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Diabetic Cardiomyopathy

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1. Introduction

Diabetes Mellitus is a syndrome characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and, or insulin action.[1] It is a genetically and clinically heterogeneous group of disorders that share glucose intolerance in common.[2] It is the most common endocrine metabolic disorder world wide affecting people of all races and of different social conditions[2]. It is estimated that approximately 120 million people have diabetes mellitus worldwide and this number is expected to double in the next 25 year.[4] The major part of the increase in the prevalence of diabetes mellitus is expected in the developing countries.[5] In most African populations, it is said that the high prevalence of impaired glucose tolerance (IGT) suggests that public health impact of diabetes could increase in these communities in the future.[6]

Diabetes mellitus is characterized by acute and long term complications and these result in increased morbidity and mortality in diabetics especially in developing countries due to inadequate facilities for treatment and the inability of patients to afford the cost of care.[7] The cardiovascular, renal, retinal and neuropathic long-term complications lead to premature disability and death.[7]

Heart disease has been singled out as a major cause of death in patients with diabetes mellitus,[8,9] and the risk of atherosclerotic coronary artery disease is substantially increased in patients with both overt diabetes and asymptomatic hyperglycaemia.[10] Several studies have suggested that diabetes may be associated with left ventricular (LV) structural and functional abnormalities in addition to, and independent of atherosclerosis.[11,12] In the Framingham Cohort, diabetes was associated with higher LV mass in women but not men[13]. High blood pressure (BP), obesity and abnormal lipid profile, which often co-exist with diabetes, tend to be associated with preclinical cardiovascular abnormalities,[14] and may contribute to the association of diabetes mellitus with cardiovascular events.

However, there is increasing evidence that diabetics have abnormalities of left ventricular function in the absence of clinical heart disease[15,16] which is an entity called diabetic cardiomyopathy.

Diastolic left ventricular abnormalities have been disclosed in the past by cardiac catheterisation[17] and abnormal systolic time interval using phonocardiograms,[18,19] and presently by abnormal left ventricular filling using standard and digitised echocardiography,[20,21] radionuclide studies[22] and subsequently by Doppler

echocardiography.[22,23.] Non-invasive methods of assessing left function have confirmed that it is frequently impaired in young asymptomatic diabetics,[24,25] in maturity onset diabetics [26] and in those with retinopathy and nephropathy.[27,28] In diabetes, the left ventricle is not usually dilated or hypertrophied[29] and abnormalities of function are predominantly in diastole, with delayed opening of the mitral valve. Reduced ejection and abnormal systolic function is probably a late event.[19,20]

Possible mechanisms for diabetic cardiomyopathy include excessive myocardial fibrosis,[30] interstitial accumulation of glycoproteins and slow sarcoplasmic calcium reuptake[31] or altered release from a dysfunctional coronary endothelium of mediators such as nitric oxide and endothelin which exert paracrine myocardial effects on diastolic properties [32,34].

2. Diastolic dysfunction

2.1 What is diastolic dysfunction?

Diastolic dysfunction can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete.[34] In its most severe form, diastolic dysfunction results in overt symptoms of congestive heart failure.[35] In modest cases, symptoms of dyspnoea and fatigue occur only during stress or activity such as exercise when heart rate and/or end diastolic volume increase[36]. In its mildest forms, diastolic dysfunction can be manifested as slow or delayed pattern of relaxation and filling with little or no elevation in diastolic pressure and no cardiac symptoms.[37] Some factors that have been implicated in left ventricular diastolic dysfunction include: diabetes mellitus, coronary artery disease, hypertensive heart disease, hypertrophic cardiomyopathy, valvular heart disease, cardiac transplantation, cardiac amyloidosis [38] and aging.[39]

