

EVALUATION OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN TYPE II DIABETES MELLITUS – THE ROLE OF VALSALVA MANEUVERUday G¹, Jayakumar S², Jnaneshwari M³, Arun Kumar N⁴**HOW TO CITE THIS ARTICLE:**

Uday G, Jayakumar S, Jnaneshwari M, Arun Kumar N. "Evaluation of Left Ventricular Diastolic Dysfunction in Type II Diabetes Mellitus – The Role of Valsalva Maneuver". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 11, March 17; Page: 2898-2906, DOI: 10.14260/jemds/2014/2222

ABSTRACT: BACKGROUND & OBJECTIVES: Left ventricular diastolic dysfunction is known to occur in early stages of diabetic cardiomyopathy but its exact prevalence is not known. The present study was conducted to assess the prevalence of diastolic dysfunction in diabetic patients in the absence of hypertension or CAD. The role of valsalva maneuver in diagnosis of diastolic dysfunction was also studied. **AIMS:** To study left ventricular diastolic dysfunction in asymptomatic normotensive patients with Type 2 Diabetes. To study the role of valsalva maneuver in diagnosing diastolic dysfunction. **METHODOLOGY:** 100 consecutive asymptomatic normotensive patients (mean age 52.34 ±8.6 yrs.) with Type 2 diabetes free of any major clinical diabetic complications and having no evidence of CAD on non-invasive testing were studied for LV diastolic functions, using pulsed Doppler at the tip of mitral valve. The peak velocities of LV filling during the early rapid (E wave) and atrial contraction (A wave) phases, the ratio of the 2 filling velocities (E/A ratio) were recorded at end expiration at baseline and again during phase II of valsalva maneuver. **RESULTS:** LVDD was found in 54% of subjects of whom 11% had pseudo normal pattern of ventricular filling and 43% had impaired relaxation. LVDD was well correlated with age and duration of diabetes. **CONCLUSION:** LVDD is much more common in Type 2 diabetes who are free of clinically detectable heart disease. Pseudonormal pattern may account for a significant number of patients with diastolic dysfunction and failure to recognize it may lead to significant underestimation of the true prevalence of LVDD in these patients. **KEYWORDS:** LV diastolic dysfunction, Pseudo normal filling, Impaired relaxation Valsalva maneuver.

INTRODUCTION: Diabetes Mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycemia, resulting from reduced insulin secretion, decreased glucose utilization and increased glucose production. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. With an increasing incidence worldwide, Diabetes Mellitus will be a leading cause of morbidity and mortality for the foreseeable future.¹

Prevalence of diabetes in adult's worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025. By the year 2025, India, China and the U S will be the countries with the largest number of people with diabetes. In future, diabetes will be increasingly concentrated in urban areas.² The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal obesity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher

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high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease.³

DIABETES AND HEART: Patients with diabetes have a two to four fold increase in the risk of coronary artery disease (CAD). Patients with diabetes have an absolute risk of CAD death more than three times higher than that in the non-diabetic cohort even after adjustment for established risk factors.⁴ The causal role of diabetes mellitus in the development of congestive heart failure was delineated more conclusively in the Framingham Heart Study.⁵

Further support for the existence of a diabetic cardiomyopathy was provided by Hamby et al⁶ who noted an increased incidence of diabetes in patients with idiopathic cardiomyopathy. The non-invasive evaluation of cardiac performance utilizing systolic time intervals, phonocardiography, M-mode and two – dimensional echocardiography and Doppler echocardiography has also documented sub clinical left ventricular dysfunction in diabetic individuals.

Doppler echocardiography has recently been increasingly employed to assess left ventricular diastolic function.⁷⁻⁹ Evaluation of early and late components of transmitral flow velocities has been shown to be a reliable means of identifying diastolic filling abnormalities.¹⁰ This study was undertaken to evaluate left ventricular diastolic dysfunction in diabetic patients who had no clinical or electro cardio graphic evidence of cardiac disease.

AIMS AND OBJECTIVES:

1. To study left ventricular diastolic dysfunction in asymptomatic normotensive patients with Type 2 Diabetes Mellitus.
2. To study the role of valsalva maneuver in diagnosing diastolic dysfunction.

