# Left ventricular mechanical dyssynchrony assessment in long-standing type II diabetes mellitus patients with normal gated SPECT-MPI

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***Background.*** **Assessment of left ventricular mechanical dyssynchrony (LVMD) using phase analysis of gated SPECT-MPI is well established. However, there is little information about the influence of diabetes mellitus on phase analysis. The present work was to evaluate the LVMD in longstanding type II diabetes mellitus (DM) patients with normal gated SPECT-MPI.**

***Methods.*** **Retrospective analysis of 146 (86 type II diabetics for > 5 years' duration and 60 nondiabetics) consecutive patients with normal gated SPECT-MPI and adequate LVEF was done. Sixty age- and sex-matched nondiabetic served as control. LVMD was determined from the cutoff values (> mean + 2 SD) observed for phase standard deviation (PSD) and phase bandwidth (PBW) from the control subjects. Multivariate logistic regression analysis was applied to assess the correlation between various confounding factors.**

***Results.*** **LVMD was detected in 24 (28%) diabetic patients with the pre-defined cut-off values for PSD (> 10.8) and PBW (> 35.6) derived from the controls. Hyperlipidemia, overweight/obesity, duration of DM and its long-term complications were independently associated with LVMD, with long-term complications being the highest risk factor (OR 28.00; $P < .001$).**

***Conclusion.*** **The evolution time of the patients with type II diabetes mellitus affects the left ventricular mechanical synchrony. (J Nucl Cardiol 2019;26:1650–8.)**

**Key Words: Diabetes mellitus • left ventricular mechanical dyssynchrony • phase analysis • SPECT-MPI • phase standard deviation • phase bandwidth**

**Abbreviations**

| | |
|---|---|
| LVMD | Left ventricular mechanical dyssynchrony |
| DM | Diabetes mellitus |
| PSD | Phase standard deviation |
| PBW | Phase bandwidth |
| DCM | Diabetic cardiomyopathy |
| TDI | Tissue Doppler imaging |
| LVEF | Left ventricle ejection fraction |
| SPECT-MPI | Single-photon emission computed tomography myocardial perfusion imaging |
| CRT | Cardiac resynchronization therapy |
| LVD | Left ventricular dyssynchrony |

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com

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## INTRODUCTION

Diabetic cardiomyopathy (DCM) first described by Rubler et al. refers to a variety of pathophysiological processes involving the myocardium in patients with diabetes mellitus (DM).[1] Several underlying mechanisms comprising of oxidative stress, changed mitochondrial function, impaired calcium handling, remodeling of the extracellular matrix, and consequently deficient myocardial contractility have been implicated in the pathogenesis of DCM.[2] Though, the exact etiopathogenesis of diabetic cardiomyopathy still remains unclear. Approximately 12% of diabetic patients may be affected with DCM and its prevalence increases up to 22% in patients of more than 64 years.[3] DCM encompasses the preclinical left ventricular diastolic dysfunction, followed by apparent systolic dysfunction and finally symptomatic cardiac failure in the absence of coronary artery disease, significant valvular heart disease, or hypertension.[4,5] The asymptomatic left ventricle (LV) diastolic dysfunction is considered the earliest sign of DCM though exact sequence of events is not clearly defined.[6] However, Korosoglou et al. described the prevalence of left ventricular mechanical dyssynchrony (LVMD) in diabetes mellitus patients even in the absence of LV diastolic dysfunction and concluded that LVMD might represent the very early phase of DCM in asymptomatic diabetic patients.[7] Heart failure patients with LVMD have greater likelihood for cardiac events without the influence of QRS width and LVEF, as LVMD has been recognised an independent factor for cardiac events.[8,9]

The presence of cardiovascular risk factors such as end stage renal disease (ESRD), hypertension and diabetes mellitus could potentially affect the phase analysis values. Gated SPECT-MPI is one of the non-invasive imaging methods to provide fully automated and reproducible phase analysis.[10] Aljaroudi et al., using gated SPECT-MPI in ESRD patients either with LVEF $\geq$ 50% or LVEF $<$ 50%, observed significantly higher phase analysis values compared to the control group even in the absence of bundle branch block, perfusion defect or cardiomypathy.[11] Diabetes is one the most important factors with potential to affect the phase analysis values [12], though the inference is not yet entirely explored and no such study has been conducted in diabetes group. This study was aimed to detect the LVMD and its correlation with various confounding factors in the patients with long-standing type II DM having normal perfusion on gated SPECT-MPI and adequate left ventricular ejection fraction (LVEF $>$ 55%).