2.2 Prevalence of diastolic dysfunction

The prevalence of asymptomatic diastolic dysfunction was estimated at 27% in an epidemilogic study, and was found to increase with age [40]. Results of early studies suggested that as many as 40% of patients with heart failure symptoms have diastolic heart failure. More recent studies showed that of patients hospitalised for heart failure, 35% to 40% present with diastolic heart failure.[41,42] In the community setting, this number was found to be between 45%and 55%.[43,44] Two recent studies found the prevalence of diastolic heart failure in women to be 1.5-to 2-fold greater than in men.[45,46.] In a study of 86 normotensive type 2 diabetic patients (43% of whom were women, mean age of 43 years and mean glycosylated haemoglobin of 6.5g/dl), greater than 40% had diastolic dysfunction on Doppler echocardiography.[47] In 1989, Shapiro et al reported a prevalence of 40% amongst a mixed patient population of both type1 and type2 diabetics.[48]

In a study of one-hundred and twenty Nigerian normotensive type 2 diabetic subjects, only 29% of the diabetic subjects had normal filling function compared to 58% of the normal controls.[49]

2.3 Clinical evidences for diabetic cardiomyopathy

The Framingham study was the first to demonstrate an increased risk of heart failure in patients with diabetes mellitus.[50] When the incidence of heart failure in men and women with diabetes mellitus was compared with that of non diabetic men and women, the

incidence in individuals with diabetes was found to be 2- and 5-fold greater respectively.[51] Since then, additional trials like Studies of Left Ventricular Dysfunction (SOLVD),[52] the Heart Outcomes Prevention Evaluation (HOPE) study[53] and the Cardiovascular Health Study (CHS)[54] have identified diabetes mellitus as a major risk factor for the development of heart failure. It has been found that close to 30% of patients with diastolic heart failure have diabetes mellitus.[55]

Left ventricular diastolic dysfunction is proposed to be the first stage of diabetic cardiomyopathy.[27,56] In the Strong Heart Study[57] which enrolled 2,411 Native Americans, individuals with diabetes mellitus had evidence of impaired left ventricular relaxation on Doppler echocardiography. In that study, the association between diabetes mellitus and abnormal left ventricular relaxation was independent of age, blood pressure, LV mass and LV systolic function. The abnormalities were more severe in the diabetes-hypertension group, showing the additive deleterious effects on active LV relaxation when both of these conditions are present. Poirier et al[58] reported that patients with well-controlled diabetes and without overt coronary artery disease, hypertension or heart failure have lower levels of exercise performance on maximal treadmill testing than do age-matched controls. This exercise limitation correlated with the severity of diastolic dysfunction as assessed by Doppler echocardiography.

Several workers have studied the correlation between left ventricular diastolic function and factors such as duration of diabetes mellitus, glycaemic control, microangiopathy, microalbuminuria and systemic hypertension. In the study of thirty patients with type 2 diabetes mellitus, Fiorini et al[59] found no correlation between duration of diabetes mellitus and diastolic dysfunction. Also, in the study of one hundred and twenty-five (125) type I diabetics, some workers[60] found no correlation between duration of diabetes and diastolic dysfunction. Also, other workers[61] in the study of twelve (12) type I diabetic patients found that diastolic abnormalities are not related to the duration of the disease. However, Bertoni et al[62] in the study of twenty-six (26) young subjects with type 1 diabetes mellitus of at least three years duration, found that there is a correlation between diastolic dysfunction and duration of diabetes mellitus.

In the Veterans Affairs Co-operative Study in type 2 Diabetes Mellitus (VACSDM)[63], it was found that two years of intensive glycaemic control did not affect the left ventricular systolic or diastolic functions in patients with type 2 diabetes. Also in the study of twenty normotensive patients with a new diagnosis of type 2 diabetes mellitus, some workers[64] found that diastolic function was impaired at diagnosis and was not affected by an improvement in the glycaemic control.However,Felicio et al[65] in the study of fifty-six hypertensive patients with type 2 diabetes mellitus concluded that even though there was no correlation between diastolic dysfunction and glycaemic control, improvement in glycaemic control may contribute to LVH regression in hypertensive patients with type 2 diabetes mellitus.

