

Comparing Left Ventricular Mechanical Dyssynchrony between Diabetic and Non-Diabetic Patients with Normal Gated SPECT MPI

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Abstract

Introduction; the aim of this study was to employ phase analysis to diagnose left ventricular mechanical dyssynchrony (LVMD) in asymptomatic patients with diabetes mellitus type 2 and normal perfusion study to prevent diabetic cardiomyopathy.

Methods & materials; Ninety-three consecutive patients with known type 2 diabetes and 81 age- and gender- matched patients without diabetes who were candidates for SPECT-MPI were considered as the control group. The presence of LVMD as an indicator of cardiomyopathy- was determined using phase analysis for each scan with quantitative gated SPECT (QGS) and corridor4DM (4DM) software. All outcomes such as phase bandwidth (PBW) and phase standard deviation (PSD) were compared between the two groups.

Results; A total of 174 patients were included in the study. There were no statistically significant difference regarding demographic factors between the two groups ($P > 0.05$). PBW showed statistically significant differences (increased in diabetics) between the control and diabetic patients ($P < 0.05$). Kruskal Wallis analysis revealed that as the duration of diabetes is prolonged, especially more than 15 years, the probability of LVMD is increased as well ($p = 0.021$).

Discussion; Fraction of asymptomatic diabetic patients with normal ejection fraction and gated SPECT MPI- especially those with prolonged diabetes- might have some degrees of LVMD. Phase analysis can detect this which in turn would prevent progress into heart failure.

Introduction

Diabetes is the most common human metabolic disease and its incidence is increasing in different societies (1–3). Cardiovascular complications include cardiomyopathies, ischemia, or asymptomatic infarction or finally heart failure. Diabetic cardiomyopathy (DCM) was first described by Rubler et al. indicating a wide range of pathologic changes in the myocardium of diabetic patients (4, 5).

Underlying reasons for diabetic cardiomyopathy include increased oxidative stress, mitochondrial dysfunction, impairment in calcium handling and extracellular matrix remodeling which lead to a defect in myocardial contractility and finally DCM progression (6, 7). Nonetheless, the exact mechanisms are not well elucidated. According to the literature the prevalence of DCM has been reported around 12% in patients with diabetes which could increase up to 22% in elderly patients. DCM would lead to a preclinical left ventricular diastolic dysfunction, which might develop to a clinical heart failure without any evident coronary artery disease or valvular involvement (8–10). Korosoglou et al. described left ventricular mechanical dyssynchrony (LVMD) in patients with DM even without any signs for LV diastolic dysfunction. They finally indicated that LVMD could occur as the first pathologic changes during the course of diabetic cardiomyopathy (11).

Prevention and early diagnosis of cardiovascular disease in the early stages can reduce mortality and late complications such as heart failure. On the other hand, myocardial perfusion scan is a fully approved, standardized and accurate tool for examining myocardial function and diagnosing heart diseases, which is widely used in both diagnosis and prognosis of patients. Besides, its irradiation is very low. The diagnostic value of myocardial perfusion scan has been confirmed in many conditions, in diabetics, or those undergoing cardiac interventions (PCI or surgery) (12–14).

The accuracy of myocardial perfusion scans is quite comparable to other diagnostic modalities and has a high sensitivity and specificity of about 90%. The prognostic value of cardiac scanning has been studied in many studies and if the result of cardiac scan is abnormal, the patient's prognosis will be worse. Moreover, it has also been shown that the treatment planning can be determined based on the results of myocardial perfusion scans (15, 16). Diabetic patients who have risk indicators can be identified and treatment can be started faster before irreversible changes. The mortality of these patients can be reduced (17). Phase analysis is a computerized reproducible technique which is applied through different software to traditional gated SPECT MPI and provides incremental value to myocardial perfusion studies. It exploits the partial volume effect and Fourier first harmonics to evaluate the onset of myocardial contraction at different myocardial locations thereby determining myocardial synchrony. Type of gamma camera, reconstruction algorithm or injected dosage has no effect on the phase analysis(18). Phase analysis can detect early signs of dyssynchrony in diabetic population before there is visual regional myocardial contractility dysfunction and can prevent diabetic cardiomyopathy(19).