## METHODS

A total of 86 consecutive patients with type II DM for more than 5 years' duration having normal gated SPECT-MPI were included in the study. Sixty age- and sex-matched consecutive nondiabetic subjects were involved in the control group for evaluation of normal phase parameters. This case–control retrospective, observational study was conducted at Nuclear Cardiology, Advanced Cardiac Centre, PGIMER, Chandigarh. The study was designed to determine the presence of LVMD in type II DM patients with normal gated SPECT-MPI and its relation to the age of the patients, duration of type II DM and long-term complications arising from diabetes mellitus. Patients with previous history of cardiac disease, coronary intervention, arrhythmia on gating, perfusion defect (s) and wall motion abnormality in gated stress SPECT-MPI were not included in the study. The study was duly accepted by the Institute Ethics Committee vide letter no. INT/IEC/2017/1363.

### Gated SPECT-MPI Acquisition

All patients underwent $^{99m}$Tc-MIBI one-day stress-first or stress-only gated SPECT-MPI protocol according to American Society of Nuclear Cardiology (ASNC) guidelines as followed in our department.[13] Gated SPECT-MPI post-stress acquisition after period of 30 to 45 minutes was performed on a dual- head camera system (Philips Bright view XCT, Philips Medical Systems, Milpitas, CA, USA) in the supine position.

### Image Processing

SPECT-MPI non-gated projection images in cine mode were reviewed in all the patients to assess their movement during acquisition, sources of potential attenuation artifacts and hepatic/gastric activity. The raw images (both non-gated and gated datasets) were reconstructed using manufacturer provided Astonish (iterative reconstruction and resolution recovery) software (AutoSPECTPlus$^{TM}$, Philips Medical Systems) by an experienced technologist, who was blinded to this research query.

### Phase Analysis Assessment

Phase analysis was performed on post-stress acquired data with Emory Cardiac Toolbox-SyncTool (ECTb-SyncTool version 3.2; Emory University/Syntermed, Atlanta, Georgia, USA) separately by two experienced nuclear physicians in blind manner. ECTb-SyncTool used structurally based 3-dimensional model for left ventricular edge detection, assuming 1 cm LV myocardium thickness at the end-diastole. Fourier harmonic functions were used to approximate the regional wall thickness changes over the cardiac cycle and the regional onset-of-mechanical contraction phase was calculated. The left ventricle normally contracts in a coordinated manner to have the almost same phase in most of the myocardial segments. Therefore, the normal phase image has a

nearly uniform distribution with narrow and highly peaked normal phase. The following phase analysis parameters were recorded: phase standard deviation (PSD, unit: degree), peak phase, 95% width of phase bandwidth (PBW, unit: degree). The 95% width includes practically full phase bandwidth with the exclusion of likely outlier values. For outcome analysis, only PSD and PBW have been used as quantitative indices of the LVMD. Values more than mean + 2SD of cut off values for PSD and PBW derived from the control group were considered for the presence of LVMD in type II DM patients.

## Statistical Analysis

Statistical Package for the Social Sciences software (SPSS Version 22.0; IBM Corp, Amonk, NY) was used for performing the statistical analysis. Continuous variables were expressed as mean ± SD, whereas categorical variables were expressed as percentage and frequencies. Following demographic and clinical analyses, an association of age, gender and DM duration, confounding factors for CAD in diabetic patients, with LVMD as defined by increasing PSD and PBW were studied using simple linear regression models. PSD as a measure of LVMD was treated as a continuous variable. Statistical significance was set at a level of $< .05$.