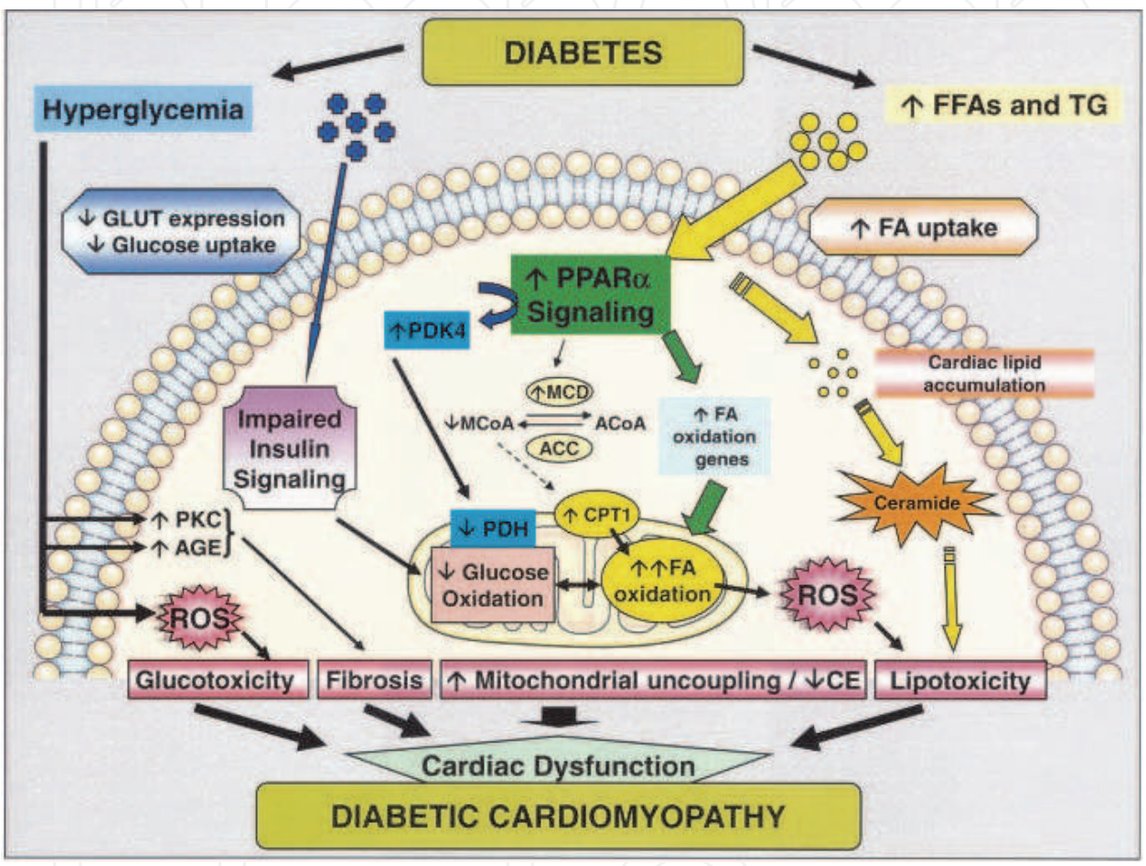
Cecchi et al[66] in the study of forty recently diagnosed type 1 diabetics (with and without microangiopathy) showed that slight preclinical diastolic dysfunction is present in young recently diagnosed type 1 diabetic without microangiopathy. But it was found that more severe dysfunction is present when there is also microangiopathy. Some other workers[56] confirmed this in the study of 26 young subjects with type 1 diabetes mellitus. They showed that there is an often sub-clinical cardiac abnormality in young diabetics resulting in impairment of diastolic function that is correlate with the presence of clinical complications such as nephropathy and retinopathy.

