<td>2 (40)</td>
<td>2 (40)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (35.4)</td>
<td>30 (36.5)</td>
<td>23 (28.1)</td>
<td>82 (100)</td>
</tr>
</tbody>
</table>

**Table 10.2: Chi-square Tests for (DDM) and E:A ratio**

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-square</td>
<td>3.208</td>
<td>2</td>
<td>.201</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>3.248</td>
<td>2</td>
<td>.197</td>
</tr>
<tr>
<td>Linear by linear association</td>
<td>3.012</td>
<td>1</td>
<td>.083</td>
</tr>
</tbody>
</table>

A 2 cells (33.3%) have expected count less than 5

The minimum expected counted is 2.26.
Table 11: Multiple Regression Analysis with E/A Ratio as dependent variable in the diabetic subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>P\text{xx} value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>4.331</td>
<td>.896</td>
<td>4.836</td>
<td>000</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-2.500</td>
<td>.009</td>
<td>-2.659</td>
<td>.010\text{xx}</td>
<td></td>
</tr>
<tr>
<td>LV MASS</td>
<td>-1.902</td>
<td>.002</td>
<td>-1.071</td>
<td>-288</td>
<td></td>
</tr>
<tr>
<td>IVRT</td>
<td>-2.718</td>
<td>.005</td>
<td>-5.546</td>
<td>.000\text{xx}</td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>3.417</td>
<td>.003</td>
<td>1.084</td>
<td>.282</td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>3.037</td>
<td>.138</td>
<td>.220</td>
<td>.826</td>
<td></td>
</tr>
<tr>
<td>LVEDD</td>
<td>.169</td>
<td>.158</td>
<td>1.070</td>
<td>.288</td>
<td></td>
</tr>
</tbody>
</table>

a. Predictors (constant); LVEDD, LA, AGE, DT, LVMASS, IVRT.
b. Dependent variable: E/A ratio

R = .805
R\text{}² = .648
df = 6, 76
F = 22, 352
P* = .000

P\text{}*.0001 for ANOVA is significant
P\text{xx} <.05 and <.0001 are significant for regression

a+b: See list of abbreviations at page for definition
Table 12: Multiple Regression Analysis with E/A Ratio as dependent variable in normal control subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>P xx value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-1.657</td>
<td>.005</td>
<td>-.432</td>
<td>-3.632</td>
<td>.001 xx</td>
</tr>
<tr>
<td>LV MASS</td>
<td>-2.758</td>
<td>.001</td>
<td>-.029</td>
<td>-.320</td>
<td>.750</td>
</tr>
<tr>
<td>IVRT</td>
<td>-7.527</td>
<td>.002</td>
<td>-.378</td>
<td>-3.166</td>
<td>.002 xx</td>
</tr>
<tr>
<td>DT</td>
<td>-1.370</td>
<td>.002</td>
<td>-.081</td>
<td>-.896</td>
<td>.373</td>
</tr>
<tr>
<td>LA</td>
<td>6.473</td>
<td>.067</td>
<td>.077</td>
<td>.966</td>
<td>.337</td>
</tr>
<tr>
<td>LVEDD</td>
<td>5.534</td>
<td>.077</td>
<td>.061</td>
<td>.722</td>
<td>.472</td>
</tr>
</tbody>
</table>

a. Predictors (constant); LVEDD, LA, AGE, DT, LVMASS, IVRT.

b. Dependent variable: E/A

R = .779

R² = .608

df = 6, 73

F = 18, 837

P* = .000

P xx .0001 for ANOVA is significant

P xx .01 for regression is significant

a+b: See list of abbreviations on page for definitions
Fig. 2:

**Frequency distribution of EA ratio in diabetics**

- Below 1: 53.70%
- 1 to 1.5: 6.10%
- Above 1.5: 40.20%

Fig. 3:

**Frequency distribution of EA ratio in normal control**

- Below 1: 71.60%
- 1 to 1.5: 17.30%
- Above 1.5: 11.10%
Fig. 4:

EA ratio frequency and relative frequency distribution according to age

<table>
<thead>
<tr>
<th>Age</th>
<th align="right">E:A &lt;1</th>
<th align="right">E:A 1-1.5</th>
<th align="right">E:A&gt;1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td align="right">33.3%</td>
<td align="right">52.3%</td>
<td align="right">60%</td>
</tr>
<tr>
<td>51-60</td>
<td align="right">63.6%</td>
<td align="right">47.7%</td>
<td align="right">40%</td>
</tr>
<tr>
<td>61-65</td>
<td align="right">60%</td>
<td align="right">40%</td>
<td align="right">3%</td>
</tr>
</tbody>
</table>

Figs. 5:

EA ratio frequency and relative frequency distribution according to gender

<table>
<thead>
<tr>
<th>Gender</th>
<th align="right">E:A &lt;1</th>
<th align="right">E:A 1-1.5</th>
<th align="right">E:A&gt;1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td align="right">45.4%</td>
<td align="right">54.6%</td>
<td align="right">60%</td>
</tr>
<tr>
<td>1-1.5</td>
<td align="right">45.5%</td>
<td align="right">54.5%</td>
<td align="right">40%</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td align="right">60%</td>
<td align="right">40%</td>
<td align="right"></td>
</tr>
</tbody>
</table>
Frequency distribution of EA ratio according to duration of diabetes mellitus (DDM) in years of presentation.

Fig. 6:
Fig. 7: A REGRESSION CURVE OF FS TO LV MASS IN THE DIABETIC SUBJECTS SHOWING REDUCED FS WITH HIGH LV MASS

Fig. 8: A REGRESSION CURVE OF FS TO LV MASS IN THE CONTROL SUBJECTS SHOWING MAXIMUM PERFORMANCE AT AN AVERAGE LV MASS
A REGRESSION CURVE OF VCF TO LV MASS IN THE DIABETIC SUBJECTS SHOWING AN INVERSE RELATIONSHIP MAXIMUM VCF RESPONSE OCCURS AT A LOWER LV MASS

Fig. 9:

A REGRESSION CURVE OF VCF TO LV MASS IN THE CONTROL SUBJECTS SHOWING MAXIMUM PERFORMANCE AT AN AVERAGE LV MASS

Fig. 10:
Fig. 11: A REGRESSION CURVE OF E:A RATIO TO IVRT IN THE DIABETIC SUBJECTS SHOWING AN INVERSE RELATIONSHIP OF E:A RATIO TO IVRT

Fig. 12: A REGRESSION CURVE OF E:A RATIO TO IVRT IN THE CONTROL SUBJECTS SHOWING AN INVERSE RELATIONSHIP OF E:A RATIO TO IVRT
A Scatterplot of EA and DT for diabetic

A Scatterplot of EA and DT for normal control

A REGRESSION CURVE OF E:A RATIO TO DT IN THE DIABETIC SUBJECTS SHOWING AN INVERSE RELATIONSHIP OF E:A RATIO TO DT

A REGRESSION CURVE OF E:A RATIO TO DT IN THE CONTROL SUBJECTS SHOWING AN INVERSE RELATIONSHIP OF E:A RATIO TO DT
Fig. 15:  CORELATION CURVE OF E:A RATIO TO Em/Am RATIO $r = .005$ IN THE DIABETIC SUBJECTS

Fig. 16:  CORELATION CURVE OF E:A RATIO TO Em/Am RATIO $r = .134$ IN THE CONTROL SUBJECTS
DISCUSSION

The study objectives were anchored on an encompassing general theme of determining the role of hyperglycaemia in the aetiopathogenesis of diabetic Heart dysfunction with specific reference to the left ventricle. Narrowing down to specifics the following sub-themes were determined; whether abnormal left ventricular function was present at an early stage of diagnosed type 2DM in Nigerian subjects: if any, the pattern and prevalence of the left ventricular dysfunction, and finally whether the left ventricular dysfunction had any sex predilection.

Bearing these in mind the principal findings at the conclusion of the study were:

(1) That hyperglycemia is indeed deleterious to the normal function of the ventricle even in the newly diagnosed unselected Nigerian diabetic subjects.