# RESULT

This case–control study included 86 type II DM patients with mean age of 61.3 ± 11.5 years (43 females), and the control group included 60 age- and sex-matched nondiabetic individuals with mean age of 56 ± 11.8 years (30 female). Patients with type II DM and control subjects had similar ages, height, weight and body mass index without any statistically significant difference between them ($P > .05$). Prevalence of risk factors for CAD like hypertension, obesity and dyslipidemia was higher in type II DM patients compared to controls (Table 1). Mean duration of diabetes in patients was 12.9 ± 7.1 years and they were on regular medications. The prevalence of dyslipidemia and long-term complications of DM were found to be significantly higher ($P < .05$) in diabetic patients with LVMD (group B) compared to diabetic patients without LVMD (group A). Mean duration of DM was also higher in group B compared to group A (16.3 ± 7.9 years vs 11.7 ± 6.4 years; $P < .05$). Long-term type II DM complications (nephropathy, neuropathy and/or retinopathy) were present in total 24 diabetic patients and 18 of these patients had LVMD. However, none of the patients were suffering from the end-stage renal disease.

Phase analysis result: The phase distribution in controls and diabetic group of patients with normal gated SPECT-MPI is shown in Figure 1. No statistically significant difference was observed among the PSD and PBW of control and diabetic patients ($P > .05$).

Based on the parameters derived from control group, value of more than mean + 2SD was used as a cutoff point for the diagnosis of the LVMD. The PSD and PBW parameter values obtained were 6.8 ± 2.0 and 22.8 ± 6.3 in the control group and 10.7 ± 6.9 and 34.2 ± 17.2 in type II DM patients. respectively. With these pre-defined cut off values of PSD (> 10.8) and PBW (> 35.6), LVMD was detected in 24 (28%) type II DM patients. Two patients in diabetic group and one patient in control group with history of hypertension had moderate left ventricular hypertrophy, though only one diabetic patient revealed LVMD. The representative dataset of a diabetic patient with normal gated SPECT-MPI and significant LVMD is shown in Figure 2.

Left ventricle ejection fraction (LVEF) and LV volumes were also calculated in these groups (Table 2). LVEF was higher in the control group compared to the diabetic patients without LVMD which in turn was higher than diabetic patients with LVMD, though none of the patients had LVEF less than 55%. The volumes, i.e. end diastolic volume (EDV), end systolic volume (ESV) and gated LV mass, however, revealed the reverse order. There was a tendency of larger volumes and gated LV mass in type II DM patients with LVMD than the type II DM alone followed by the control group. EDVs were in range of 20 to 82 ml in control group vs 14 to 145 ml for both diabetic patients and diabetic patients with LVMD, respectively. ESV ranged from 1 to 34, 1 to 60 and 3 to 58 ml for controls, diabetic patients and diabetic patients with LVMD, respectively. However, no significant differences were observed for quantitative parameters (LVEF, EDV, ESV and LV mass) among these groups ($P > .05$).

The relationship between PSD with LVEF and LV volumes was also examined. Taking PSD, a significant negative correlation with LVEF was observed in both control ($r = -0.35$, $P$ .006) and diabetic group ($r = -0.47$, $P < .001$). When PSD was plotted vs end-diastolic and end-systolic volumes, positive correlations were obtained with correlation coefficients ranging from 0.43 to 0.52 ($P < .05$) (Figure 3).

Univariate logistic regression analysis of type II DM patients revealed that presence of obesity, smoking, dyslipidemia and long-term diabetic complications were associated with LVMD. The odds ratio (OR), 95% confidence interval (CI) and $P$ value for each of these variables are given in Table 3. Hypertension, alcoholism and duration of diabetes were also independently associated with LVMD. Two variables, i.e. duration (OR 1.09; 95% CI 1.02-1.17; $P$ .01) and long-term complications (OR 28.00; 95% CI 8.02-97.73; $P < .001$) of DM were found to be significant by the univariate analysis. The most important variable in the identification of LVMD was long-term complications of DM (OR