Liu et al in the strong Heart study[57] showed that albuminuria is independently associated with LV systolic and diastolic dysfunction in type 2 diabetics. Some other workers[67] in the study of forty-two patients with mild-to-moderate essential hypertension and type 2 diabetes mellitus found that an elevated urinary albumin excretion is associated with an increased left ventricular mass index. They also found that urinary albumin excretion is associated with a higher prevalence of concentric left ventricular hypertrophy pattern, a depressed midwall systolic performance and a markedly impaired diastolic function. Also Mori et al[68] in the study of twenty-one type 2 diabetics found that left ventricular diastolic function may be related to both hypertension and proteinuria.
In the study of ten age-controlled type 2 diabetes, it was found by Poirier et al[69] that left ventricular diastolic dysfunction and cardiac autonomic neuropathy are associated in patients with otherwise uncomplicated well-controlled type 2 diabetes mellitus.

3. Pathogeesis of diabetic cardiomyopathy

The pathogenesis of diabetic cardiomyopathy has been illustrated in figure1.The morphologic changes in the diabetic heart include myocyte hypertrophy, increased matrix collagen, interstitial fibrosis, and intra-myocardial microangiopathy.[70] These changes are probably consequences of altered myocardial glucose and fatty acid metabolism due to diabetes.[50] Chronic hyperglycaemia leads to nonenzymatic glycation of vascular and membrane proteins, producing advanced glycation end products (AGEs) and reactive oxygen species.[67] Once AGEs develop in the arterial wall and myocardium, they form stable and irreversible crosslinks with adjacent collagen polymers thereby decreasing the compliance of the blood vessels and myocardium.[67] The AGEs and reactive oxygen species will also affect ion channel, calcium homeostasis, and mitochondrial function, as well as initiating apoptosis, leading to contractile dysfunction-glucotoxicity.[67]
Diabetes is also characterised by an increased turnover of free fatty acids. The increased free fatty acid turnover leads to increased myocardial oxygen consumption and enhances the intracellular accumulation of intermediates, leading to deleterious effects-lipotoxicity.[67] These effects include interference with ATP-dependent ion pumps and mobilisation of intracellular calcium, thereby creating calcium overload and relaxation abnormalities. Impaired glucose oxidation also leads to lactic acid accumulation that further promotes the degradation of free fatty acids.[68]
Other myocardial changes in diabetes include impairment of beta-receptor signal transudation and induction of fetal gene pattern.[70,71] The fetal gene pattern leads to upregulation of beta-myosin heavy chain and downregulation of alpha-myosin heavy chain gene which is the fast –contracting isoform of myosin heavy chain that contains much greater ATPase activity than does beta-myosin heavy chain.[72] In addition, there is downregulation of the SERCA gene,[73] leading to impaired myocardial calcium handling.[74] These changes in gene expression are closely associated with abnormalities in diastolic function.[75]
To support the theory that abnormalities in high-energy phosphate metabolism may cause diastolic dysfunction in diabetes, magnetic resonance imaging study demonstrated LV diastolic dysfunction in 12 asymptomatic, normotensive, nonobese patients with well-controlled diabetes when compared with control subjects matched for age, sex, body mass index, and blood pressure.[76] These findings were associated with a significantly lower ratio of myocardial phosphocreatine to ATP in-patients with diabetes compared with controls.[91]

Results of previous studies in non-diabetic individuals with LV hypertrophy suggested that the lower phosphocreatine content and the switch in substrate preference from glucose to fatty acids may lead to lower levels of ATP in the sarcomeres that cannot be overcome by increased mitochondrial ATP production[77]. Lower cytosolic ATP concentrations are associated with impaired calcium sequestration by the sarcoplasmic reticulum and impaired relaxation of cardiomyocytes[76].



