ORIGINAL ARTICLE

DIASTOLIC DYSFUNCTION IN DIABETES MELLITUS

Nikhil M Dikshit[1], Parizad Z Wadia[2], Deepak K Shukla[3]

Authors' Affiliation: [1]Physician**,** Rugved Multispecialty Hospital, Surat; [2]Professor, Department of Medicine, Government Medical College, Surat; [3]Associate Professor, Department of Medicine, Surat Municipal Institute of Medical Education and Research, Surat

Corresponding author email: drnikhil_surat@yahoo.com

ABSTRACT

Introduction: Diabetes Mellitus is a disease with multi-system complications. Congestive heart failure is the end result of cardiovascular complications, and is heralded by the presence of diabetic cardiomyopathy, indicated by diastolic left ventricular dysfunction, which can be easily assessed with echocardiography.

Objectives: To note prevalence of LV diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus.

Methods: A study was carried out on 50 diabetics and compared with 50 age and sex matched controls. In all the patients, detailed history, physical examination and specific investigations (conventional Doppler echocardiography at rest) were done to find out the prevalence of diastolic dysfunction.

Results: The prevalence of diastolic dysfunction, defined by echocardiographic criteria was 66%. E/A, DT and peak A velocity were sensitive indices of diastolic LV dysfunction. Left ventricular hypertrophy, as indicated by an increased LV mass, was an early marker of diabetic cardiomyopathy.

Conclusion: Echocardiography is a sensitive method to investigate for diastolic dysfunction. There is a high prevalence of diastolic dysfunction in diabetes, which is an early marker of diabetic cardiomyopathy.

Keywords: diastolic dysfunction, diabetes, echocardiography, diabetic cardiomyopathy.

INTRODUCTION

Diabetes Mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. It is associated with a multitude of cardiovascular complications. Clinical, epidemiological and pathological studies attribute the increased occurrence of clinical congestive heart failure in diabetic subjects to diabetic cardiomyopathy, which could take the form of diastolic and/or systolic left ventricular dysfunction[1,2]. Left ventricular diastolic dysfunction may represent the reversible first stage of diabetic cardiomyopathy[2], reinforcing the importance of early examination of diastolic ventricular function in individuals with diabetes. The risk of heart failure is increased even in diabetic patients with no clinical evidence of coronary artery disease. Myocardial involvement in diabetics may occur relatively early in the course of disease, initially impairing early diastolic relaxation and when more extensive, it causes decreased myocardial contraction. Prior to the development of symptomatic congestive heart failure, sub-clinical left ventricular dysfunction (systolic or diastolic) exists for sometime[3]. However, frequency of progression from pre-clinical to clinically evident myocardial dysfunction is not established. With the availability of echocardiography and Doppler, the natural history of cardiac involvement from pre-clinical to clinical stage in patients with diabetes can be elucidated. The present study was performed to assess normotensive diabetic patients by echocardiographic and Doppler parameters.

MATERIALS AND METHODS

This prospective study was undertaken in 50 patients with diabetes mellitus, who were referred to the outdoor department of New Civil Hospital, Surat over a period of six months. All subjects were determined to be otherwise healthy by a medical history and physical examination (including ocular fundoscopy). A normal resting electrocardiogram and chest radiograph were prerequisites for participation. Plasma glucose (fasting and post prandial) was measured by the glucose oxidase method and the urine sugar by Benedict's reagent. Biochemical investigations in the form of blood urea, serum creatinine and serum cholesterol were also carried out enzymatically. BMI (Body Mass Index) was calculated as weight (kgs.) ÷ [height (m)]^2. A standard 12 lead electrocardiogram and a transthoracic echocardiogram in all its modes (M, 3d and colour Doppler) were also carried out. Following patients were excluded:

1. Patients with coronary artery disease diagnosed by symptoms, electrocardiogram or regional wall motion abnormality on echocardiogram.
2. Patients with congestive cardiac failure diagnosed by signs and symptoms, chest radiograph or echocardiography.
3. Heart rate < 50 or > 100 per minute and 1° AV block, atrial fibrillation of any other cardiac arrhythmias diagnosed by clinical examination and electrocardiogram, as they would interfere with Doppler studies.
4. Patients found as hypertensive (BP > 140/90 mmHg).