Therefore, the aim of this study was to employ phase analysis to diagnose left ventricular mechanical dyssynchrony (LVMD) in asymptomatic patients with diabetes mellitus type 2 and normal perfusion study .This would help early diagnosis of patients who are prone to diabetic cardiomyopathy.

Methods And Materials

Patient selection

This was a case control descriptive study. Ninety-three consecutive patients with known type 2 diabetes who referred to the Cardiovascular Clinic of Shohada Tajrish Hospital to undergo cardiac perfusion scans for preoperative evaluations were included. Inclusion criteria were patients aged between 35 and 80 years, systolic function above 55% in echocardiography and life expectancy of more than one year. Exclusion criteria were a history of valvular heart disease, ischemic heart disease, abnormal EKG, abnormal renal or hepatic failure, coronary intervention, arrhythmia, and perfusion defect and wall motion abnormality in gated stress SPECT-MPI. Moreover, 81 age- and gender- matched patients without diabetes who were candidates for myocardial perfusion scans were considered as the control group. The demographic characteristics of participants were recorded in a questionnaire.

Gated SPECT MPI: All patients underwent a myocardial perfusion scan in two stages of rest and stress (two day protocol) with Dipyridamole /exercise testing. Myocardial perfusion scan technique was as follows; after injecting 740 MBq of Tc99m-Sestamibi, the patient was scanned with a gamma camera in

supine and prone positions using the Gated SPECT method based on the American Society of Nuclear Cardiology (ASNC) guidelines (Collimator: low energy high resolution, Matrix: 64×64, Orbit: 180°, 32 frame from RAO till LPO, 15% window centered on 140-KeV photopeak, Gated: 8 frame per cardiac cycle: acceptance window:20%, Reconstruction with iterative metode,3D flash algorithm) The gamma camera used was the Evo-Voxel Siemens with Variable Angle Dual Heads.

Interpretation: Patient scans were then interpreted by a nuclear medicine specialist.. All studies were checked for presence of perfusion defects both visually and semi-quantitatively using 4DM and QPS software and patients were perfusion defects were excluded. Then all studies were checked with QGS and 4DM software and mechanical systolic and diastolic function indices of the left ventricle were extracted. Severity of left ventricular dyssynchrony was determined based on phase analysis for each scan and assessment of phase standard deviation (PSD, unit: degree), peak phase, mean phase and phase bandwidth (PBW, unit: degree) which is defined as 95% of the histogram width that includes practically full phase bandwidth with the exclusion of likely outlier values. For outcome analysis, only PSD and PBW were used as quantitative indices of the LVMD.

Statistical analysis

Descriptive data was reported as mean and standard deviation for quantitative variables and number and percentage for qualitative variables. A T-test was used to compare the means between the two groups. For all tests, p value below 0.05 was considered as statistically significant. SPSS software (SPSS Inc., Chicago, Il, The USA) was used for data analysis. Kruskal Wallis analysis was also deployed to determine any probable relation between duration of DM and progression into LVDM.

A written informed consent was obtained from all patients before entering the study. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

Results

A total of 174 patients (141 female) with a mean age of 58.50 ± 7.37 years (range: 36–80) were included in the study. There were 93 patients with diabetes mellitus type 2 in the case group with a mean age of 59.86 ± 8.63 years (77 females), and 81 age- and sex-matched non-diabetic individuals with mean age of 56.95 ± 6.31 years (64 female) in the control group. There were no statistically significant differences regarding demographic factors between the two groups ($P > 0.05$). CAD risk factors such as hypertension and dyslipidemia were more common in the case group compared to the controls ($P = 0.002$, $p = 0.001$). Mean duration of diabetes in patients was 8.56 ± 4.50 years. The baseline and clinical characteristics of the study participants are presented in Table 1.