Increased free FA (FFA) activates PPAR- signaling, leading to the increased transcription of many genes involved in FA oxidation. Increased FA oxidation leads to the generation of ROS at the level of the electron transport chain. ROS, which also can be generated by extramitochondrial mechanisms such as NADPH oxidase, plays a critical role in several pathways involved in the pathogenesis of diabetic cardiomyopathy, including lipotoxicity, cell death, and tissue damage, as well as mitochondrial uncoupling and reduced cardiac efficiency. TG= triglycerides; GLUTs= glucose transporters; PDK4=pyruvate dehydrogenase kinase 4; MCD=malonyl-coenzyme A decarboxylase;MCoA= malonyl-coenzyme A; ACoA=acetyl-coenzyme A; ACC= acetyl coenzyme A carboxylase; CPT1= carnitine palmitoyl-transferase 1; PDH= pyruvate dehydrogenase; CE= cardiac efficiency; PKC= protein kinase C; and AGE= glycation end products

4. Diagnosing diastolic dysfunction

Differentiating between diastolic and systolic dysfunction on clinical grounds is very difficult, although clues may be given by the patient's past history, clinical presentation, physical examination, radiographic and electrocardiographic findings.[78] Exertional dyspnoea because of pulmonary congestion is frequently an early event in diastolic dysfunction.[78]

More commonly, estimates of left ventricular size and systolic function are needed in order to determine whether congestive heart failure is caused by systolic or diastolic dysfunction. These measurements can be made using echocardiography, radionuclide ventriculography, or contrast ventriculography.[79]

Precisely, the definite diagnosis of diastolic dysfunction or failure depends on the observation of an appropriate upward shift of the (end-) diastolic pressure – volume relation.[80] Therefore, objective evidence of ventricular diastolic dysfunction requires cardiac catheterisation with volume determinations using frame-by-frame analysis of left ventricular contrast angiograms or impedance measurements and high – fidelity measurements of ventricular pressure with a micromanometer.[81] However, due to the invasive nature, high cost, and limited availability of haemodynamic studies, this remains impractical for widespread use or for serial follow-up examinations[82] thereby leaving echocardiography as the gold standard.

4.1 Echocardiography

Doppler echocardiography has become the most widely used and accepted method for the diagnosis and follow-up of patients with diastolic dysfunction. Its reliability, reproducibility, ease of performance, and advances in applications over the past decade makes it the ideal tool for the assessment of "diastology"[83.] The basis of the Doppler echocardiographic assessment of diastolic function relies on a careful, integrated approach.[84,85] The main stay of this approach involves the recording of flow velocities across the mitral valve and within the pulmonary veins to assess filling patterns and estimate left ventricular filling pressure indirectly.[85] Mitral flow velocities are obtained by pulse-wave Doppler echocardiography placing the sample volume located between the tips of the mitral valve leaflet during ventricular diastole (as shown in figure 2). The peak velocity of early rapid filling (E), peak velocity of late filling caused by atrial contraction (A), E/A ratio, the interval from the peak of E velocity to its extrapolation to baseline or the deceleration time (DT) and the interval from aortic valve closure to mitral valve opening or isovolumic relaxation time (IVRT) is measured.[86]

