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ROLE OF 2D SPECKLE TRACKING (STE) AND 4D ECHOCARDIOGRAPHY IN THE ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION IN TYPE II DIABETIC PATIENTS WITH NEGATIVE MYOCARDIA PERFUSION IMAGING IN CORRELATION TO MUGA SCAN.

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Abstract

Background: 2D Speckle tracking echocardiography (STE) hold promise to be more reliable indexes of "myocardial performance" in patients with DM. Also, 3D echocardiography has shown to be accurate in the assessment of LV systolic function, The MUGA scan provides a more accurate representation of cardiac ejection fraction.

Aim of the Work: To Assess the role of 2D Speckle Tracking (STE) and 4D Echocardiography in the assessment of left ventricular systolic function in type II diabetic patients with negative myocardial perfusion imaging in correlation to MUGA scan.

Patients and methods: The study was conducted in cardiology department of Al Zahraa University hospital. It included 30 patients with T2DM (group I, 25 (83%) female & 5 (16%) male with mean age 48.40±7.44), whom stress (MPI) was proved to be negative. And 15 apparently healthy age and sex matched subjects as a control group (group II, 11(73) female & 4 (26%) male with mean age 50.20±7.74), LV systolic function was evaluated using conventional, TDI, 2D STE (LV-GLS), 4DE and MUGA scan.

Results: The diabetic group showed statistically highly significant reduction in LV-GLS (-18.07±2.73 in group I VS -21.24±1.29 in group II, P<0.001), 4D LVEF (52.30±5.28in group I VS 58.93±4.69 in group II, P<0.001). We found an agreement between three modalities (speckle tracking, 4D echocardiography and MUGA scan) by 33% in 10 patients (3 patients (10%) are impaired function and 7 patients (23%) are preserved one). Also, there was an agreement between two modalities (speckle tracking & 4D echo) by 76.6% in 23 patients (16 patients (53.3%) are impaired function and 7 patients (23.3%) are preserved one).

Conclusion: T2DM is associated with subclinical left ventricular systolic dysfunction that can be assessed by different noninvasive modalities (speckle tracking, 4D echocardiography and MUGA scan). 2D speckle tracking and 4D echocardiography might be more powerful than MUGA scan in the detection of subclinical left ventricular systolic dysfunction.

INTRODUCTION

Early detection of diabetic heart disease is of paramount importance, because timely life-style modifications and medical interventions could prevent or delay the subsequent development of heart failure which is considered one of major burdens for health insurance costs**.** Speckle tracking echocardiography (STE) hold a promise to be more reliable indexes of "myocardial performance" in patients with DM. It is accurate, reproducible, and angle independent, and it enables a complete assessment of regional and global function in three directions **(1)**.

Real-time 3DE has the advantages of low cost, portability, and live 3D imaging without offline reconstruction. It has shown promise for more accurate assessment of LV function **(2)**.

Myocardial perfusion single photon emission computed tomography (SPECT MPI) has been found to help prevalence and prognosis of LV systolic dysfunction in asymptomatic diabetic patients without known coronary artery diseases **(3).** The MUGA scan was first introduced in the early 1970s and quickly became accepted as the gold standard method for measurement of left ventricular ejection fraction (LVEF) with a high degree of accuracy **(4)**.

Aim of the work

To Assess the role of 2D Speckle Tracking (STE) and 4D Echocardiography in the assessment of left ventricular systolic function in type II diabetic patients with negative myocardial perfusion imaging in correlation to MUGA scan.

Patients

This study was conducted on 30 patients with type II diabetes-with low risk for coronary artery disease - who presented to the cardiology clinic in Al Zahraa University Hospital by chest pain or dyspnea in whom stress myocardial perfusion imaging (MPI) was proved to be negative (group I).

Another group of 15 healthy age and sex matched individuals that collected retrospectively from cases candidate for MPI study, has been enrolled as a control group (group II). All patients and control groups were collected in the period from December 2020 to January 2022.

Group I further classified in to 3 subgroups (A, B & C) according to their MUGA LVEF, LV-GLS and 4D LVEF respectively). All patients and control groups accepted an oral and written consent, and the study was approved by faculty medicine for girls ethical committee.