Table 1
Demographic Characteristics of the Participants

Variable		DM (n = 93)	Non-DM (n = 81)	P-value*
		N (%)	N (%)	
Gender	Female	77 (82.79)	64 (79.01)	0.11
	Male	16 (17.20)	17 (20.98)	
	Total	93 (100)	81 (100)	
HTN	Yes	31 (34.44)	47 (58.02)	0.002
	No	59 (65.56)	34 (41.98)	
	Total	90 (100)	81 (100)	
Duration of Diabetes	< 5 years	27 (29.03)	-	-
	≥ 5 years	66 (70.96)	-	
	Total	93 (100)	-	
Smoking	Yes	9 (10.11)	16 (19.75)	0.07
	No	80 (89.89)	65 (80.25)	
	Total	89 (100)	81 (100)	
HLP	Yes	60 (64.51)	18 (22.22)	< 0.001
	No	33 (35.48)	63 (77.78)	
	Total	93 (100)	81 (100)	
Type of stress	Treadmill	17 (18.27)	16 (18.76)	0.78
	DIP	76 (81.72)	65 (81.24)	
	Total	93 (100)	81 (100)	

*Based on Chi-Square Test; HTN = hypertension; HLP = high lipid profile; DIP = dipyridamole.

According to some previous studies, obtained values of QGS (QGS Mean 30.9–80.2, PBW QGS 24, SD 8.6, Entropy 31) and 4DM (Mean 4DM 6.1–10.2, PBW 24, PSD 9.4) were used as a cutoff value for the diagnosis of LVMD (left ventricular myocardial dyssynchrony)(20). Considering PBW in QGS software, LVMD was detected in 8% of diabetics and 16% of non-diabetics (not statistically significant). In 4DM software these measures were 23.9% and 8.6% for diabetics and non-diabetics respectively. Except for PBW and mean phase in of 4DM software, no statistically significant difference was observed between control and diabetic patients ($P < 0.05$) (Table 2).

Based on Pearson's test poor correlation exists between findings of QGS and 4DM software ($p = 0.04$, $r = 0.2$).

Moreover, the duration of DM was divided into four groups : below 5 years (26 patients), between 5–10 (34), between 10–15 (17) and more than 15 years (16). Kruskal Wallis analysis to assess the impact of duration of DM revealed that as the duration of diabetes is prolonged, especially more than 15 years, the probability of LVMD [PBW in both QGS and 4DM] is increased as well ($p = 0.021$). However, there were no statistical significant differences between diabetic patients below 15 years, and non-diabetic patients (Figs. 1). Samples of normal and LVDM are shown in Figs. 2 and 3 respectively.

EDVs were in the range of 16 to 137 ml in control group compared to 6 to 95 ml for both diabetic patients and diabetic patients with LVMD, respectively. ESV ranges were 1 to 72, 0 to 40 and 10 to 42 ml for controls, diabetic patients without and with LVMD, respectively. However, no significant differences were observed for quantitative parameters (LVEF, EDV, ESV and LV mass) between these groups ($P > 0.05$).

Univariate linear regression analysis showed an association between higher EDV-ESV and lower ejection fraction (EF) and presence of diabetes, obesity, smoking and older age (Table 2).

Table 2
Distribution of Demographic and Clinical Characteristics in Diabetic and Non-Diabetic Patients

Variable	All (n = 174)	DM (n = 93)	Non-DM (n = 81)	P-value*
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (year)	58.50 (10.37)	59.86 (8.64)	56.95 (11.31)	0.21
Weight (kg)	76.34 (13.7)	77.32 (13.48)	75.23 (13.96)	0.35
	Median (IQR)	Median (IQR)	Median (IQR)	P-value**
QGS				
PBW	18 (12)	18 (9)	18 (12)	0.25
Entropy	21 (13)	20 (13.5)	23 (15)	0.17
PSD	3.7 (2.7)	3.35 (2.55)	3.9 (2.8)	0.27
mean	143 (22.2)	146.85 (22.95)	142 (19.8)	0.08
PFR	3.1 (1.57)	3.04 (2)	3.21 (1.37)	0.3
PFR2	1.52 (2.97)	1.85 (3.38)	0.91 (2.35)	0.11
MFR3	1.33 (0.82)	1.32 (0.93)	1.33 (0.61)	0.58
TTPF	163 (84.5)	152 (91)	171 (78)	0.23
PER	-4.33 (0.99)	-4.41 (0.98)	-4.24 (1.01)	0.25
EDV	49 (27)	45.5 (24)	53 (30)	0.03
ESV	13 (12)	11 (9)	15 (13)	0.01
EF	75 (14)	76 (12)	73 (15)	0.02
4DM				
Mean	50.2 (14.6)	51.4 (13.9)	47.6 (14.4)	0.009
SD	7.32(3.1)	7.75(2.8)	6.85(3.3)	0.14
PBW	26 (16)	28 (17)	24 (12)	0.02