The control group consisted of 50 healthy, non-diabetic volunteers (confirmed by blood sugar values) comparable for age and sex distribution to diabetic patients. Institutional approval was obtained for the study and informed consent was obtained from the subjects, who did not have to pay for any of the tests.

Echocardiography:

Echocardiograms were recorded with a commercially available ultrasound system (ESAOTE MEGAS CVX e GPX). Subjects were examined in the left lateral decubitus and supine position using standard parasternal long axis, short axis and apical views. All recordings and measurements were obtained by the same observer according to the recommendations of the American Society of Echocardiography[4] and were always performed at midday to avoid the influence of circadian rhythm on left ventricular diastolic function[5].

M mode echocardiographic measurements of the following left ventricle function parameters were taken:
1. Left ventricular internal dimensions: EDD and ESD (cms)
2. Interventricular septal thickness in systole and diastole: IVSS and IVSD (cms)
3. Left ventricular posterior wall thickness in systole and diastole: LVPWS and LVPWD (cms)
4. Ejection fraction: EF (%)
5. Fractional shortening: FS (%)
6. E point septal separation: EPSS (cm)

Criteria for left ventricular hypertrophy were based on values > 13mm for interventricular septum and left ventricular posterior wall.

Systolic dysfunction was indicated by Ejection fraction < 50%; Fractional shortening; Regional wall motion abnormalities; and E point septal separation: normal value – 6-9 mm, with higher values indicating systolic dysfunction.

Doppler echocardiography was carried out to assess left ventricular diastolic function. Under simultaneous 2-dimensional echocardiographic visualization of cardiac anatomy in the apical four chamber view, a Doppler sample volume was positioned within inflow area of the left ventricle just below the mitral valve annulus (near the mitral valve tips and parallel to the presumed axis of blood flow)[6]. To minimize potential effects of transducer angulations, Doppler sampling volume was aligned in different planes until maximum diastolic flow velocities were recorded till optimal spectral pattern was obtained. From the transmitral recording, following measurements were carried out:

1. Peak E velocity in m/sec - peak early transmitral filling velocity during early diastole (normal: 0.5-0.8).
2. Peak A velocity in m/sec – peak transmitral atrial filling velocity during late diastole (normal: 0.3-0.5).
3. Deceleration time (DT) in msec – time elapsed between peak E velocity and point where extrapolation of deceleration slope of E velocity crosses the zero baseline (normal: 150-220).
4. Acceleration time (AT) in msec – time elapsed between point where extrapolation of acceleration slope of E velocity crosses zero baseline and peak E velocity. (normal: 60-100)
5. Isovolumic relaxation time (IVRT) in msec – duration between aortic valve closure and mitral valve opening (normal: 60-100).
6. Ratio of peak E to peak A (E/A) (normal: 1-2).

The Echocardiographic Diastolic Dysfunction Criteria[7,8] for enrollment in the study were as follows:

Diastolic Parameters	Criteria
Mitral E/A ratio	< 1 or > 2
Deceleration time (msec)	< 150 or > 220
Isovolumic Relaxation time (msec)	< 60 or > 100

Left ventricular mass was calculated using the following formula[9]:

$$LV\ mass\ (gm) = 0.8 \times 1.04[(LVEDD + IVSD + PWD)^3 - (LVEDD)^3] + 0.6$$

All the data collected was analyzed statistically using the Z test. Statistical significance was estimated by calculating the 'p' value, with significance assigned at $p < 0.05$. p values < 0.01 were considered to be highly significant.

RESULTS

Table 1: Basic Characteristics of Study Population.

Parameter	Diabetics (Study Group) Mean±SD	Controls Mean±SD	p value
Age	43.88±13.74	38.5±14.36	0.056
Mean BMI (kg/m²)	24.06±2.53	22.65±1.92	**<0.05**
Mean BP (mm of Hg)	120/78	118/74	-
Total cholesterol (mg/dl)	206.2±58.18	189.2±28.12	**<0.05**
Mean FBS (mg/dl)	180.8±78.41	86.44±16.31	**< 0.01**
Mean PPBS (mg/dl)	231.8±86.95	118.2±14.2	**< 0.01**

Out of a total of 50 diabetics, 33 (66%) patients had diastolic dysfunction. The average age of patients with diabetes observed was 43.88 ± 13.74 yrs. The mean age for controls was 38.5 ± 14.36 yrs. The male-female ratio in the study group was 1.94:1 and in the control group was 2.33:1.