Patients with documented ischemic heart disease, valvular heart disease or congenital heart disease, hypertension, arrhythmias, chronic pulmonary disease, and patients with associated co-morbidity were excluded from the study.

Methods

All patients included in this study were subjected to the following:
Through medical history taking and clinical examination.

Echocardiography

Conventional transthoracic echo-Doppler examination was performed for all patients in both supine and left lateral position using Vivid-9GE system with tissue Doppler imaging capability. All cases were examined using multi frequency (2.5- 3.5 MHz) matrix probe M3S with simultaneous ECG physio signal displayed with all recorded echo images and loops.For image acquisition, 3- Cardiac

cycles were taken in each view with the patient holding breath.

All images were digitally stored for off line analysis (EchoPAC.GE VERSION 113-1-2).

The following data were obtained:
a- Using 2D and 2D guided M-mode to assess: LV end-systolic and end-diastolic volumes (ml^3), LV ejection fraction (%), fractional shortening (%), interventricular septum end-diastolic diameter (mm), LV posterior wall end-diastolic diameter (mm).
b- Using Convention Doppler Echo to assess: Mitral E and A wave Velocities (cm/s), E/A Ratio.
c- Using Tissue Doppler imaging to assess: S velocity, Ea velocity, Aa Velocity and E/Ea Ratio, The average LV longitudinal strain.

Two-dimensional speckle tracking:
Speckle tracking analysis performed on LV was obtained in apical 4, 2and 3 chambers. The LV longitudinal were assessed using 2D speckle-tracking analysis with QRS onset as the reference point, applying a commercially available LV strain software package to the left ventricle, During analysis, the endocardial border was manually traced at end systole and the region of interest width was adjusted to include the entire myocardium, The LV deformation parameters in each of 18 segments were assessed. Global strain assessed by averaging strain of all segments.

Real time 3 Dimensional Echocardiography (4DE):
RT3DE imaging was performed from the apical window with the patient in the left lateral decubitus position. To include the entire LV cavity within the pyramidal scan volume, data sets were acquired using the wide-angled mode, where in 4 wedge-shaped subvolumes were acquired during a single breathhold. Acquisition of each subvolume was triggered by the ECG R wave of every other heartbeat (total of 6 heart beats) to allow sufficient time for each subvolume to be stored. Six automatically selected long-axis planes rotated around the long axis of the left ventricle at 30° steps were subsequently used to analyze LV function **(5)**.

It included the followings:
Left ventricular end diastolic volume (LVEDV), Left ventricular end systolic volume (LVESV), Left ventricular ejection fraction (EF %) **(6).**

MUGA Scan:
Radionuclide angiography was performed for all patients using Philips Cardio-MD system by in vivo method of labeling autologous red blood cells. The patient was injected with 1.5 mg stannous pyrophosphate. Twenty minutes later, 30 MCi technetium-99m pertechnetate was injected in another line. After 10 minutes, imaging was performed in the left anterior oblique (30° to 40°) view with a digital Gamma camera with a slant-hole collimator positioned at a caudal angulation of 30°. The data were processed with standard software and background correction. The LVEF was computed by digital or manual tracing of the LV end-diastolic and end-systolic images**,** This is a technique in which patient's red blood cells are labeled with technetium 99m pertechnetate. Planar images of the left ventricle are obtained. Planar imaging to calculate LVEF calculation requires differentiation of left and right ventricle with left anterior oblique projection. LV region of interest is determined following which the radioactivity counts within that region are analyzed. Analyzing radioactivity counts within that identified region is important as this technique studies the changes in radioactivity in the left ventricle between end-systolic phase and end-diastolic phase instead of truly measuring volumes of the left ventricle. ECG guidance is used to gate image acquisition over multiple cardiac cycles. Each cardiac cycle is later separated into a predetermined number of intervals (16 or 32), relating to the number of frames (images) per cardiac cycle. Frame with the highest count represents the end-diastole and frame with the lowest count represent the end-systole **(7)**.