* Based on t-test; ** Based on Mann-Whitney test; IQR = Interquarter Range;

QGS = Quantitative Gated SPECT; PBW = Phase Bandwidth; PSD = Phase Bandwidth;

PFR = Peak Filling Rate; PFR2 = Second Pick Filling Rate; MFR3 = Mean Filling Rate in the first

1/3 of the diastole; TTPF = Time to Peak Filling Rate; PER = Peak Ejection Rate; EDV=

End Diastolic Volume; ESV = End Systolic Volume; EF = Ejection Fraction

Mean duration of DM was also higher in diabetic patients with LVMD compared to those without LVMD ($P < 0.05$).

Discussion

To our knowledge there are very few studies assessing LVMD in patients with type 2 diabetes with no defects in perfusion scan. In our study, LVMD was detected in 23% of patients with type II DM which is slightly lower than the rate reported by Dharmender et al. (19). These patients had LVDM without any defect in scan or ECG abnormalities, which highlights the importance of phase analysis in cardiac perfusion scan to detect LVDM. Moreover, LVDM was more found in those patients with diabetes mellitus of more than 15 years, which is consistent with many other studies showing increased risk of cardiac events with prolonged diabetes mellitus (21–23).

Cardiac perfusion scan and the phase analysis provided a very useful tool to predict cardiac events in the future by revealing LVDM in our study. As seen there was a meaningful statistical difference regarding 4DM PBW, between the control and diabetic patients. This is in accordance with the Dharmender investigation, which claimed that phase analysis is a very helpful technique to predict LVMD without any additional study/radiation dose to the patients (19). Divergences (increased PBW) in left ventricular contractibility has been mentioned as the main pathophysiology of LVMD in diabetic patients in the recent studies (24). Many evidences indicate that LVMD is an independent risk factor for further cardiac complications in the diabetic patients (25), therefore, it necessitates detection of LVMD in patients by phase analysis. Despite the fact, phase analysis ability would be much more than the current definition of LVMD based on QRS width, as 12.5% of our patients had a normal QRS width but an abnormal phase analysis. Hence, it seems that phase analysis is more accurate for these patients who might be candidates for a resynchronization therapy. On the other hand, phase analysis is more accessible and easily performed compared to other evolving modalities such as Magnetic Resonance Imaging or newly discovered biomarkers, as there are very few evidence to support their values to predict further cardiac events. However, cardiac perfusion scan and phase analysis is performed faster, less affected by inhalation and beat variability. Moreover, it offers an automated evaluation and is less operator dependent.

Mahfouz et al in a recent 2020 study evaluated resting left ventricular dyssynchrony and mechanical reserve in asymptomatic normotensive subjects with early type 2 diabetes mellitus. They concluded that The LV dyssynchrony was a strong predictor of defective LV mechanical reserve and could be considered as a primary marker to reveal subclinical cardiac dysfunction in patients with asymptomatic diabetes mellitus with a normal LVEF. They also claimed that HbA1c, high-sensitivity C-reactive protein and left atrial volume index were inversely correlated with LVMR. This is in line with our study to show the importance of early detection of ventricular dyssynchrony in early stages to detect those diabetic patients who would benefit from early resynchronization therapy (25).

Other investigations also indicated some evidences of LVMD in asymptomatic diabetic patients (11). Early diagnosis of LVMD in asymptomatic diabetic patients helps to prevent dilated cardiomyopathy and irreversible fibrotic changes, which enhance the life expectancy of patients to a great extent.

Some other studies also found an association between obesity or hyperlipidemia and LVMD, which is consistent with our findings (26). These have been rarely evaluated in previous studies and could be considered as a novelty of our investigation. However, more studies are necessary to find the exact role of patient confounding factors in the progression of LVMD.