MATERIALS AND METHODS:

STUDY DESIGN: This was a prospective cross sectional study where diabetic patients attending the outpatient department and admitted to various wards of KIMS Hospital attached to Karnataka Institute of Medical Sciences, Hubli, were selected randomly for enrollment into the study after consideration of inclusion and exclusion criteria. A detailed history was taken, clinical examination and investigations performed as per proforma in all cases. Ethical clearance for the study was obtained from Ethical committee of KIMS, Hubli.

STUDY SUBJECTS: A total of 100 patients diagnosed to have Type 2 Diabetes Mellitus with preserved systolic function (EF > 58%) were studied from November 2007 to October 2008. Total of 100 patients were enrolled in the study to obtain the diastolic parameters. Investigations were done in the clinical biochemistry laboratory of KIMS Hospital, Hubli. Echo-cardiographic studies were performed by a qualified cardiologist.

INCLUSION CRITERIA:

1. All patients with Type 2 Diabetes Mellitus between age group of 35-60 years.
2. BP<130/85mm Hg in sitting posture on \geq 2 separate occasions.
3. Asymptomatic, without prior history or symptoms suggestive of hypertension.
4. Coronary artery disease, valvular heart disease or congestive cardiac failure.

EXCLUSION CRITERIA:

1. Newly detected Type 2 Diabetes Mellitus i.e. less than 1 year duration.
2. Any kind of acute complication of diabetes.
3. Patients on antihypertensive medication.
4. Past history of myocardial infarction, unstable angina.
5. Patients with rheumatic heart disease.
6. Evidence of renal dysfunction.

METHODOLOGY: A detailed clinical history of subjects was taken. Each subject underwent a detailed physical examination and systemic examination. A standard 12 lead ECG was recorded in all subjects to look for any abnormalities. Routine hematological and biochemical investigations including, hemoglobin concentration, blood sugars, blood urea and serum creatinine, lipid profile and urine routine were done. Chest X-ray was done to rule out any abnormality. An optic fundus examination was done to rule out diabetic retinopathy.

ECHOCARDIOGRAPHY: A qualified cardiologist performed the transthoracic echocardiographic examination on all subjects, with the subjects in the left lateral position. Two-dimensional and M-mode Echocardiography was performed on Philips Envisor C HD using 4 MHz transducer. Blood pressure and heart rate were measured at the time of echocardiography.

Ejection fraction was calculated by measuring the internal diameter of left ventricle (LV) at the end diastole (LVIDd) and at the end systole (LVIDs) using the Penn convention method. Two dimensional and two-dimensional guided M-mode echocardiograms and pulse wave doppler transmitral flow velocity curves were obtained to study LV inflow pattern. The transmitral flow velocity curves were recorded at the mitral tips, at the cardiac apex. Combined study of Doppler echocardiography and phonocardiography were used to measure IVRT. The average values of all echocardiographic parameters of at least 3 consecutive beats were used for the analysis. Doppler velocity curves were recorded at a horizontal sweep speed of 100mm/s.

Left ventricular diastolic dysfunction was assessed by reversed E/A ratio (transmitral flow velocity curve). Normal E/A ratio was defined as E/A ratio ≥ 1 . Abnormal E/A ratio was defined as E/A ratio < 1 . E/A ratio ≥ 1 was taken as having normal diastolic function and E/A ratio < 1 taken as having diastolic dysfunction.

UNMASKING OF PSEUDO NORMAL PATTERN: All patients with normal E/A ratio i.e. ≥ 1 were subjected to valsalva maneuver and the evaluation was repeated. This helped in unmasking of Pseudo normal pattern of left ventricular filling.

Following Doppler echocardiography indices of left ventricular function were measured:

DOPPLER STUDY:

1. Peak velocity of early mitral flow – E velocity cm/sec.
2. Peak velocity of late mitral flow – A – velocity cm/sec
3. E/A ratio
4. Deceleration Time (DT in m sec)
5. M – Mode Left Ventricular Study

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$$\begin{aligned} & \text{LVIDs (mm)} \\ & \text{LVIDd(mm)} \\ & \text{Ejection Fraction} = \frac{(\text{LVIDd}^3 - \text{LVIDs}^3) \times 100}{\text{LVIDd}^3} \end{aligned}$$

STATISTICAL METHODS:

1. For different qualitative parameters mean and standard deviation were calculated.
2. To compare the means between two groups, student unpaired 't' test was used. Level of significance was taken as $P = <0.05$
3. Chi-square Test is used to find the association between two qualitative variables.
4. The test of proportions for two samples was applied to compare the percentages in the two groups.