LVEF can be calculated from the following equation: Net counts in the end-diastolic frame - net counts in the end systolic frame/net counts in end-diastole. Net counts are determined by subtracting counts from a background region of interest (next to the left ventricle) from measured LV counts. This technique can be performed especially in patients whose body habitus limits the use of other modalities. There are no contraindications to this modality **(7)**.

It included the followings:
Left ventricular end diastolic volume (LVEDV), Left ventricular end systolic volume (LVESV) and Left ventricular ejection fraction (EF %) **(8).**

Statistical Analysis of Data:
Numerical variable was expressed as mean and standard deviation (SD), the following statistical tests were used for analysis of data by SPSS version 19, Independent t test: for testing statistical significant difference between means of the two groups in each classification. Pearson's correlation test with the determination of the correlation coefficient (r) to test a positive or negative relationship between two variables. (P) Value less than 0.05 was considered statistically significant and <0.001 highly significant.(r) Value less than 0.2 was considered very weak correlated. 0.2-0.4 (weak correlation), 0.4-0.6 (moderate correlation), 0.6-0.8 (strong correlation) and >0.8 (very strong correlation).

RESULTS

The study included (30) patients, (25) females and (5) males with mean age of (48.40±7.44 y) and control group included 15 healthy individuals (11 female and 4 male) with mean age 50.20±7.74.

As regard the different echo modalities (conventional, 2D strain & 4D Echo) and MUGA parameters: There were a statistically significant lower values of LV-GLS & 4D-EF in the patient group and higher values of 4D LV ESV and 4D LV EDV in the same group compared to the control group and a non-significant difference between the two groups as regard the following parameters (2D-EF, 2D LVESV, 2D LVEDV, IVSD, PWD, MUGA-EF, MUGA LV ESV and MUGA EDV), as shown in Table (1).

Table (1) Comparison of the different echo modalities (conventional, 2D strain & 4D Echo) and MUGA parameters between the patient and the control group.

Variable	Patient	Control	P value
2D-EF	70.77±7.9	70.27±4.89	0.796
2D LVESV	28.03±3.9	28.6±2.6	0.569
2D LVEDV	47.40±3.96	45±6.09	0.118
IVSD	9.50±1	9.13±.743	0.176
PWD	9.13±1.1	9.60±2.67	0.410
LV-GLS	-18.07±2.73	-21.24±1.29	0.000
4D-EF	52.30±5.28	58.93±4.69	0.000
4D LV EDV	67.73±13.32	60.13±11.079	0.051
4D LV ESV	31.87±6.11	25.53±7.15	.003
MUGA EF	65.50±9.164	67.07±5.66	.485
LV MUGA EDV	113.20±54.74	92.73±17.64	.070
LV MUGA ESV	40.83±22.91	37.27±9.13	.462

Left Ventricular Systolic Function In Patients Group
We assessed the left ventricular systolic function of all diabetic patients (No 30) by different echo modalities (conventional, 2D strain & 4D Echo) and MUGA scan.

We found that 23 patients (76.67%) with impaired LV-GLS (5 of them had impaired LV EF measured by MUGA and 16 patients had impaired LVEF by 4D Echo), Seventeen (17) patients (56.67%) with impaired LV-4DEF (3 of them had impaired LV EF measured by MUGA and 16 patients had impaired LV-GLS), 5 patients (16.67%) with impaired MUGA LVEF all of them had impaired LV-GLS and 3 patients had impaired LVEF by 4D Echo.

There was an agreement between three techniques (2D strain & 4D

Echo and MUGA scan) by 33% in 10 patients (3 patients (10%) with impaired function and 7 patients (23%) with preserved function), Also there was an agreement between two techniques (2D speckle tracking & 4D echo) by 76.6% in 23 patients (16 patients (53.3%) with impaired function and 7 patients (23.3%) with preserved function) as showed in figure (1)

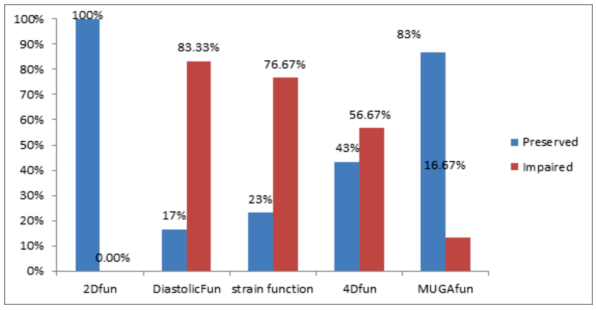

Figure (1): LV function in the study group by different modalities.