(2) The deleterious effect leading to left ventricular dysfunction is significantly prevalent and affects both the systolic and the diastolic phases of cardiac physiology though more pronounced in the diastole.

(3) There are some gender differences in the manifestations of the dysfunction especially in diastole.

(4) Age and isovolumic relaxation time (IVRT) are the other major factors affecting diastolic dysfunction.
Effects of hyperglycaemia on the heart

From the results of this study there is no doubt that hyperglycaemia has adverse effect on the heart. This is evidenced from the various changes observed in the left ventricular geometry and functions in the diabetic subjects when compared to those of the normal controls. The degree and extent of these changes were found more in women than in men. There was significant difference in the level of fasting blood sugar between the diabetic and control groups (see table 3). The FBS level in the female diabetics was more (178.88±68.30g/dL) as against 163.67±66.45g/dL of male diabetics (see table 9).

Implication of Alterations in left ventricular Geometry (LV geometry)

The increased left ventricular mass (LV mass) and left ventricular mass index (LVMI), the increased septal wall thickness and the posterior wall thickness in the diabetic subjects compared to the normal control in this study were all evidence of significant alterations in LV geometry (a possible consequence of hyperglycaemia) in diabetic subjects. These geometric changes which collectively, are composites of left ventricular hypertrophy (LVH), (LVmass≥ 134g in males and LV mass ≥110g in females) may be at the root of the observed systolic and diastolic dysfunctions in this study.

LVH is known to be a powerful independent predictor of morbidity and mortality in hypertensive patients. Kannel and Levy et al have argued that LVH in diabetics is also of similar prognostic value even though some investigators have posited that concomitant systemic hypertension is mainly responsible for the cardiac changes observed in
diabetics. Yet others have associated the manifestation of systemic hypertension and DM with the observed geometric alterations to insulin resistance syndrome.\textsuperscript{323-326} While Galvan in his recent work did not find any independent relationship between LV mass and insulin resistance.\textsuperscript{330} Nevertheless the accumulation of evidence in support of DC have sort of placed its existence beyond much further debate.\textsuperscript{22, 122-127,129-142} In DC the geometric profile are embracive of increased LV mass septal and free wall thickness among other changes.

The structural changes observed in this study as enumerated above are consistent with observations in other studies.\textsuperscript{22-25, 326-329} Whereas very few works to the best of the author’s knowledge have examined people of black African descent let alone Nigerians in this context\textsuperscript{38,271, Babalola and Ajayi found interventricular septal thickness and left ventricular mass index to be higher in diabetic than non diabetic Nigerian subjects. While Chaturvedi\textsuperscript{331}, in his comparative study between White and Black diabetics of the United kingdom posited among other things that African Carribeans with glucose intolerance generally have a worse echocardiographic profile than their European counterparts particularly in interventricular septal thickness and left ventricular end diastolic dimension (LVEDD), though he attributed the changes to higher body mass index and systemic blood pressure observed in the Blacks than the Whites.

The mechanisms of these alterations have already been discussed.\textsuperscript{22,122-140} In summary, hyperglycaemia expresses its toxicity through the formation of non
enzymatic glycation of tissue macromolecules such as proteins lipids and DNA to form irreversibly bound AGES and AFES. Such products accumulate in the heart and may cause oxidative damage directly or indirectly through stimulation of cytokines\textsuperscript{332}.

**Systolic Dysfunction**

In this study systolic phase indices, ie ejection fraction (EF), fractional shortening (FS) and mean velocity of circumferential fibre shortening VCF were depressed in diabetics by 16.8%, 6.2% 13.9% respectively when compared to their normal control counterparts.