STATISTICAL SOFTWARE: The statistical software namely MICROSOFT EXCEL 2007, MEDCALC and GENSTAT version 9.0 were used for the analysis of data and Microsoft Word and Excel have been used to generate graphs, tables etc.

RESULTS: A total of 100 patients with Type 2 Diabetes were included in the study.

Table 1 shows the number of males was 49 and of that of females was 51. Most cases (41%) were between 56-60 years of age.

Table 2 shows the mean age of subjects was 49.7 ± 3.0 yrs. among normal group and 54.59 ± 2.4 yrs. in DD group. This was not statistically significant. The mean duration of diabetes was 4.04 ± 1.2 yrs. among normal group and 10.20 ± 3.2 yrs. in DD group. This was highly significant. The mean body mass index of subjects was 25.02 ± 4.2 among normal group and 28.02 ± 3.8 in DD group was not statistically significant. The mean fasting blood sugar of subjects was 129.9 ± 12.0 mg/dl among normal group and 138.64 ± 11.2 mg/dl in DD group was not statistically significant. The mean total cholesterol of subjects was 173.4 ± 8.6 mg/dl among normal group and 192.8 ± 12.6 mg/dl in DD group was not statistically significant.

Table 3 shows there were 29 male and 25 females in the DD group. In normal group males constituted 20 and females 26 respectively. Sex is not significantly associated with DD.

Table 4 shows the age group of study subjects ranged between 36 to 60 years. The prevalence of diastolic dysfunction was minimum in younger age group patients and maximum among older age group patients. High statistical significance was found between age and incidence of diastolic dysfunction signifying that age is important contributor.

CORRELATION WITH DURATION OF DIABETES: Table 5 shows among 41 patients with 1 – 5yrs duration of diabetes, 34 had normal filling pattern, whereas among 28 patients with >10yrs duration of diabetes all patients had diastolic dysfunction. This was a statistically significant finding ($p < 0.001$). This shows that diastolic dysfunction correlates positively with duration of diabetes.

ASSESSMENT OF DIASTOLIC DYSFUNCTION IN CASES: A total of 100 patients with Type 2 Diabetes were evaluated for diastolic function of LV by Doppler echocardiography. E/A ratio ≥ 1 , was taken as

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normal diastolic function. E/A ratio <1, was taken as diastolic dysfunction (Impaired relaxation). In patients with E/A ratio ≥ 1 i.e. normal diastolic function, valsalva maneuver was done and study parameters were repeated. Reversal of E/A ratio after valsalva maneuver was taken as pseudo normal filling pattern and was considered under diastolic dysfunction.

Table 6 shows among 100 subjects studied 46 patients had normal diastolic function, 43 patients had impaired relaxation (i.e. E/A ratio < 1) 11 patients has Pseudo normal filling pattern. Totally 54 patients had diastolic dysfunction.

Table 7 shows E velocity (cm/sec) was decreased in DD group compared to normal (63 ± 12 mm/sec Vs. 69 ± 13 mm/sec). P value was highly significant $P < 0.001$.

- A velocity (cm/sec) was increased in DD group compared to normal group (73 ± 14 mm/sec Vs. 51 ± 12 mm/sec) Data was highly significant $P < 0.001$.
- E/A Ratio – was reduced in DD group compared to normal group (0.81 ± 0.06 mm/sec Vs. 1.36 ± 0.12 mm/sec) Data was highly significant.
- Deceleration time (DT) was increased in DD group as compared to normal group (232 ± 12 msec Vs. 186 ± 10). This was statistically significant $P < 0.001$.
- Ejection fraction was lesser in DD group compared to normal group (59 ± 4 Vs. 62 ± 4) Data was not statistically significant.
- Analysis of Data shows that diastolic filling abnormalities are common in patients with impaired relaxation, than in patients with normal relaxation.