All subjects showed normal systolic function. Interventricular septum thickness, left ventricular dimensions

(both end-systolic and end-diastolic) and left ventricular posterior wall thickness were greater in the diabetic group ($p < 0.01$). Left ventricular mass was increased by ~ 20% in the patient group (223.4 ± 54.44 vs 187 ± 29.84, $p < 0.01$). With regard to the pattern of left ventricular diastolic filling, diabetic patients showed a higher atrial peak filling velocity ($p < 0.01$) and, consequently, a reduced E/A ratio ($p < 0.01$). The diabetic patients also showed prolonged isovolumic relaxation and deceleration times ($p < 0.01$).

Table 2: M Mode Parameters in Diabetics and Controls.

Parameter	Diabetics (Study Group) Mean±SD	Controls Mean±SD	p value
EDD (cms)	4.72±0.54	4.28±0.31	**< 0.01**
ESD (cms)	3.46±0.39	3.07±0.2	**< 0.01**
EF (%)	61.43±4.6	62.7±5.59	0.215
FS (%)	27.6±2.9	28.2±3.68	0.3649
EPSS (mms)	9.22±1.63	8.86±1.11	0.1967
IVS(cms)	1.34±0.35	1.04±0.14	**< 0.01**
LVPW (cms)	1.25±0.24	1.05±0.11	**< 0.01**
LV Mass (gms)	223.4±54.44	187±29.84	**< 0.01**

Table 3: 2-D Echo and Doppler Parameters in Diabetics and Controls.

Parameter	Diabetics (Study Group) Mean±SD	Controls Mean±SD	p value
E (m/sec)	0.54±0.13	0.57±0.05	0.1278
A (m/sec)	0.62±0.16	0.43±0.04	**< 0.01**
E/A	0.9±0.27	1.36±0.2	**< 0.01**
AT (msec)	86.32±24.47	80.14±7.09	0.0863
DT (msec)	236.5±40.01	181.2±10.67	**< 0.01**
IVRT (msec)	76.44±7.29	68.4±7.34	**< 0.01**

DISCUSSION

The present study provides evidence that left ventricular diastolic function is impaired in patients with diabetes mellitus. Left ventricular diastolic function has been shown to be affected at an early stage in several myocardial diseases when systolic functions remain normal. Till the recent past, all importance was being given to systolic functions of the heart. But in the last decade clinicians and researchers have discovered that both reversible and irreversible abnormalities of left ventricular diastolic functions contribute significantly to symptoms and morbidity in individuals with a variety of cardiac disorders, including those with normal or near normal systolic function.±

It was observed that E/A ratio was significantly abnormal (< 1) in diabetics as compared to the value in normal controls (> 1). This abnormality was seen in 66% of diabetics. Left ventricular wall thickness defined as the sum of ventricular septal and posterior wall thickness and LV mass were statistically significant both in systole as well as in diastole when compared with normal controls. These data indirectly suggest that metabolic and/or hormonal factors may play a role in the development of a greater ventricular mass. Among these, insulin resistance with its associated hyperinsulinemia is the most likely candidate. The deceleration time (DT) of the E wave was an even more specific indicator of diastolic dysfunction, with a highly significant increase in its duration in the diabetic group. This index is an important variable to differentiate the diabetics with a normal filling pattern and normal diastolic function from those with a pseudonormalised pattern of diastolic dysfunction. The difference in the acceleration times (AT) of the E wave between diabetics and controls was not significant.

The present study did not show any significant decrease in the ejection fraction in diabetics.