**Table 1.** Baseline & clinical characteristics of patients

| Clinical data | Controls ($n$ = 60) | Type II DM patient without LVMD ($n$ = 62) (group A) | Type II DM patient with LVMD ($n$ = 24) (group B) | $P$ value between group A and B |
|---|---|---|---|---|
| Age (years) | 56 ± 11.8 | 62.7 ± 10.6 | 57.9 ± 13.0 | .49 |
| Male/female | 30/30 | 29/33 | 14/10 | .78 |
| Height (cm) | 160.9 ± 9.4 | 161.7 ± 8.2 | 164.4 ± 9.6 | .88 |
| Weight (Kg) | 62.6 ± 13.2 | 68.8 ± 14.5 | 70.8 ± 18 | .79 |
| Body Mass Index ($Kg/m^2$) | 24.2 ± 5.2 | 26.2 ± 4.7 | 26.08 ± 5.0 | .98 |
| Hypertension, $n$ (%) | 35 (58) | 49 (79) | 20 (83) | .43 |
| Obesity, $n$ (%) | 21 (24) | 34 (55) | 10 (41) | .74 |
| Smoking, $n$ (%) | 12 (20) | 10 (16) | 8 (33) | .13 |
| Alcohol, $n$ (%) | 14 (23) | 09 (15) | 6 (25) | .31 |
| Dyslipidaemia, $n$ (%) | 11 (18) | 21 (34) | 13 (54) | .04 |
| DM duration (years) | - | 11.7 ± 6.4 | 16.3 ± 7.9 | .014 |
| Long-term complications, $n$ (%) | - | 06 (10) | 18 (75) | < .001 |
| Type of stress performed, $n$ (%) | | | | |
| Treadmill test | 29 (49) | 19 (30) | 1 (4) | |
| Adenosine | 28 (46) | 38 (61) | 20 (83) | |
| Dobutamine | 3 (5) | 5 (8) | 3 (13) | |

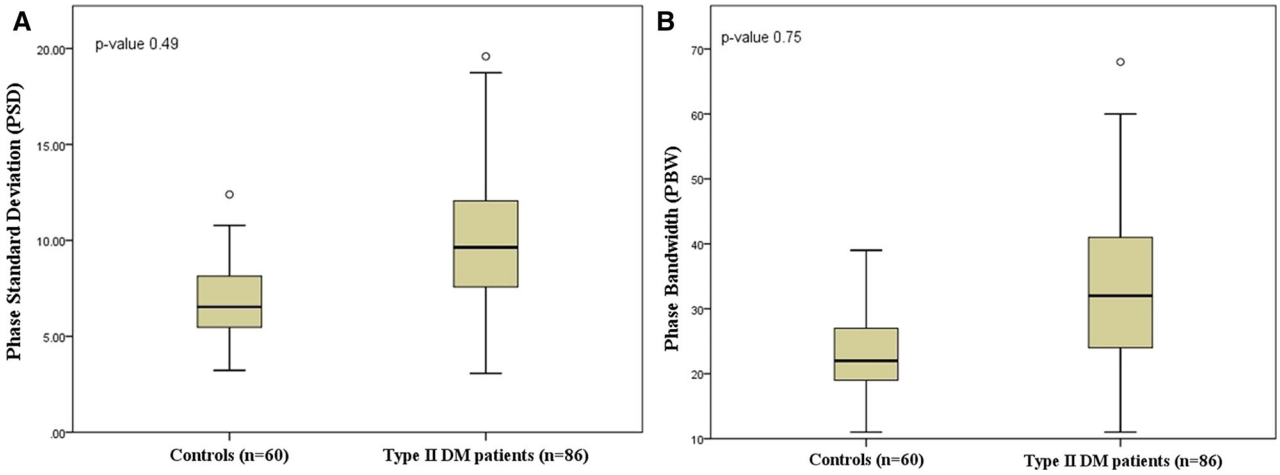


**Figure 1.** The box-and-whisker plots of PSD (**A**), and PBW (**B**), in controls and type II DM patients with no perfusion abnormalities and adequate left ventricular ejection fraction (LVEF > 55%) on gated SPECT-MPI. More extreme values are plotted individually.

