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DETECTION OF SUB CLINICAL LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN DIABETIC PATIENTS WITH DIABETIC RETINOPATHY BY 2D SPECKLE TRACKING ECHOCARDIOGRAPHY

By

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ABSTRACT

Background: Retinopathy is one of the microvascular complications of DM. In some studies, it has been proposed that diabetic retinopathy might be associated with LV diastolic dysfunction, development of heart failure, and diabetic cardiomyopathy in the future

Objective: To detect subclinical left ventricular Systolic dysfunction by 2D Speckle Tracking Echocardiography in Patients with DM with Diabetic retinopathy and to Correlate between the class of retinopathy and the subclinical systolic dysfunction.

Patients and Methods: Our study comprised 70 patients (31 male & 39 females) suffering from diabetes mellitus (type I& type II) were recruited from the endocrinology clinic & ophthalmology clinic and 30apparently normal people with matched age, sex status as controls (14 males and 16 females). The studied population was classified into two groups: *First group (patient group) consisted of 70 patients with Type I &II DM {31 males and 39 females with mean age 46.44±8.05 years & mean duration of diabetes is 13.29±6.04years and mean HbA1C 8.63±1.75.*Second group (control group) consisted of 30 healthy subjects {16 males and 18 females with mean age 44.30±7.91.

Results: in comparison with healthy subjects, patients with diabetic retinopathy were found to have lower LV systolic function using 2D speckle tracking. According to LV GLSS% showed that the mean values were -14.87±1.28 and -20.62±1.31 in the patients and control groups, respectively. They showed highly statistically significant difference between the two groups according to LV GLSS%. The mean values of the patient subgroups were -14.87±1.28 and -16.75±0.75in subgroup R +VE and R -VE, respectively. They showed a statistically highly significant difference (P <0.001).

Conclusion: the 2D speckle tracking method appears to be useful in the detection of LV systolic dysfunction in patients with diabetic retinopathy (one of the microvascular complications of DM). Subclinical left ventricular systolic dysfunction in diabetic patient with diabetic retinopathy is associated with the fact that DM is known to cause the development of heart failure even in the absence of coronary artery disease. The presence of diabetic retinopathy signifies an excess risk of HF, independent of known risk factors. Parameters of LV systolic function were worsened with increasing severity of retinopathy.

Keywords: Subclinical LV dysfunction, 2D speckle tracking echocardiography, diabetic retinopathy.

INTRODUCTION

Cardiovascular complications are the leading causes of morbidity and mortality in the diabetes mellitus (DM) population *(Maisch et al., 2011)*.

DM can lead to disharmony in cardiac structures and functions with absence of coronary artery disease and without affecting blood pressure, which is known as diabetic cardiomyopathy *(Maisch et al., 2011)*.

The pathogenesis of diabetic cardiomyopathy is believed to be multifactorial but the exact cause is not known *(Maisch et al., 2011)*.

Impaired cardiac insulin metabolic signaling, mitochondrial dysfunction, increases in oxidative stress, reduced nitric oxide bioavailability, elevations in advanced glycation end products and collagen-based cardiomyocyte and extracellular matrix stiffness, impaired mitochondrial and cardiomyocyte calcium handling, inflammation, renin–angiotensin–aldosterone system activation, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and a myriad of cardiac metabolic abnormalities have all been implicated in the development and progression of diabetic cardiomyopathy *(Jia et al., 2018)*.

All these underlying pathogenic conditions change cardiac structure and may lead to cardiac fibrosis.

Echocardiography is a fundamental technique in the diagnosis of diabetic cardiomyopathy. Cardiomyopathy changes in the earlier course of DM are known as a state of preserved LV ejection fraction (LV-EF) with abnormalities in diastolic functions. It is known that LV-EF is not an objective tool in the evaluation of systolic functions. Therefore, subclinical LV systolic dysfunction may not be recognized at that stage *(Lee and Kim, 2017)*.

STE is the procedure of choice, compared with tissue Doppler imaging, because it eliminates angle dependency and the need of high frame rates and allows echocardiographic measurement of radial and circumferential strain. Moreover, when compared with magnetic resonance imaging as a bedside tool, it is a cheap and readily available procedure *(Mor-Avi et al., 2011)*.

Retinopathy is the most frequent and serious complication of DM. It is also among the most important causes of vision loss in people of working age *(Sivaprasad et al., 2012)*.