We divided the diabetic group into three groups (A, B & C) according to their MUGA LVEF, LV-GLS and 4D LVEF respectively.

A) Comparison between the diabetic subgroups as regard MUGA LVEF: We divided the diabetic group into two groups according to their LV EF measured by MUGA:

Group 1A:
Included 5 patients (4 females and 1 male) with impaired MUGA LVEF <50% (50.2%±4.44%).

Group 2A:
Included 25 patients (21 females and 4 males) with preserved MUGA LVEF >50% (68.56%±6.3%).

Patients with impaired LV function by MUGA (Group 1):
All patients with impaired MUGA LV EF had preserved function by conventional echo and impaired LV GLS, but only 3 patients (60%) had impaired systolic function by 4D Echo, as shown in table (2).

Patients with preserved LV EF by MUGA (Group 2) (LV EF = 67.44%±5.7%), were found to be with the following parameters; LV GLS (-17.27±1.9) LV 4DEF (51.2%±5.9%)

Table (2): Showing The Relation Between Group 1A And Group 2A Regarding Other Different Parameters.

Variable		MUGA LV EF		P value
		Impaired	Preserved	
LV GLS	Impaired	5	18	.177
	Preserved	0	7	
LV 4DEF	Impaired	3	14	.869
	Preserved	2	11	

Comparing the two groups (1A & 2A) as regard the different echo modalities (conventional, 2D strain & 4D Echo) and MUGA parameters:
There were a statistically significant higher values of IVSD, MUGA LV ESV and EDV in group1A and lower value of LV-GLS in the same group compared to the group 2A (P<0.05) and a non significant difference between the two groups as regard the following parameters (2D-EF, LVESV, LVEDV, PWD, 4D EF, 4D LV ESV and EDV), as shown in Table (3).

Table (3): Showing The Comparison Between Group 1A And Group 2A Regarding The Different Echo Modalities (conventional, 2D Strain & 4D Echo) And MUGA Parameters.

Variable	Group1A	Group 2A	P value
2D-EF	68.00±3.32	71.32±8.51	.160
2D LVESV	28.20±1.79	28.00±4.23	.866
2D LVEDV	45.60±4.33	47.76±3.87	.273
IVSD	10.20±.45	9.36±1.03	.011
PWD	9.00±.71	9.16±1.18	.694
LVGLS	-15.78±1.47	-18.53±2.71	.009
EF4D	52.32±5.55	52.20±4.15	.957
4D LV EDV	66.60±18.02	67.96±12.64	.839
4D LV ESV	32.00±10.42	31.84±5.19	.958
LVMUGA EDV	166.80±83.23	102.48±41.81	.014
LV MUGA ESV	79.00±30.6	33.20±10.67	.000

Correlation between MUGA LV EF and different parameters:
There was a moderately positive correlation between the MUGA LVEF and LV-GLS at value of (r=.511, P value=0.004), a weakly positive correlation with 4D LVEF at value of (r=.395, P value=0.031) and a weakly negative correlation with HbA1c value of (r=.384, P value=0.036), as shown in table (4).

Table (4): Showing The Correlation Between The MUGA LVEF And Different Parameters.

Variables		Person correlation	Significance
MUGA LVEF	EF4D	.395*	.031
	LVGLS	.511**	.004
	HbA1c	-.384*	0.036

B) Comparison between the diabetic subgroups as regard LV-GLS:
We divided the diabetic group as regard LV-GLS into: **Group 1B**: Included 23 patients (18 females and 5 male) with impaired LV-GLS <-20 (-16.94±1.9).

Group 2B: Included 7 patients (all are females) with preserved LV-GLS function >-20 (-21.78±1.9)

Patients with impaired LV function by LV-GLS:
All patients with impaired LV-GLS had preserved function by conventional echo, but only (5 patients) with impaired MUGA LVEF and (16 patients) had impaired systolic function by 4D Echo, as shown in table (5).