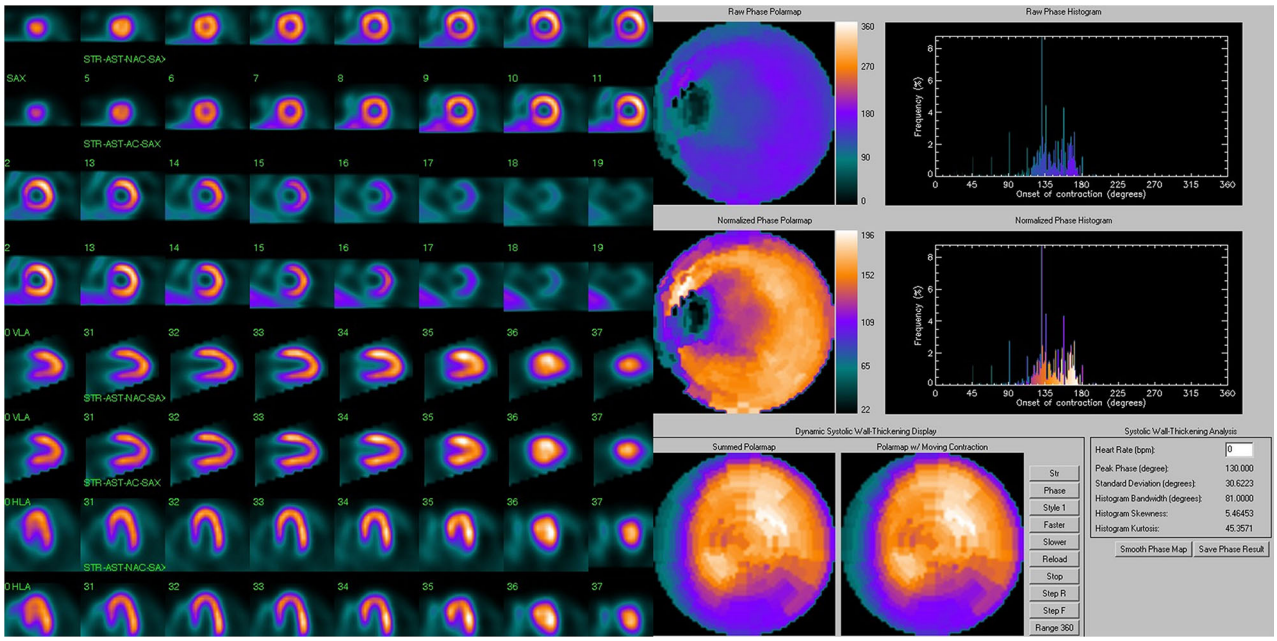


**Figure 2.** The dataset of diabetic patient number 20. Cross-sectional images (**a**) reveal no perfusion defect with SSS of < 4 and LVEF of > 60%. Phase analysis done with ECTb-SyncTool reveals significant LVMD (PSD 30.6° & PBW 81°).

100.05; 95% CI 10.89-918; $P < .001$), followed by duration of DM (OR 2.19; 95% CI 1.56-3.24; $P$ .007), which remained statistically significant in multivariate analysis also.

An overall fit model based on clinical variables, including age, gender and hypertension ($\chi^2 = 4.34$) was developed for sequential logistic regression analysis, which was improved by the addition of duration of DM ($\chi^2 = 11.52$, $P$ value .02) and further enhanced by the addition of long-term complications ($\chi^2 = 39.43$, $P < .001$) as variables. Figure 4 shows incremental value of duration of DM and long-term complications in detection of LVMD.

**Table 2.** Left ventricular ejection fraction and volumes, and gated LV mass values in different patients group

| | Controls ($n$ = 60) | Type II DM patient without LVMD ($n$ = 62) (group A) | Type II DM patient with LVMD ($n$ = 24) (group B) |
|---|---|---|---|
| End diastolic volume (EDV; ml) | 43.0 ± 14.8 | 47.8 ± 21.2 | 71.3 ± 35.5 |
| End systolic volume (ESV; ml) | 10.2 ± 8.3 | 13.2 ± 12.2 | 27.0 ± 17.6 |
| Left ventricular ejection fraction (LVEF; %) | 79.3 ± 11.5 | 76.3 ± 12.7 | 64.9 ± 10.2 |
| Gated left ventricle mass (gm) | 89.2 ± 18.7 | 95.0 ± 29.2 | 120.9 ± 37.1 |

A point-biserial correlation test revealed a statistically significant positive correlation between the duration and long-term complications of DM (rpb = 0.379, $n = 86$, $P < .001$). However, no significant correlation was observed between phase parameters (PSD & PBW) and duration of DM in both groups (i.e. diabetes patients with and without long-term complications).