We had some limitations in performing the study. We would like to perform perfusion scans 2–3 times more to evaluate changes in phase analysis parameters, especially in those who underwent early resynchronization therapy. Despite the fact, it was not possible due to limitations in expenses and time. However, it is recommended to be considered in further studies. Furthermore, the exact effects of some confounding factors such as underlying diseases, age, or smoking was not assessed here. It is recommended to be evaluated in larger prospective clinical trials to clarify the exact role of underlying patients' conditions. However, it would help to better understand the pathophysiology of LVMD in asymptomatic diabetic patients.

We found poor correlation between 4DM and QGS software. Difference between PBW in diabetics and non-diabetics was only statistically significant in 4DM and QGS seemed insensitive to access some dyssynchrony. These findings were noted in some studies before (27, 28), however some other studies found 4DM and QGS both helpful in detection of LVDM (29, 30).

Conclusion

Asymptomatic diabetics, especially those with prolonged diabetes, with normal myocardial perfusion might have some degrees of LVMD, which might progress to dilated cardiomyopathy if not considered appropriately. Phase analysis helped us to detect this in our study. These patients might benefit from different preventive or therapeutic options like better glycemic control or resynchronization therapy to avoid unwanted and irreversible cardiac events and enhance their overall life expectancy. We recommend that phase analysis should be done for all patients for early diagnosis of LVDM.

Declarations

Acknowledgment

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Conflict of interest

No conflict of interest.