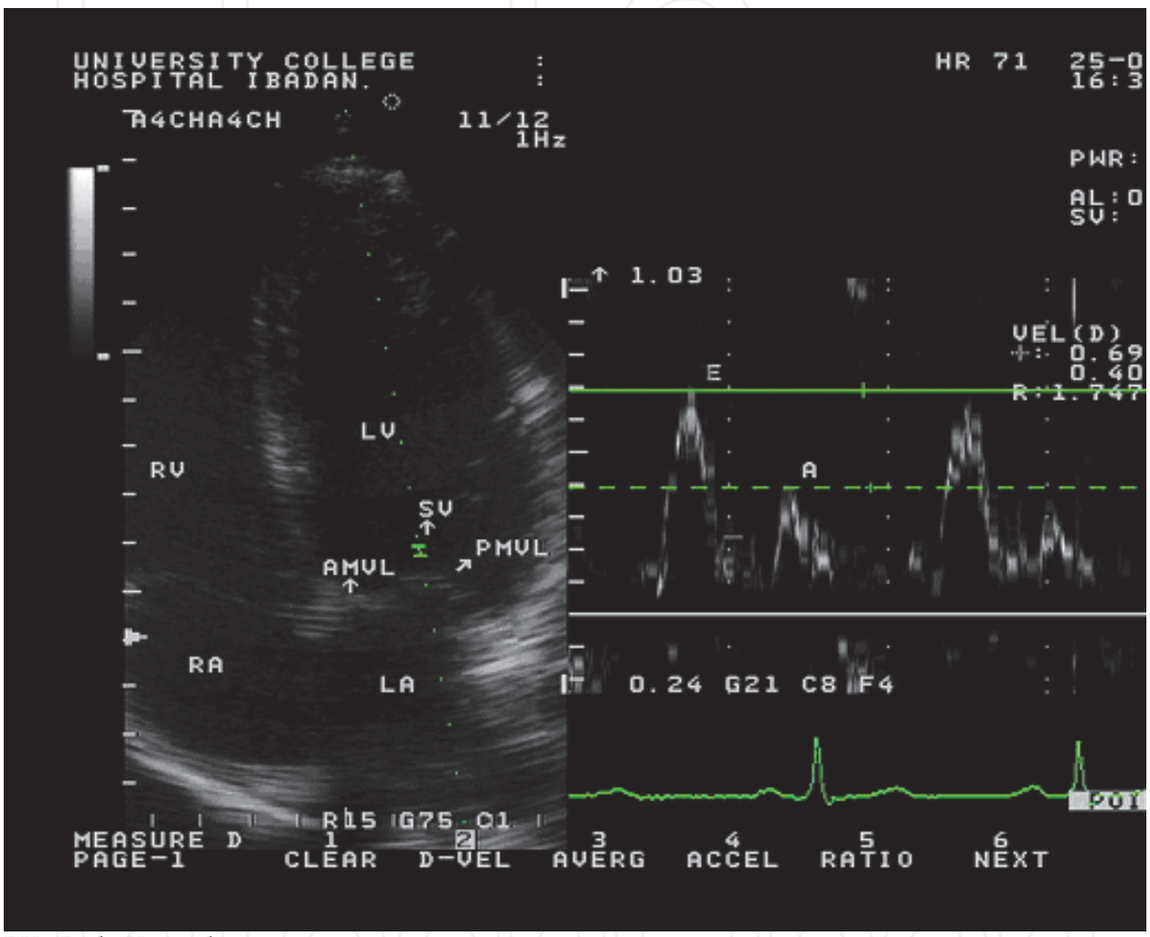
Pulmonary venous flow is measured using pulse-wave Doppler echocardiography with sample volume located 1-2cm into a pulmonary vein, proximal to its insertion into the left atrium(as shown in figure 3). The systolic peak velocity which is biphasic in 30% of cases (S), diastolic peak velocity (D), the S/D ratio, atrial systolic reversal velocity (A) are measured.[87]

Based on Doppler echocardiographic studies, diastolic filling is classified into:[86] normal, impaired relaxation or mild diastolic dysfunction, moderate diastolic dysfunction or pseudo normal filling and severe diastolic dysfunction or restrictive filling.

4.2 Normal filling

The determinants of LV filling, ventricular relaxation and effective chamber compliance change with increasing age. This leads to different diastolic filling patterns for different

groups.[88] In normal young individuals aged (20s – 30s), LV relaxation is rapid, the majority of filling (85-95%) occurring in early diastole and only a small proportion (5-15%) occurring with atrial contraction. This results in mitral inflow parameters of E/A between 1-2 (mean1.8), and relatively short deceleration time (mean 182msec) and isovolumetric relaxation time (mean 71msec). Pulmonary venous inflow usually shows a slight systolic predominance (S>D) with a mean pulmonary 'A' of 0.19m/sec.[89]