Even though these differentials were statistically significant \(P< 0.0001\) across, they were not within or below the critical cut-off point that would engender fears of immediate systolic failure. However, the observation was important enough to highlight concerns of systolic dysfunction sufficiently to support the advocacy for preventive intervention through strict glycaemic control and other risk factor modifications.\textsuperscript{333, 143- 144, 278-283}

Furthermore the stable clinical state and the apparently normal systolic indices should not be taken for granted as any sudden perturbation of the equilibrium as might occur with the development of uncontrolled systemic hypertension and myocardial ischemia may convert it to clinically important heart failure. In the same vein there may also be marked depression of the indices during exercise\textsuperscript{38}, leading to intolerance of physical exertion.
The reduction in systolic function Indices in diabetic subjects have been severally documented by various investigators.\textsuperscript{22, 37,276,38,277} Dibonito et al\textsuperscript{275} rather found an improved systolic Indices in their diabetics when compared to their control subjects. The reasons for this discrepancy may be related to the patient’s selection that were younger in Dibonito’s group. In a recent study by Devereux et al,\textsuperscript{276} a 5\% reduction of stress corrected LV mid wall shortening which is a better index of contractility than FS and EF was found in the diabetic subjects when compared to the normal control. The Vcf depression in diabetics of this study when compared to control was 13. 9\%. The ejection phase findings in this study have further corroborated and strengthened the hypothesis that DM could indeed adversely affect systolic function. The possible mechanism may be related among other things to disturbance in \(\text{ca}^{2+}\) handling by SR in which less \(\text{ca}^{2+}\) is made available for regenerative release purposes for the contractile process \textsuperscript{274}. In the simple regression analysis carried out with fractional shortening (FS) and mean velocity of circumferential fibre shortening (VCF) against left ventricular mass (see Fig: 9 and 10), there was a negative correlation of left ventricular mass to the systolic indices, showing that the more hypertrophied (from disease process) the left ventricle becomes up to a certain degree (perhaps beyond the stage of compensation) the systolic performance declines.

**Diastolic Dysfunction**

The evidence of diastolic dysfunction in this study include significant reduction in the initial passive E- velocity and marked rise in terminal A – velocity both of which ultimately translate into reduced E/A ratio in the diabetic subjects
when compared to normal. Other evidence includes significantly prolonged IVRT and DT in the diabetic subjects when compared to the control subjects (see table 7). The mean E/A ratio in diabetic group was $1.09 \pm .25$ compared to $1.22\pm .25$ of the normal control group. However the prevalence of E/A ratio <1 as an index of diastolic dysfunction in the diabetic group was 40.2% as against 17% of the control group (see fig:2 and 3). This finding is consistent with findings in previous studies with a prevalence range of 24 – 69% among diabetic subjects$^{32 - 37}$. Also the finding of diastolic dysfunction in the newly diagnosed, diabetic subjects(<1yr after presentation) in the time course of the disease could be attributed to its long period of asymptomatic presence in the subjects$^{72, 275}$.

Studies have shown that systolic and diastolic dysfunctions could be found even in subjects with impaired glucose tolerance$^{43}$. Chaturvedi$^{331}$, apart from demonstrating altered left ventricular structure in those with impaired glucose tolerance in his study, also showed that there was a strong correlation between fasting blood glucose and abnormal echocardiographic indices even in normoglycaemic subjects. In this present study 14 out of the 33 diabetic subjects with E/A ratio < 1, representing 42.4% of the total number of E/A ratio <1 were found to have had the disease within 1 year or below since diagnosis, showing manifestation of the cardiac complications of the disease even in the newly diagnosed diabetic Nigerian subjects.
The prolonged IVRT and DT of the early passive filling velocity are supportive of impaired relaxation represented by the E/A ratio of <1 and are consistent with findings elsewhere 28, 270, 333.

Diastolic dysfunction as evidenced by E/A ratio of <1, a reliable index of impaired relaxation is dependent on active ventricular relaxation process and passive compliance. While active ventricular relaxation is dependent on active removal of ca\(^{2+}\) from the contractile complex to the sarcoplasmic reticulum against concentration gradient, an energy requiring process\(^{53, 290}\), passive compliance is determined by myocardial characteristic and load. Diabetic situation is surfeit with the above conditions, there was significant increase in LV mass in the diabetic subpopulation even when it was indexed for body surface area reflecting a significant LVH independent of body size. LVH is associated with marked collagen deposition and fibrosis both of which affect systolic and diastolic functions. In the regression scatter plot of E/A ratio to IVRT and DT respectively (see figs:13-14), there was an inverse relationship in the two scattergrams of diabetics and non diabetics showing that the more reduced the E/A ratio less than 1 the more prolonged is the IVRT or the DT or vice-versa. With LV hypertrophy compliance is impaired, when superimposed upon a subsisting energy imbalance and poor ca\(^{2+}\) handling as obtainable in DM the result is poor diastolic function. This was evident in the study.