There was a statistically significant relation between both groups in 4D LVEF with (P < 0.05).

Table (5): Showing The Relation Between Group 1B And Group 2B Regarding Other Different Parameters.

Variable		LV-GLS		P value
		Impaired	Preserved	
LV-MUGA EF	Impaired	5	0	.847
	Preserved	18	7	
LV 4D EF	Impaired	16	1	.010
	Preserved	7	6	

Correlations between the LV-GLS and different parameters:
There was a moderately positive correlation between the LV-GLS and MUGA LVEF at value of (r=.511, P value=0.004) and weak to moderate negative correlation with MUGA LVESV at value of (r=.491, P value=0.006) & MUGA LVESV at value of (r=.456, P value=0.011), as shown in table (6)

Table (6): Showing The Correlation Between The LV-GLS And Different Parameters.

Variables		Person correlation	Significance
LV-GLS	MUGA LVEF	.511**	.004
	MUGA LVEDV	-.456**	0.011
	MUGA LVESD	-.491**	0.006

C) Comparison between the diabetic subgroups as regard LV-4DEF:
Patients were classified into two groups according to their LV 4DEF:
Group 1C: Included 17 patients (15 females and 2 male) with impaired function < 54% (49.76±5.5).

Group 2C: Included 13 patients (10 females and 3 males) with preserved function > 54(55.61±2.4).

Patients with impaired LV function by 4D Echo:
All patients with impaired LV-4DEF had preserved function by conventional echo, but only (3 patients) with impaired MUGA LVEF and (16 patients) had impaired LV-GLS, as shown in table (7)**.** There was a statistically significant relation between both groups in LV-GLS with ($P < 0.05$)

Table (7): Showing The Relation Between Group 1C And Group 2C Regarding Other Different Parameters.

Variable		LV-4DEF		P value
		Impaired	Preserved	
LV-GLS	Impaired	16	7	.010
	Preserved	1	6	
MUGA LVEF	Impaired	3	2	.869
	Preserved	14	11	

Correlations between the 4D-LVEF and different parameters:
There were a weakly positive correlation between 4D LVEF and MUGA LVEF at value of (r=.395, P value=0.031) and a weakly negative correlation with LDL at value of (r=.378, P value=0.039) and, as shown in table (29)

Table (8): Showing Correlations Between The 4D-LVEF And Different Parameters.

Variables	Person correlation		Significance
4D-LVEF	MUGA LVEF	.395*	.031
	LDL	-.378*	.039

DISCUSSION

Myocardial involvement in type II DM has been proved as subclinical LV and RV systolic dysfunction **(9)**. Early detection of diabetic heart disease is of paramount importance, because timely life-style modifications and medical interventions could prevent or delay the subsequent development of heart failure which is considered one of major burdens for health insurance costs **(10).**

Our results were in agreement with **Labombarda et al.** who, suggested that LV longitudinal function is impaired in patients with T2D, and glycaemic control may be the main risk factor for the myocardial changes **(11),** at the same time our results were in disagreement with **Di Cori et al.** who did not find a relationship between HbA1c and LV systolic strain or velocity **(12).**

In our study we found that the LVEF by MUGA was subnormal in 16.67% diabetic patients.

There was a little difference between our result and that of **Daya et al.,** who studied 30 type 2 diabetic subjects without cardiac **symptoms** and 30 prediabetics that assessed by MUGA as well as pulse Rheography, the LVEF was subnormal in 29% of diabetics and 16.6% of prediabetics **(13).** And our explanation to this difference is that most of our patients were under strict control of their diabetes as their HbA1c was 6.7±1.2**%.**

In our study results we found that there was no correlation between 2DE EF% and that by MUGA and this finding was concordant to the finding of **Naik et al.,** who compared 2DE and MUGA in the determination of LVEF and concluded that the 2D method demonstrate the unsatisfactory nature because of its geometric assumptions for the assessment of LVEF **(14).**