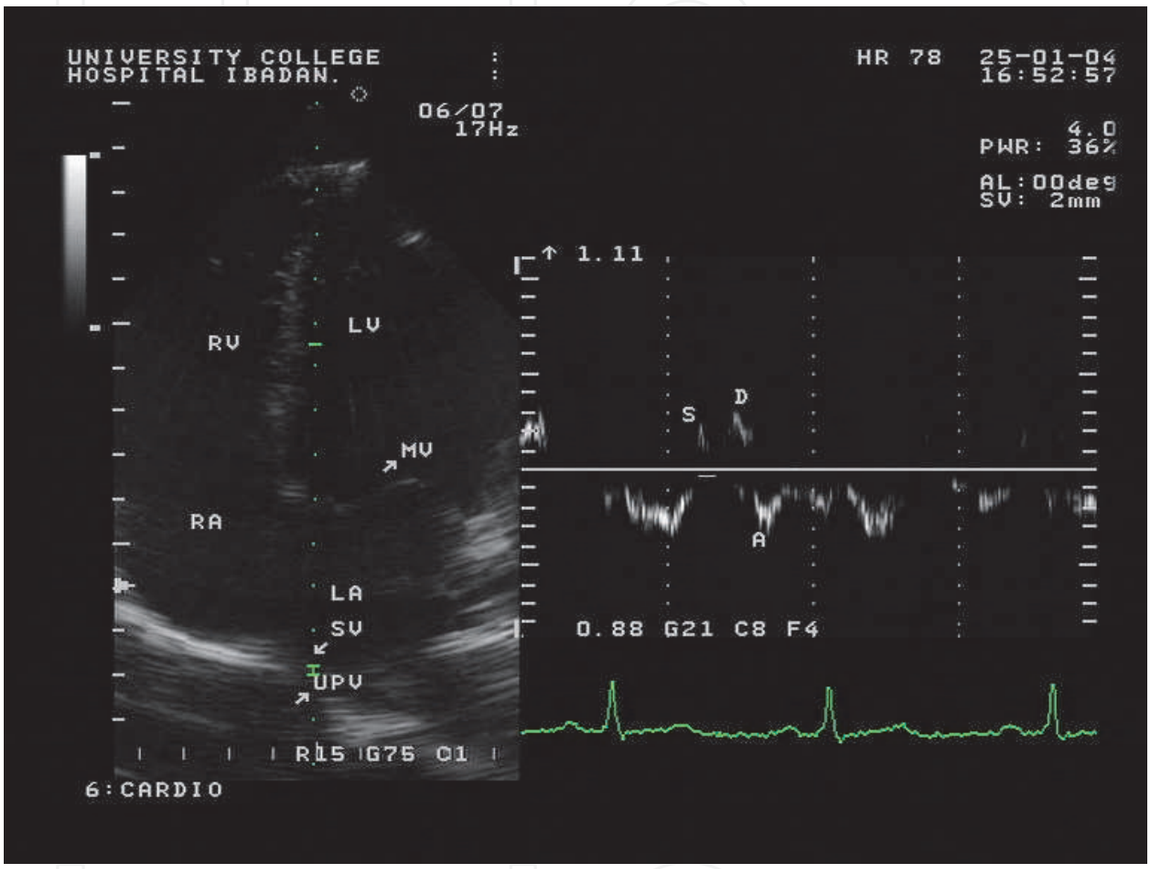


RV =Right Ventricle
LV=Left Ventricle
RA=Right Atrium
LA =Left Atrium
SV=Sample Volume
AMVL=Anterior Mitral Valve Leaflet
PMVL=Posterior Mitral Valve Leaflet
E=Mitral E wave
A=Mitral A wave

Fig. 2.Echocardiogram showing measurement of Transmitral Flow Velocity Profile ('E' and 'A' Waves)

With aging, the rate of LV relaxation decreases with slower and less filling in early diastole and an increased contribution to LV filling by atrial contraction. This leads to a prolongation

of the IVRT and DT, a reduction in E velocity, and an increase in A velocity with a subsequent reduction in E/A ratio. Individuals >65 years have the following average parameters: E/A ratio of less than 1, a mean DT greater than 214msec, and IVRT greater than of 94msec. As pulmonary D parallels the pulmonary S velocity, the pulmonary venous flow now shows diastolic predominance (D>S). As well, the A increases slightly, but does not exceed the upper limit of normal (0.35m/sec).[90]