**Determinants of E/A Ratio**

When E/A ratio was subjected to multivariate analysis to evaluate its determinants in the study populations. Age and IVRT proved to be the most
significant, consistent and powerful across the population groups. Even when the populations were pooled together the results were the same (see tables 11, and 12). The multiple regression analysis showed $\beta = -.293$ and $P< .01$ in diabetics, and $\beta = -.432$ and $p < .001$ in control subjects. Age appears to be a very powerful determinant of cardiovascular function both in disease and normal process. Aging is characterized by gradual loss of function in many organ systems unrelated to pathological conditions. Aging produces major cardiovascular changes including moderate hypertrophy of the LV myocardium probably in response to decreased elasticity and compliance of the aorta and other great arteries. With LVH there is outstripping of the capillary and vascular growth and subsequent interstitial fibrosis. These lead to decrease in the rate of myocardial relaxation and increase in LV stiffness resulting in limitation and prolonged passive filling rate in diastole. In consequence, there is a greater contribution of atrial filling to normal LV end diastolic volume. This forms the basis for the reduced E/A ratio and consequent diastolic dysfunction. However kitzman and colleagues posited that the age related alterations in Doppler diastolic filling indices are independent of LV mass, heart rate, contractility and loading conditions. In this study the contribution of LV mass as a determinant of E/A ratio was not significant $\beta = .091$ and $P = .288$ in diabetic subjects.

The IVRT contribution as a determinant of diastolic dysfunction is the most significant and powerful in strength of association, $\beta = -.627$ with $P < .0001$ in the diabetic subjects and $\beta = -.378$ with $P < .001$ in the control subjects.
However, in the overall analysis in which LVEDD, LA, DT, LV mass in addition to age and IVRT as predictors of E/A ratio, $R^2 = .648$ and $P < .0001$ in diabetics while that of the normal control group was $R^2 = .608$ and $P < .0001$. This showed that LVEDD, LA, DT, LV Mass in addition to age and IVRT could account for between 61 to 65% of mitral filling indices across the population groups.

**Gender Differences in the left Ventricular Dysfunction**

In the present study the men were significantly taller than the women with a mean height of $167.05 \pm 6.77$cm, $P < 0.01$ against the women’s $154.84 \pm 5.77$cm. The men also had higher systolic and diastolic blood pressures than the women (see Table 3). Conversely the women weighed more with a significantly higher mean BMI in the over weight range of $26.97 \pm 4.28$ kg/m$^2$ than the men’s mean of $24.67 \pm 3.00$ kg/m$^2$, $P$ value $< 0.01$. In the geometric dimensions the women had increased LVPWD $0.860 \pm 0.12$ cm than the men’s $0.842 \pm 0.12$cm, though not significantly. On the other hand the men had increased IVSTD, LV mass and LV mass index with values as $0.839 \pm 0.14$cm, $141.53 \pm 39.10$g, $78.00 \pm 23.16$ g/m$^2$ respectively against the women’s $0.811 \pm 0.09$cm, $128.00 \pm 30.13$g and $73.00 \pm 16.95$g/m$^2$. This inhomogeneity in LV structural alterations between the sexes cannot be readily accounted for by the differences in gender alone. This is based on the fact that studies$^{200,323,324,325}$ have demonstrated positive linear correlations between blood pressures and LV mass and LV mass index. Therefore, the higher LV mass and LV mass index observed in men in this study may be explained by their higher blood pressures and body size. However, the possible contributions of blood pressure
and body size (BSA) as independent predictors of LV mass and geometry were not determined in this study.

Nevertheless, the finding of increased LVPWD in women was not statistically weighty enough to be ascribed to the influence of feminine gender irrespective of it being a composite of LV mass. This observation is however at variance with findings of Tenebaum et al\textsuperscript{21}, SOLVD Trials\textsuperscript{23} and the Framingham Heart Studies\textsuperscript{337} where it was shown clearly that LVH, increased IVSTD among other parameters in women, were ascribed to gender influence and consequently invoked as responsible for the poorer cardiovascular outcome in them when compared to men with DM.