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Figures

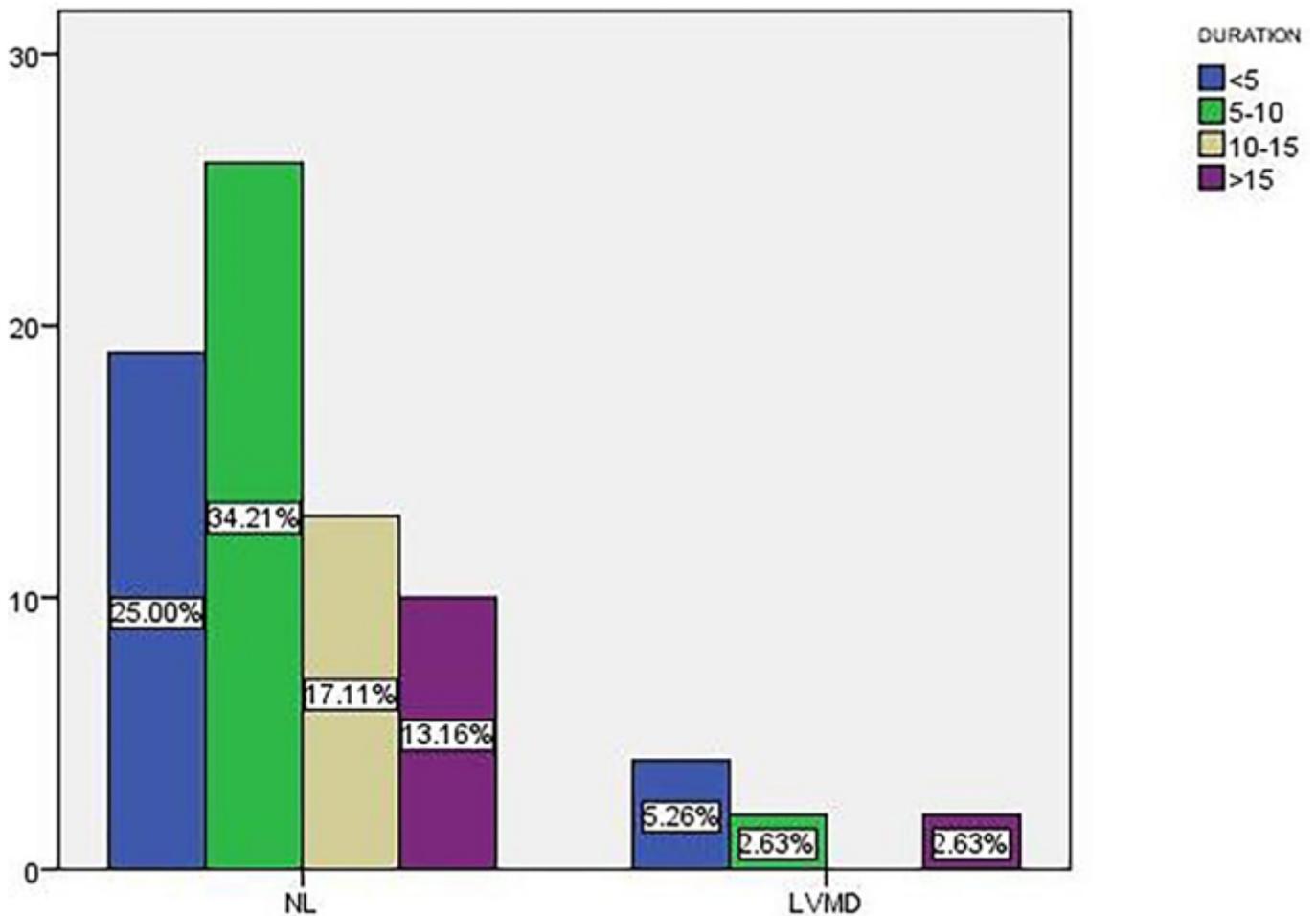


Figure 1

LVMD in Different Diabetic Groups, figures in vertical axis shows number of patients, color bars indicates duration of diabetes in year.; LVDM=Left Ventricular Mechanical Dyssynchrony