LV=Left Ventricle,
RV =Right Ventricle,
RA=Right Atrium,
A =Left Atrium,
SV=Sample Volume,
UPV= Upper Pulmonary Vein (Right),
S=Pulmonary Vein Systolic Velocity,
D=Pulmonary Vein Diastolic velocity,
A=Pulmonary Reverse flow Velocity

Fig. 3. Echocardiogram showing measurement of Pulmonary Flow Velocity Profile

4.3 Mild diastolic dysfunction

This represents the earliest stage of diastolic dysfunction. There is impaired LV relaxation with initially normal LV filling pressures, leading to decreased early filling and increased filling with atrial contraction. Mitral inflow patterns show an E/A less than 1 which is

abnormal for the age. The IVRT is prolonged (>100msec), with prolongation of the DT (>200msec). Pulmonary venous inflow normally remains normal with systolic predominance (S>D), and with pulmonary 'A'<0.35m/sec.[90]

4.4 Moderate diastolic dysfunction

As diastolic dysfunction progresses, LV relaxation becomes further impaired and LV stiffness increases.[90] In an attempt to maintain LV filling and cardiac output, the filling pressure, specifically left atrial (LA) pressure becomes elevated. This increased transmitral pressure gradient leads to increased early filling with the E/A ratio 'normalizing' to a value >1, with prolongation of IVRT and DT to high values. This mitral pattern is similar to the pattern in normal individuals, leading to the term 'pseudonormal'. The differentiation from normal is done on the basis of an abnormal response to the valsalva manoeuvre or as abnormal pulmonary venous flow pattern.[90]

4.5 Severe diastolic dysfunction

As diastolic dysfunction progresses further, LV relaxation continues to be impaired, however, it is marked by rising LV filling pressures and a markedly reduced LV compliance. This mimics the physiology of restrictive cardiomyopathy.[90] The increased LA pressure causes an early mitral valve opening and rapid early filling (increased E velocity). As early rapid filling occur into a noncompliant LV, there is rapid equalization of LV and LA pressured leading to a shortened DT.[90] Atrial contraction into a noncompliant LV with high diastolic pressure leads to a reduced A velocity. Therefore, the E/A ratio is >2, and occasionally >4 to 5. Pulmonary venous inflow shows a marked blunting of systolic inflow (PS<<PD) corresponding to the markedly elevated LA pressure and reduced LA compliance.[87]

5. Conclusion

Abnormal left ventricular relaxation seen in diabetics, independent of other factors has been shown to contribute to the incidence of congestive heart failure despite normal left ventricular ejection fraction.[55] It is therefore another cause of clinical cardiovascular morbidity. In addition, reduced or increased mitral E/A ratio has been shown to be independently associated with increased all cause mortality as well as cardiovascular mortality.[91]

It is therefore necessary to detect early, diabetic patients with left ventricular diastolic dysfunction and commence treatment modalities such as use of selective β – blockers and ACE inhibitor.[131] However, there have not been prospective intervention studies to determine the reversibility and effectiveness of such treatments.

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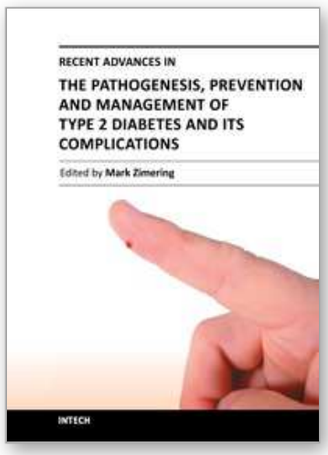

Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications
Edited by Prof. Mark Zimering

ISBN 978-953-307-597-6
Hard cover, 442 pages
Publisher InTech
Published online 29, August, 2011
Published in print edition August, 2011

Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Dike Bevis Ojji (2011). Diabetic Cardiomyopathy, Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications, Prof. Mark Zimering (Ed.), ISBN: 978-953-307-597-6, InTech, Available from: http://www.intechopen.com/books/recent-advances-in-the-pathogenesis-prevention-and-management-of-type-2-diabetes-and-its-complications/diabetic-cardiomyopathy

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