There is a relative decrease in mean values of FS and VCF in diabetic women $32.93 \pm 7.20$ % and $1.20 \pm 0.39$ circ./sec when compared to their male counterparts with mean values of $34.40 \pm 10.00$ and $1.28 \pm 0.31$ circ./sec respectively. The mean Doppler parameters showed significant changes in values in women when compared to men: E velocity $57.10 \pm 11.00$cm/sec in women against $61.83 \pm 9.30$cm/sec, of men $P<0.05$. IVRT is $122.60 \pm 9.53$msec in women against $111.96 \pm 20.69$ of men, $P<0.01$. Also DT was more prolonged in women than in men though not within significant level. The inter- gender distribution of E/A ratio showed that 18 out of the 33 people with E/A ratio <1 constituting greater percentage of 54.6% were women.

These findings inevitably reflect poorer LV performance in women with DM in the context of systolic and diastolic dysfunctions when compared to their men counterparts in this study. Perhaps an explanation to this worsening gradient
of LV function in women may not fully be rested in the domain of gender influence. This position is supported by the fact that in this study the women were overweight with higher BMI when compared to their men counterparts as earlier mentioned. Obesity is known to be associated with decreased systolic and diastolic functions. Peterson in her evaluation of systolic and diastolic functions in young obese women found significant positive correlation between BMI and LV mass and geometry, while LV functions were inversely correlated with BMI. The mechanism by which obesity causes LV dysfunction can be partly explained thus: (apart from its ability to promote other cardiovascular risk factors such as hypertension, DM and dyslipidaemia amongst other factors), obesity has been associated with neuroendocrine activation, increased renal sodium absorption and heightened systemic oxidative stress. This process is enhanced by the fact that adipose tissue which is found in excess in obese individuals is a major domain for the activation of proinflammatory cytokine cascade. A lipocentric mechanism of cardiac toxicity with resultant cardiac steatosis and lipoapoptosis has been demonstrated in the heart of obese rats.

**COMPARISON OF SENSITIVITY OF E/A RATIO BY DOPPLER AND Em/Am RATIO BY M MODE**

Doppler E/A ratio as an indirect non invasive measure of diastolic function has been well validated with high level of correlation with cardiac catheterization and therefore has high sensitivity as a predictor of impaired ventricular relaxation. The Pearson correlation coefficients between Doppler E/A ratio and Em/Am ratio by M-mode were extremely very weak \((r = .005)\)
and \( r = 0.134 \) and not significant \( (P > .05) \) in diabetic and control subjects respectively. This exposes the insensitivity of the Em/Am ratio as a measure of diastolic dysfunction.

The predictive value of Doppler E/A ratio as a reliable index of evaluating various degrees or spectrum of diastolic dysfunction has been shown in various studies and its sensitivity has been found to be high – hence E/A ratio < 1 is an indicator of impaired relaxation, E/A ratio > 1.5 to 2 is a feature of pseudonormalization, while E/A ratio > 2 is indicative of restrictive pattern of diastolic dysfunction. These values of E/A ratio could be supported by the corresponding values of IVRT and DT or by the various readings of pulmonary venous velocity profile.

In the frequency distribution of this study there was established the prevalence of impaired relaxation of the LV to the tune of 40.2% in the diabetic population using E/A ratio of <1 as benchmark while that of the control group was 17%. Conversely it was not possible to make the diagnosis of impaired relaxation using Em/Am ratio. The frequency distribution of Em/Am ratio below 1 was nil in all the study populations thus bringing its sensitivity to 0%. This discrepancy has further strengthened the point that Em/Am ratio is a less sensitive or poor indicator of diastolic dysfunction and so not used in the evaluation of diastolic dysfunction.
CONCLUSION

In this study there were evidence of alterations in the geometry, systolic and diastolic dysfunctions of the LVs of the hearts of Nigerian diabetic subjects when compared to their normal control counterparts. There were also features suggestive of slight female preponderance in some of the observed changes. These alterations and dysfunctions may largely be accounted for by the deleterious effects of uncontrolled hyperglycaemia in the Nigerian diabetics. The mean FBS level for the diabetic group was 171± 63.4g/dl as against a mean value of 80.70± 18.5g/dl for the normal control group p<0.0001. However, there is the probability of other independent confounders such as BMI, BP, TCH and heart rate influencing the findings even though the level of their contributions may not have been determined in the study.