## DISCUSSION

This study is perhaps the first attempt showing LVMD in type II DM patients with no perfusion defects on gated SPECT-MPI. Hypertension, alcoholism and history of smoking were associated with increased incidence of LVMD in the present study and it identified that 28% asymptomatic type II DM patients had the presence of LVMD despite having preserved LVEF, normal QRS duration and in absence of any perfusion defect. Duration of diabetes mellitus and presence of long- term complications (i.e., nephropathy, neuropathy and/or retinopathy) of diabetes mellitus were two most important significantly associated confounding factors for LVMD. There was an inclination of higher incidence of LVMD with increase in duration of diabetes mellitus and in presence of long-term complications.

Phase analysis derived by gated SPECT-MPI provides a new tool to rapidly assess LVMD without any additional study/radiation dose to the patients. LVMD may occur because of temporal delays in electrical activation resulting in a wide QRS (electrical dyssynchrony) or contractile disparities due to abnormal myocardial loading (mechanical dyssynchrony). LV regional contractility discrepancies are regarded as the major mechanism responsible for LVMD in diabetic patients.[14,15] Mechanical dyssynchrony can be present in the absence of electrical dyssynchrony as observed in the present study. Literature has shown that LVMD is an independent predictor of cardiac complications in patients with advanced coronary artery disease.[16,17] The current definition of LVMD is solely based on the QRS width (i.e. > 120 ms) appears to be imperfect, as the present study has also shown that 28% of diabetic patients had LVMD in spite of having normal QRS interval. Phase analysis helps in identifying this subset of patients, who might be the potential candidates for cardiac resynchronization therapy (CRT). Studies have shown that assessment of mechanical LVD rather than QRS duration might be the better predictor of response to CRT.[18,19]

Quantitative dyssynchrony parameters can be obtained by echocardiographic strain rate imaging and TDI, but their normal findings cannot exclude DCM at rest. TDI may detect earliest left ventricular diastolic dysfunction at stress only. Higher values of the myocardial performance index in patients with diabetic cardiomyopathy compared to controls have been shown to be the earliest echocardiographic indication in DCM,[20] but these methods are highly operator-dependent and time-intensive. Cardiac MRI can assess left ventricular dysfunction by highlighting the myocardial fibrosis as well as increased FFA oxidation in the course of DCM. Certain biomarkers for cardiovascular risks in diabetics have also been evaluated. However, they are still not established for their diagnostic value due to lack of strong evidence [21,22] Whereas, gated SPECT-MPI offers numerous potential advantages like the averaged acquisition over several minutes, minimizing the impact of respiratory or cardiac beat variability, automated analysis, provides superior reliability and repeatability in addition to the myocardial perfusion status in the same sitting.[23] The phase analysis derived from gated SPECT-MPI is now widely used for assessment of LVMD in predicting the response to CRT.[24]