DISCUSSION: Diabetes affects various organs like heart central nervous system, retina, kidneys and blood vessels. Diabetes Mellitus is associated with a multitude of cardio vascular complications like increased incidence of atherosclerotic coronary artery disease, myocardial infarction, congestive heart failure, coronary microangiopathy and systemic arterial hypertension. In, addition, structural myocardial involvement termed as diabetic cardiomyopathy may be there.^{11, 12}

Several lines of evidence indicate that left ventricular diastolic dysfunction represents the earliest pre-clinical manifestation of diabetic cardiomyopathy that can progress to symptomatic heart failure.¹³ The aim of our study was to assess the diastolic function in Type 2 diabetic patients with preserved left ventricular systolic function by Doppler echocardiography, particularly focusing on the transmitral flow velocity curves to detect diastolic dysfunction. An attempt was also made to unmask the pseudo normal filling pattern. This prospective study was done on a relatively homogenous and ambulatory diabetic population.

Subjects in our study underwent echocardiographic examination where diastolic function was assessed by transmitral flow velocity curves and E/A ratio (ratio of mitral early diastolic filling wave (E) velocity to mitral atrial contraction wave (A) velocity). E/A ratio ≥ 1 was taken as having normal diastolic function and E/A ratio <1 was taken as having diastolic dysfunction. In addition, reversal of E/A ratio to <1 after valsalva maneuver was taken as pseudo normal filling pattern which is a part of diastolic dysfunction.

LEGENDS TO TABLES: Number of subjects in the study, it was 100 which was comparable with Zabalgoitia et al¹⁵ (n=86). The other two studies had relatively smaller sample size.

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The mean age of patients was 52.34 ± 8.6 yrs. This was comparable with Poirier et al¹⁴, Zabalgoitia et al¹⁵ and Khan et al¹⁶ whose mean age was 56 ± 7 yrs., 49 ± 7 yrs. and 47.54 ± 6.78 yrs. respectively. (Table 1)

The mean body mass index of patients was 26.6 ± 4.2 . This was comparable with Poirier et al¹⁴, Zabalgoitia et al¹⁵ and Khan et al¹⁶ whose mean body mass index was 29.9 ± 4.7 , 30 ± 2 and 24.62 ± 3.68 respectively.

The mean duration of diabetes of patients was 7.37yrs. This was comparable with Poirier et al¹⁴, Zabalgoitia et al¹⁵ and Khan et al¹⁶ whose mean duration was 6.5 yrs., 6.5 yrs. and 6.3 yrs. respectively. (Table 3).

The mean ejection fraction of patients was $64 \pm 2.6\%$. This was comparable with Poirier et al¹⁴, Zabalgoitia et al¹⁵ and Khan et al¹⁶ whose mean ejection fraction was $66 \pm 5\%$, $65 \pm 5\%$ and $68.75 \pm 6.42\%$ respectively.

The mean E wave velocity in our study was 63 ± 12 mm/sec which was comparable with Khan et al¹⁶ (67 ± 16 mm/sec).

The mean A wave velocity In our study was 73 ± 14 mm/sec which was comparable with Poirier et al¹⁴ and Zabalgoitia et al¹⁵ where A wave velocity was 71 ± 13 mm/sec and 72 ± 10 mm/sec respectively.

The mean E/A ratio in our study was 0.81 ± 0.06 which was comparable with Poirier et al¹⁴ and Khan et al¹⁶ where E/A ratios were 0.79 ± 0.07 and 0.76 ± 0.12 respectively. (Table 5).

Our study was conducted on 100 normotensive Type 2 diabetic patients out of whom 54% had diastolic dysfunction. Among these 43% had impaired relaxation and 11 % had pseudonormal filling. These results were comparable with Poirier et al¹⁴ where study of 46 patients revealed a total diastolic dysfunction of 60% of which 32% were impaired relaxation and 28% were pseudonormal pattern. Khan et al¹⁶ study showed a diastolic dysfunction of 60 % where 36% were impaired relaxation and 24% were pseudonormal filling pattern. (Table 7)

CONCLUSION: Diastolic dysfunction was observed in 54% among 100 subjects out of these 43% had impaired relaxation and 11 % had pseudo normal filling.

By using Valsalva maneuver, pseudo normal pattern of diastolic dysfunction can be detected. Recognition of pseudo normal filling is more important because it is an intermediate stage between impaired relaxation and restrictive filling thus more advanced stage of left ventricular diastolic dysfunction. Diastolic dysfunction was well correlated with duration of diabetes.

Diastolic dysfunction is earliest manifestation of diabetic cardiomyopathy. Hence, detecting and treating it in early stage would prevent disease progression to symptomatic heart failure.