In addition this study showed that age is an important determinant of the functional abnormalities observed particularly, diastolic dysfunction. This influence of age, is evident even in the normal control group. This assertion is derived from the results of the multiple regression analyses done across the groups in which E/A ratio determinants were analysed, the β value for age was -0.293 with P<05 in the diabetics while in the normal control β value = -0.432 and P = 0.001 (See tables 11 & 12), thus, signifying an inverse relationship. Besides, in the analysis E/A ratio distribution according to age groups, the greatest percentage, (63.6%) of E/A ratio < 1 was found in those between 51 – 60 years age range.

The alterations in LV geometry is significant among the diabetic group. This was shown by LVmass of 134.9±35.5g as against 109.2±25.7g for control P<0.0001.
In the same vein the composites of LVmass were all significantly increased in the diabetics when compared to control P<0.0001 across. The evidence in support of systolic dysfunction in the diabetics is the global depression of the systolic indices measured. The FS, EF and the VCF were all depressed in the diabetic group by 6.2%, 16.8% and 13.9% respectively, when compared to normal control group. The 13.9% depression of VCF is noteworthy since it is less dependent on loading conditions than FS and EF, as such a more reliable index of systolic function.

Diastolic dysfunction was evidenced by E/A ratio of <1 with prolongation of IVRT and DT. The E/A ratio of <1 was observed in 40.2% of the diabetic subjects when compared with the 17% found in normal control group. These changes in diastole were more pronounced in women than in men with DM with a resultant female male ratio of E/A ratio <1 of 1.2:1. It is important to interpret the observed apparent female predelection to some of the alterations in geometry and functions with caution so as not to fall into the temptation of ascribing them to the influence of feminine gender alone, because the degree to which other independent confounders such as BMI, TCH etc. contributed to the observed comparative changes were not determined.

As to the question of sensitivity, and which is a better index of diastolic function between Doppler E/A ratio and M-mode Em/Am ratio, the Doppler E/A ratio is more a better index of detecting diastolic dysfunction.

Therefore from the above highlights, it could be said that Hyperglycaemia might be an important cause of cardiac dysfunctions and abnormal geometry in the newly diagnosed Nigerian diabetic subjects.
RECOMMENDATIONS

Since about 40.2% of the diabetics in this study showed evidence of diastolic dysfunction with marked depression of indices of systolic function, it is recommended that echo screening be included in the investigations of newly diagnosed diabetic patients.

There is the need to determine normative reference data for the various Doppler and two-dimensional parameters for Nigerians since the values we use are basically Caucasian’s. The possibility is there that Nigerians might have peculiar echocharacteristic features as has already been demonstrated in some studies between Whites and Blacks. Thus, it is recommended that a large population based study, if possible multicentre in dimension be carried out to achieve this.

Other more sensitive echocardiographic techniques are fast gaining grounds in clinical studies such as the Doppler tissue imaging in which strain rate can be determined. Strain rate imaging technique and strain are less load dependent than ejection fraction and therefore very accurate and more sensitive than ejection fraction. Also diastolic dysfunction assessment can be made more accurate by the use of annular velocity ratio Ea/Aa which is not volume dependent and not affected by atrial fibrillation or rapid heart rate which obviously confound evaluation of mitral inflow patterns. The use of myocardial performance index or the Tei index which combines features of systolic function isovolumic contraction time, ejection time and the diastolic
parameter, isovolumic relaxation time is said to be very accurate especially in ischaemic conditions. Therefore, future evaluation of the heart functions with the above mentioned modalities are recommended so as to improve on the qualities of results obtainable.