Our results were compared with various studies. Patil et al[10] in their study of 127 asymptomatic Type II diabetics found a significant incidence (54.33%) of diastolic dysfunction in diabetics. Similarly, in the present study, 66% diabetics were found to have diastolic dysfunction. Van Heerebeek et al[11] in their study of 36 Type II DM patients stated that, the cardiomyocyte resting tension is more important when LVEF is normal. Excessive diastolic left ventricular stiffness is an important contributor to heart failure in subjects with DM. Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products. Similarly, in the present study, 66% of subjects from the case group had diastolic dysfunction with normal LVEF. Sohail et al[12] in their study of 212 diabetic population found that 30.76% patients with Type II DM had diastolic dysfunction. The LV diastolic dysfunction is much more prevalent in patients with Type II diabetes mellitus and LV diastolic dysfunction is an early marker of diabetic cardiomyopathy. In our study, the prevalence was 66%. Patil et al[13] in their cross-sectional hospital based study found that in 64% of patients with Type II diabetes, myocardial damage affects diastolic dysfunction in diabetics before systolic dysfunction – very similar to the present study.

CONCLUSION

From the foregoing discussion, it can be concluded that diastolic dysfunction in patients of diabetes is present in 66% of patients even when diabetes is present at a younger age, and is of a shorter duration. This dysfunction is suggestive of pre-clinical diabetic cardiomyopathy. E/A, DT and peak A velocity are sensitive indices of diastolic LV dysfunction. It is suggested that all patients of diabetes should be routinely and repeatedly subjected to 2-D color Doppler echocardiographic assessment of cardiac functions in the long-term management of this metabolic disease. This has important therapeutic implications and helps physicians planning early intervention strategies. Thus, diastolic dysfunction can be used as an early indicator, as it is a precursor to increased LV hypertrophy and clinical left ventricular dysfunction.

REFERENCES

1. Zarich SW, Nesto RW : Diabetic Cardiomyopathy. American Heart Journal 118: 1000-1012, 1989.

2. Raev DC : Which left ventricular function is impaired earlier in the evolution of dilated cardiomyopathy : an echocardiographic study of young Type I diabetic patients. Diabetes Care 17:7; 633-639, 1994.

3. Rajput R, Jagdish, Siwach SB et al : Echocardiographic And Doppler Assessment Of Cardiac Functions In Patients Of Non-Insulin Dependent Diabetes Mellitus. Journal, Indian Academy of Clinical Medicine, 2002, 3(2): 164 – 168.

4. Sahn DJ, Demaria A, Kisslo J et al : Recommendations regarding quantitation in M mode echocardiography : results of a survey of echocardiographic measurements. Circulation, 1978, 58: 1072-1083.

5. Voutilainen S, Kupari M, Hippelainen M et al : Circadian variation of left ventricular diastolic function in healthy people. Heart, 1996, 75: 35-39.

6. Appleton CP, Hatle LK, Popp RL : Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic sudy. Journal of American College of Cardiology, 1988, 12: 426-440.

7. Rakowski H, Appleton CP, Chan KL et al : Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography from the investigators of Consensus on Diastolic Dysfunction by echocardiography. Journal of American Society of Echocardiography, 1996, 9: 736-760.

8. Garcia MJ, Thomas JD, Klein AL : New Doppler echocardiography applications for the study of diastolic function. Journal of American College of Cardiology, 1998, 32: 865-875.

9. Guidelines from the Canadian Cardiovascular Society and the Canadian Hypertension Society on the Echocardiographic determination of left ventricular mass – Task Force of the Echocardiography Section. Canadian Journal of Cardiology, 1995, 11: 301-395.

10. Patil VC, Patil HV, Shah KB, Vasani JD, Shetty P : Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function – Journal of Cardiovascular Disease Research, 2011 Oct-Dec; 2(4): 213–222.

11. Van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, et al. Diastolic stiffness of the failing diabetic heart: Importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation, 2008, 1(117): 43–51.

12. Ashraf SM, Basir F: Association of hypertension and diastolic dysfunction with type 2 diabetes mellitus. Pakistan Journal of Medical Sciences, 2007, 23: 344–8.

13. Patil MB, Burji NP: Echocardiographic evaluation of diastolic dysfunction in asymptomatic type 2 diabetes mellitus. Journal of the Association of Physicians of India, 2012 May, 60: 23-6.