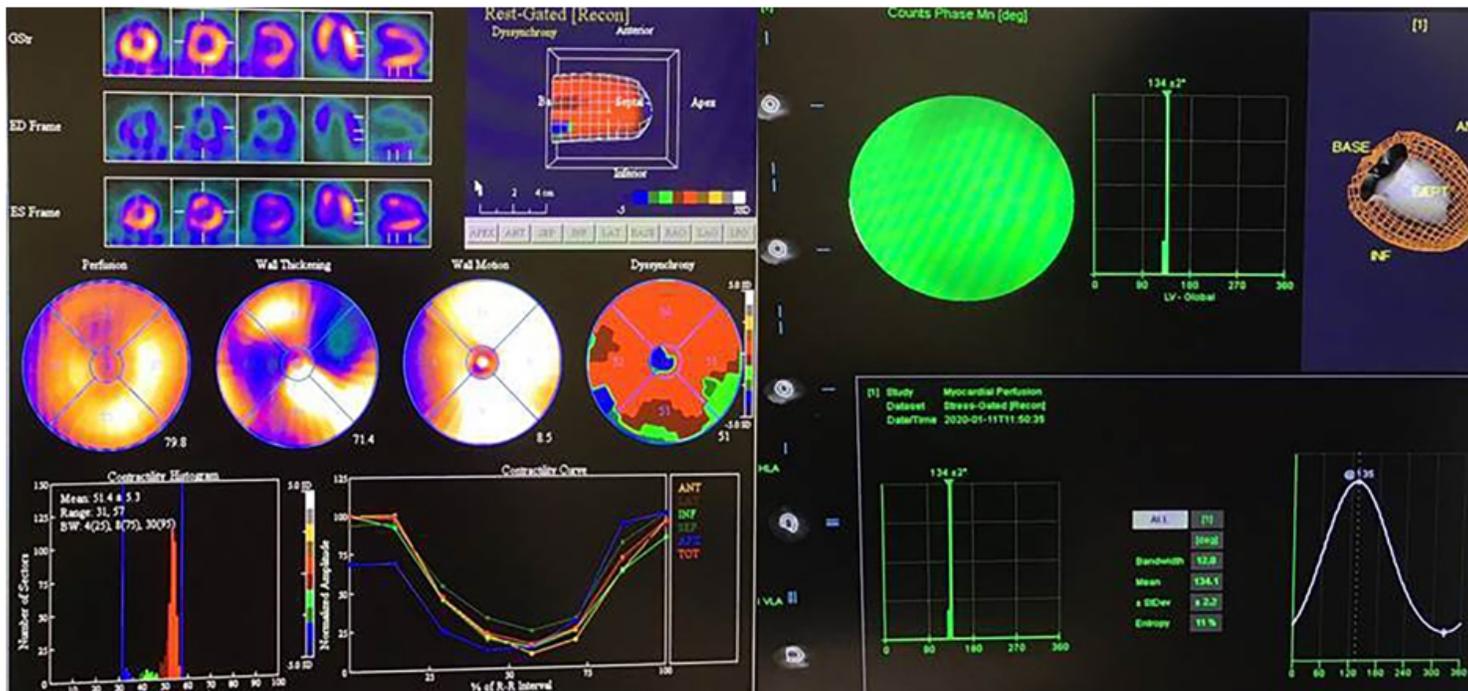


Figure 2

Sample of synchronous LV contraction. 4DM (left) and QGS (right) both show normal Phase analysis. Measured bandwidth (PBW) in both software are within normal limits (calculated BW is 30 for 4DM and 12 for QGS); QGS=quantitative gated SEPECT

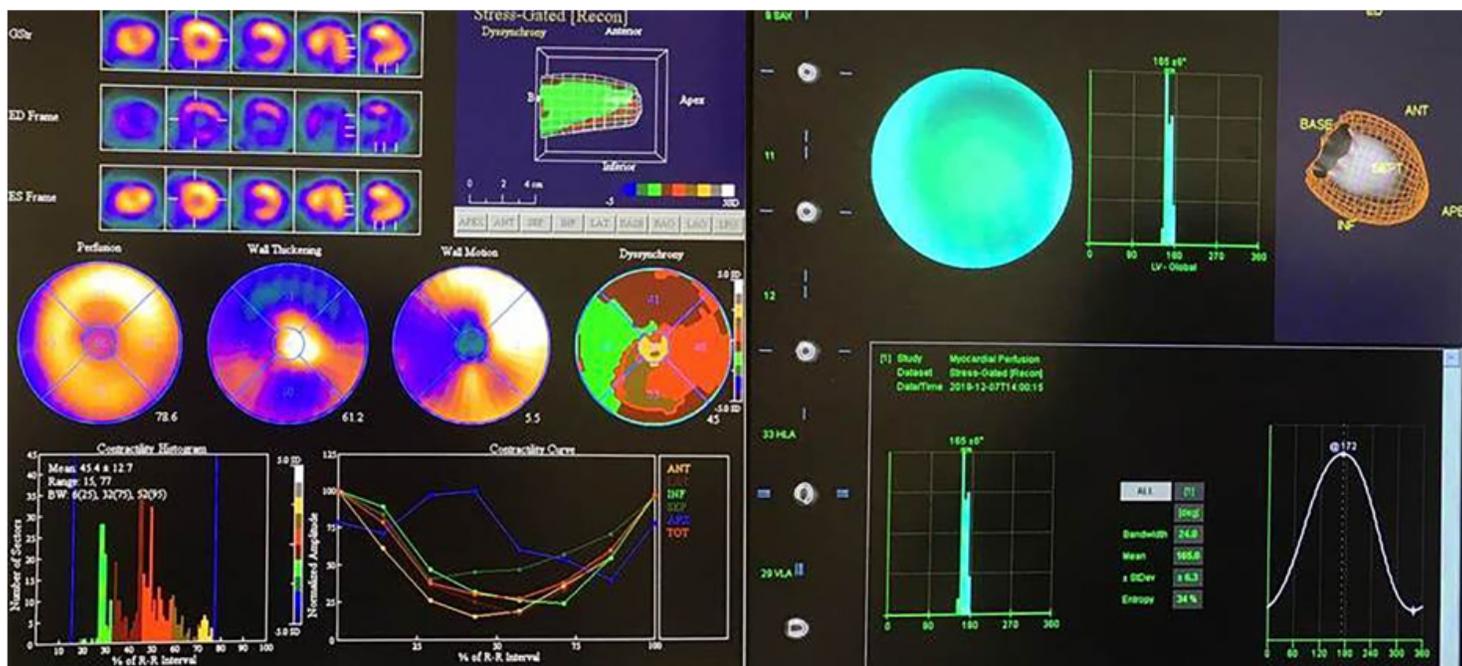


Figure 3

Sample of dyssynchronous LV contraction. The BW is significantly increased in 4DM (measured BW is 52); apex and septum show out of order contraction. In QGS, PBW is moderately increased (measured BW is 24 and anterior wall seems to have mild dyssynchrony).