Finally, there was no discrimination between those on oral hypoglycaemic drugs and those on diet in this study. Future studies should focus on this point in order to determine the effects of the commonly used anti-diabetic agents on the heart.
LIMITATION OF STUDY

In the screening process use was not made of genetic mapping techniques that would have obviated the exclusion of those subset of type 2 DM that are of the maturity onset in the young (MODY). This group was excluded just on the basis of age alone (< 40 years). There exclusion may have affected the prevalence rate of some of the findings particularly in women.

However, there may still be a subset of diabetic subjects who would have otherwise been excluded if more sophisticated equipment and techniques were made available during the screening process. The non exclusion, may have inflated the prevalence rate of the various parameters evaluated. For example, cardiac catheterization and coronary arteriography remain the gold standard technique that can define coronary anatomy with sufficient precision to support clinical decisions in patients with coronary artery disease (CAD)\textsuperscript{78}. In the same vein alternative technique of high precision such as PET, ultrafast CT, MRI and exercise thallium myocardial perfusion scintigraphy also could not be deployed.

Furthermore, the exercise electrocardiogram (ECG) has lower sensitivity in women than men for multiple reasons including higher prevalence of resting ECG changes, particularly during menses or preovulation. Also during exercise women tend to have greater release of catecholamines which could potentiate coronary vasospasm and augment the incidence of abnormal exercise ECGs and false positive tests. Therefore, some female patients who
could have formed part of the study populations may have been screened off for the above reasons.

The fourth limitation rests on the fact that Doppler flow studies are subject to vagaries of chamber and systemic vascular haemodynamics. These include factors influencing left ventricular diastolic filling such as the confounding physiologic factors like loading conditions (after load and preload), active ventricular relaxation and myocardial stiffness or poor distensibility. Others include passive chamber stiffness or poor compliance, coronary vascular tugor, increased sympathetic tone leading to increased heart rate and vascular constriction. All these may have attenuated the quality and precision of measurements obtained by the Doppler flow technique used in this study.

In recognition of the above facts interests are gradually shifting to Doppler tissue imaging technique (DTI) which can still utilize the ratio of E and A velocities this time from myocardial tissues and strain rate parameters to arrive at diagnosis of diastolic and systolic dysfunctions with greater accuracy since they are less affected by loading conditions.

Pulmonary vein flow velocities were not evaluated as part of the study design. However, it was done in a few patients in whom suspicions were high about a pseudonormal reading which tended to mask the underlying diastolic dysfunction. The additional evaluation of pulmonary vein flow systolic and diastolic flow velocities and the reverse atrial contraction velocity would have enhanced the accuracy of the data collected.

It was also not possible to determine a reliable cut-off values of Em: Am ratio
of M-mode that will correspond to E/A ratio value by Doppler Mode in the
determination of diastolic dysfunction. This would have provided useful
alternative to Doppler echocardiography in the assessment of flow dynamics.

Finally the contributions of the independent variables like systemic blood
pressures, heart rate, TCH and BMI to the observed dysfunctions of the heart
were not analyzed. This would have given a fuller picture of the extent to
which a single variable such as hyperglycaemia could determine cardiac
dysfunction in the midst of other contending independent factors.
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APPENDIX 1

Fig. 17: A parasternal long axis view of 2-D Echo image at diastole

Fig. 18: An Apical 4 chamber view of 2-D Echo image at systole
Fig. 19: Shows M-mode measurement of aortic root and left atrial dimensions.

Fig. 20: Shows M-mode measurement of left ventricular cavity and posterior wall thickness.
Fig. 21: Shows end diastolic volume by Simpson’s method.

Fig. 22: Shows end diastolic volume in one of the diabetic subjects.
Fig. 23: Shows measurement of E-amplitude or D-E height in one of the diabetic subjects.

Fig. 24: normal E:A ration in one of the subjects.
APPENDIX 5

Fig. 25: Shows reversed E:A ratio in one of the diabetic subjects.

Fig. 26: Shows normal E:A ratio in one of the subjects.
Fig. 27: Shows reversed E:A ratio in a control subject.

Fig. 28: Shows demonstrates normal IVRT in one of the subjects.
Fig.29: Shows IVRT with a time duration of 160m sec. In one of the diabetic subjects.