In our study we found that all patients with impaired MUGA LVEF had impaired LV-GLS and we found that even in diabetic patients with preserved LVEF by MUGA, 72% had impaired LV-GLS. Discordant to our result what was found by **Ernande et al.**, who found that only 23% (14/60) of studied diabetic patients with impaired LVEF by MUGA had LV longitudinal systolic dysfunction determined as their LV-GLS **<** -18 **(15)** and our explanation to our finding is the high ability of 2D-STE to predict subclinical LV systolic dysfunction which is unmasked by the alteration of longitudinal strain **(16).**

Also, we found a moderately positive correlation between EF by MUGA and LV-GLS. **Gopal et al. in 1995** conducted a comparative study between 3DE and MUGA. In that study, LVEF measured by MUGA ranged from 9% to 75%, with a mean of 47% ± 19%, they showed an excellent correlation between the 3DE method and MUGA **(17)** and this was consistent with our results as we found a 60% of patients with impaired MUGA LVEF with impaired 4D LVEF and also we found a weakly positive correlation between these two methods.

We found that even in diabetic patients with preserved LVEF by MUGA, 56% had impaired 4D LVEF. In our study we found a statistically significant reduction in the LV-GLS in the diabetic group compared to in the control group. Additionally LV-GLS was lower in diabetic group with impaired MUGA LVEF. Also, LV-GLS was lower in diabetic group with impaired 4D LVEF, and all those patients with preserved 2D LVEF being Concordant to our results the result of **Nakai et al. in 2009** who, reported that GLS in DM patients was significantly lower than that in age-matched normal subjects despite of similar 2D LVEF, and 43% (26/60) of DM patients showed LV longitudinal systolic dysfunction determined as GLS < 17.2% **(16).**

Also, **Yasuhide et al. in 2015** studied 144 diabetic patients without overt heart failure or and cardiac disease included type 1 and type 2 diabetic patients found that 37% of patient group had reduced GLS but this results was associated with diabetic complications especially diabetic nephropathy and neuropathy and hypertriglycridaemia **(18).**

Also, **Jędrzejewska et al.** studied LV in 50 patients with type 2 DM and found that there was a statistically significant reduction in LVGLS in the diabetic patients compared to the control group **(19).** Some studies explained pathophysiological causes of LV longitudinal dysfunction in DM patients as microvasculopathy, myocardial hypertrophy and cardiac fibrosis due to hyperinsulinemia, and dysregulation of extracellular matrix due to hyperglycemia **(20). Ceyhan et al.** found that all LV-GLS were reduced in patients with uncontrolled DM **(21)**, which is consistent with our study results.

In our study, a significant relation between LV-GLS and HbA1c was observed, Our results were in agreement with **Labombarda, et al.** who, suggested that LV longitudinal function is impaired in patients with T2D, and glycaemic control may be the main risk factor for the myocardial changes **(11).** And, there were disagreement with **Di Cori et al.** who did not find a relationship between HbA1c and LV systolic strain or velocity **(12).**

Qingqing et al. studied 82 patients with type 2 diabetes including 46 subjects with diabetes alone and 36 subjects with diabetes and hypertension, their study results showed that despite a similar 2D LVEF, 4D LVEF was significantly lower in patients with diabetes only than in control ($p < 0.001$) **(22).**

We are in agreement with that, as in our study results we found a significantly lower 4D LVEF in diabetic patients than in control and all those patients were with preserved 2D LVEF**,** 94% impaired LV-GLS and 17.6% with impaired MUGA LVEF. **Vinereanu et al.** had observed inverse correlation between LDL and subclinical left ventricular dysfunction by real time 3D echocardiography and found that LDL was an independent determinant of systolic function**.** In our study, a weakly negative correlation between 4D LVEF and LDL was observed, and this was concordant with the result of the previous study **(23).**

CONCLUSION:

Type II diabetes mellitus is associated with subclinical left ventricular systolic dysfunction that can be assessed by different non invasive modalities (speckle tracking, 4D echocardiography

and MUGA scan). New non invasive modalities like speckle tracking and 4D echocardiography might be more powerful than MUGA scan in the detection of subclinical left ventricular systolic dysfunction, for further evaluation. So we recommend STE should be considered as a routine investigation in the assessment of patients with type II DM.

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