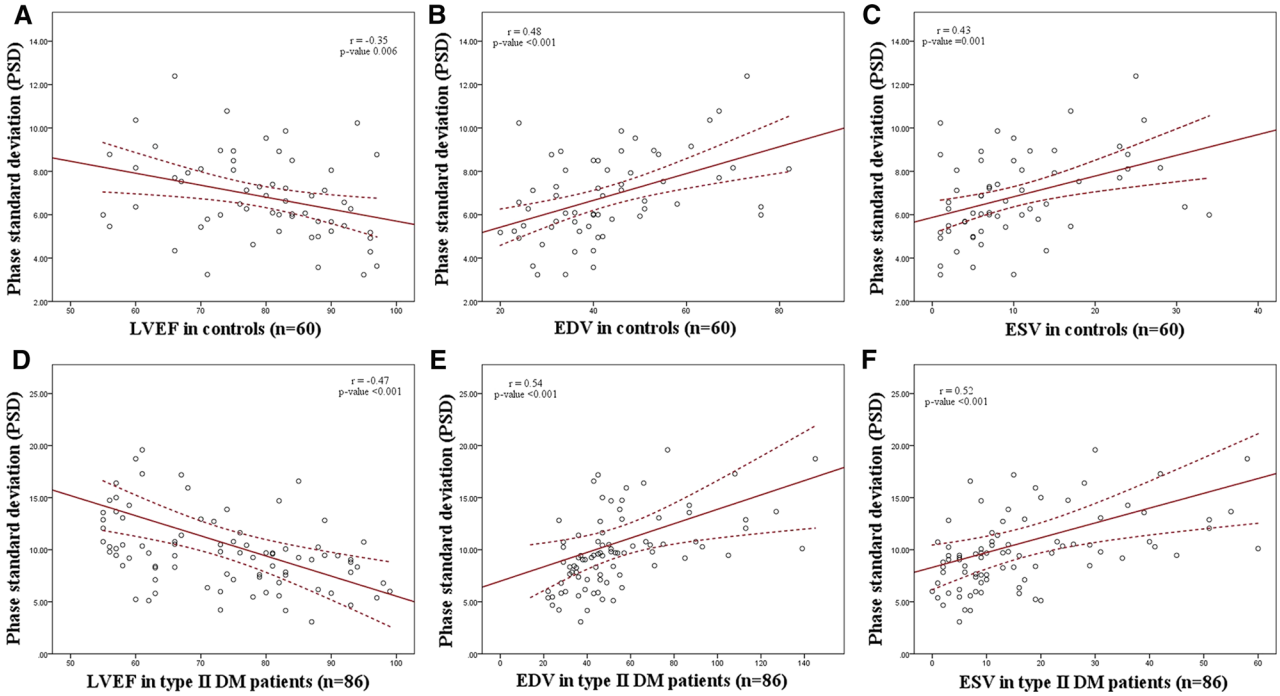


**Figure 3.** Scatter plot diagrams showing the relationships between PSD with left ventricle ejection fraction (LVEF) and volumes (end-diastolic & end-systolic), respectively, in controls (**A**–**C**) and diabetic patients (**D**–**F**). The red line represents the regression line and red dotted lines indicate 95% confidence limits.

**Table 3.** Univariate and multivariate logistic regression analysis for detecting LVMD in type II DM patients

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***P* value** | **OR** | **95% CI** | ***P* value** |
| Age | 0.96 | 0.92-1.06 | .09 | 0.97 | 0.91-1.03 | .30 |
| Gender (female) | 1.60 | 0.62-4.13 | .34 | 0.24 | 0.05-1.30 | .24 |
| Obese | 0.59 | 0.23-1.53 | .28 | 0.51 | 0.12-2.18 | .37 |
| Hypertension | 1.33 | 0.39-4.56 | .65 | 0.62 | 0.11-3.69 | .60 |
| Smoke | 2.60 | 0.88-7.70 | .08 | 4.75 | 0.71-31.7 | .11 |
| Alcohol | 1.96 | 0.61-6.28 | .23 | 0.05 | 0.04-1.72 | .82 |
| Dyslipidaemia | 2.31 | 0.88-6.02 | .09 | 1.04 | 0.19-5.76 | .97 |
| DM duration | 1.09 | 1.02-1.17 | .01 | 2.19 | 1.56-3.24 | .007 |
| Long-term complications | 28.00 | 8.02-97.73 | < .001 | 100.05 | 10.89-918 | < .001 |

*LVMD*, left ventricular mechanical dyssynchrony; *DM*, diabetes mellitus; *OR*, odds ratio; *CI*, confidence interval

Several studies done in diabetic patients have identified LV diastolic dysfunction as the initial functional alteration during DCM with preserved LVEF.[25–27] Korosoglou et al. in their study of 24 diabetic patients with LVMD showed that 12 patients had significant diastolic dysfunction and rest of the patients had normal diastolic function; however, both groups showed similar extent of dyssynchrony. In their study, there was significant LVMD in asymptomatic diabetic patients without clinical evidence of heart disease using echocardiographic phase imaging and Doppler imaging. They concluded that asymptomatic diabetic patients without diastolic dysfunction might have a new feature in form of LVMD in very early stage of the DCM.[7] However, it