The Mitral E: A ratio has equal or even superior prognostic value compared with left ventricular systolic indices (EF) thereby reinforcing importance of screening for asymptomatic left ventricular diastolic dysfunction.

STUDY LIMITATIONS: Our study group consisted of small homogenous group of diabetics. Hence the prevalence of LV diastolic dysfunction obtained in the current study may not be identical when applied to a larger or different population of diabetes, and a study with larger population may be required. Although electrocardiogram and 2D Echocardiography was done to exclude IHD, definite

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means would be cardiac catheterization to exclude coronary artery disease. Sub clinical CAD might have influenced the results. This study included patients who were on medication. Diastolic function may be affected by medications. This may affect the prevalence of diastolic dysfunction in the current study subjects. The medications were continued by the patients in our study for ethical reasons.

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Parameters	Normal	DD	P value	Significant
Age (years)	49.7 ± 3.0	54.59 ± 2.4	0.549	NS
Duration of diabetes (years)	4.04 ± 1.2	10.20 ± 3.2	0.001	HS
Body Mass Index	25.02 ± 4.2	28.02 ± 3.8	0.343	NS
Fasting Blood Sugar (mg/dl)	129.9 ± 12.0	138.64 ± 11.2	0.364	NS
Total Cholesterol (mg/dl)	173.4 ± 8.6	192.8 ± 12.6	0.464	NS

TABLE 1: BASE LINE CHARACTERISTICS OF STUDY SUBJECTS

Sex	Normal	DD	X ² value	significant
Male	20 (43.5%)	29 (53.70%)	0.946	P = 0.36 Not significant
Female	26 (56.52%)	25 (46.29%)		

TABLE 2: SEX DISTRIBUTIONS OF CASES

Duration of Diabetes	Normal n = 46	DD n = 54
1 - 5 yrs.	34 (73.91%)	7 (12.96%)
5 - 10 yrs.	12 (26.08%)	19 (35.18%)
> 10 yrs.	0 (0%)	28 (51.85%)

TABLE 3 : RELATIONSHIP BETWEEN DURATION OF DIABETES AND DIASTOLIC FUNCTION

Diastolic function	Number n = 100	%
Normal	46	46.0
Impaired relaxation	43	43.0
Pseudo normal filling	11	11.0

TABLE 4: DIASTOLIC FUNCTION IN CASES

Parameters	Normal N = 46	Impaired (DD) Relaxation N = 43	P value	Significant
E wave (mm/s)	69 ± 13	63 ± 12	P < 0.001	HS
A wave (mm/s)	51 ± 12	73 ± 14	P < 0.001	HS
E/A ratio	1.36 ± 0.12	0.81 ± 0.06	P < 0.001	HS
Deceleration Time (ms)	186 ± 10	232 ± 12	P < 0.001	HS
Ejection Fraction (%)	62 ± 4	59 ± 4	P < 0.005	NS

Table 5: Doppler Echocardiographic Characteristics of Study Subjects

Study	Poirier et al ¹⁴	Zabalgaitia et al ¹⁵	Khan et al ¹⁶	Present Study
Sample size (n)	46	86	50	100
Age (yrs.)	56 ± 7	49 ± 7	47.54 ± 6.78	52.34 ± 8.6
Body mass index	29.9 ± 4.7	30 ± 2	24.62 ± 3.68	26.6 ± 4.2
Diabetes duration(yrs.)	6.5	6.5	6.3	7.37
Ejection fraction (%)	66 ± 5	65 ± 5	68.75 ± 6.42	64 ± 2.6
E wave(mm/sec)	56 ± 10	52 ± 10	67 ± 16	63 ± 12
A wave (mm/sec)	71 ± 13	72 ± 10	92 ± 14	73 ± 14
E/A Ratio	0.79 ± 0.07	0.7 ± 0.1	0.76 ± 0.12	0.81 ± 0.06

Table 6: Comparison of Variables

Study	N	Normal Study	Impaired relaxation	Pseudonormal filling	Total DD
Present Study	100	46 %	43 %	11 %	54 %
Poirier et al ¹⁴	46	40 %	32 %	28 %	60 %
Zabalgaitia et al ¹⁵	86	53 %	30 %	17 %	47 %
Khan et al ¹⁶	50	46 %	36 %	24 %	60 %

Table 7: Results

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