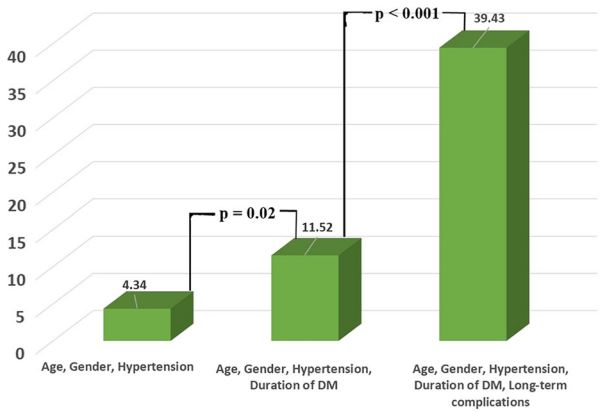


**Figure 4.** Sequential logistic regression model, showing the incremental value of duration of DM ($\chi^2 = 11.52$, $P$ value .02) for the prediction of LVD in type II DM patients, which was further enhanced by the addition of long-term complications ($\chi^2 = 39.43$, $P < .001$).

was difficult to predict which was the earlier to appear and whether both were independent events or not, based on their observations. The present study had a higher number of patients and all patients had EDV and ESV values within the normal range of established literature data.[28] The phase analysis parameters in our patient population were derived from gated SPECT-MPI, which is an automated, reproducible and observer-independent technique. Our study has shown that duration of diabetes and its long-term complications were independent factors associated with LVMD in type II DM patients with normal gated SPECT-MPI and adequate LVEF. Previous investigators have established the interaction of long-term diabetic complications and LV functions in diabetic patients.[29–31] Hypertension, overweight/obesity and dyslipidemia were also recognised as the contributing factors for LVMD in the present study, while other studies reported hypertension, obesity and metabolic syndrome as detrimental factors for LVMD.[32,33] Our findings were in agreement with previously published studies. The pathogenesis of DCM is multifactorial, but the exact cause is still unknown. The presence of LVMD in asymptomatic diabetic patients with preserved LV volumes/function may have an important role in the early pathogenesis of DCM on the basis of findings of the present study. The early diagnosis of DCM helps in preventing the irreversible changes. Duration and long-term complications of diabetes mellitus were most closely associated with LVMD. Diabetic patients may require aggressive management to prevent the heart failure in these patients in spite of no perfusion abnormalities and adequate LVEF. Additionally, gated SPECT-MPI provides a complete array of information including synchrony indices, perfusion analysis and quantitative data on LV function in a fully automated way.

## Study Limitations

This observational case–control study was done in a single centre (tertiary care academic institution) and, therefore, subject to the limitations inherent to such studies. Being a retrospective study, confounding factors for regression analysis were based on previously reported findings.

## NEW KNOWLEDGE GAINED

Assessment of LVMD using phase analysis of gated SPECT-MPI is now well established. Long-standing diabetes mellitus type II may potentially affect the phase analysis in these patients; however, the confounding factors affecting the LVMD are not well studied. The present study showed that around one-third asymptomatic diabetic patients had LVMD despite having normal perfusion and ejection fraction in gated SPECT-MPI. The duration of diabetes and long-term complications were two significant factors associated with LVMD in these patients and may require aggressive clinical management for the prevention of diabetic cardiomyopathy.

## CONCLUSION

The findings of this study suggest that long-standing diabetic patients with normal myocardial perfusion and LVEF may have a higher incidence of LVMD, might be because of that LVMD appears at a very early stage of cardiac dysfunction. The duration of DM and its long-term complications are most closely associated factors with LVMD in diabetic patients. The presence of LVMD might be one of the earliest parameters in the patients with diabetic cardiomyopathy and may require aggressive management for the prevention of diabetic cardiomyopathy.

## Disclosure

*There is no potential conflict of interest to disclose.*

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