Retinopathy is one of the microvascular complications of DM. In some studies, it has been proposed that diabetic retinopathy might be associated with LV diastolic dysfunction, development of heart failure, and diabetic cardiomyopathy in the future *(Kurioka et al., 2013)*.

The present study aimed to detect subclinical left ventricular systolic dysfunction by 2D speckle tracking echocardiography in patients with DM with Diabetic retinopathy and to correlate between the class of retinopathy and the subclinical systolic dysfunction.

PATIENTS AND METHODS

This cross-sectional comparative study involved 70 diabetic patients collected from the Endocrinology and

ophthalmology clinics of Al-Azhar University Hospitals. The patients were screened for the study enrollment prospectively. The study was performed at Cardiology Department, Faculty of Medicine, Al-Azhar University during the period from October , 2019 to April, 2020.

The protocol and all corresponding documents were approved by Ethical and Research committee, Faculty of Medicine, Al-Azhar University and patients provided informed consents.

The present work studied and evaluated the subclinical left ventricular (LV) systolic dysfunction by 2D speckle tracking echocardiography in all diabetic selected patients and control.

The patients were classified into two groups matched in age:

Group (1): Patients: Seventy patients with diabetes mellitus.

Group (2): Control group: Thirty sex-and age-matched apparently healthy individuals.

Inclusion criteria:

Patients who were diagnosed as DM according to the definition of a fasting blood glucose of >126 mg/dl measured on two different occasions or patients treated with on oral anti diabetic drugs and/or insulin. Patients with DM were divided into two groups according to the findings of the funduscopic examination based on the modified Airlie–House classification (Early Treatment Diabetic Retinopathy Study Research Group (1991), i.e. Patients with retinopathy (proliferative or non-proliferative) and without retinopathy.

Exclusion criteria:

Documented IHD, patients with congenital heart diseases, Patients with heart failure, patients with atrial fibrillation, end Stage renal disease, Patient refusal, poor acoustic window patients with reduced ejection fraction ≤ 50%, significant comorbidities, patients with bad compliance, uncooperative patients, patients that refused the consent or the study or inability to give informed consents.

All patients were subjected to the following:

Complete history, HBA1C, resting surface 12 leads ECG, echocardiography and fundus examination.

Echocardiographic examination:

All patients were examined at rest in the left lateral decubitus position to obtain adequate images in different standard views.

- Chamber quantification was performed in accordance with the recommendations of the American society of echocardiography and Assessment of the Left Heart in Adults (Marwick, 2006) respectively.
- Left ventricular end diastolic dimension (LVEDD): this will be done using long axis view with M-mode sampling and 2D.
- Left ventricular Ejection fraction (LVEF %) will be determined using Simpson’s biplane volume try.

Two-dimensional Speckle tracking Echocardiography (STE)

Two-dimensional (2D) strain represents myocardial deformation from a

2D point of view. STE analysis using the commercially available automated function image technique was applied to apical long axis slices (long axis two chamber and four chamber views) for assessment of LV global longitudinal strain (GLS).

The endocardial borders were traced in the end systolic frame of the 2D images from each of the three apical views (each divided into six conventional segments). Speckles were tracked frame by frame throughout the LV wall until the software automatically approved the tracking for the six segments. Segments that failed to track were adjusted manually by the operator until the software approved them. GLS was calculated as the average longitudinal strain of all six segments for each of the three views (two chamber, four chamber and long-axis, i.e. as the mean strain of all 18 segments), GLS reference values was according to Kocabay et al. (2014).

Statistical analysis:

Data were collected in a master sheet, coded, entered and analyzed using both SPSS version 22 medical statistics software and Microsoft Excel v. 2016.

Quantitative data were expressed as mean ± standard deviation (SD) and range and compared by independent t-test.

Qualitative data were expressed as frequency and parentage range and compared by Chi-square test

One-way ANOVA with post hoc test: Least Significant Difference (LSD) was used for multiple comparisons

Probability (P value): P value of < 0.05 indicated significant results,

RESULTS

There was no statistically significant difference between control and patient groups according to demographic data. **(Table 1**).

Table (1): Comparison between patients and control according to demographic data

Parameters \ Groups	Control (n=30)	Patient (n=70)	p-value
Sex			
Female	16 (53.3%)	39 (55.7%)	>0.05
Male	14 (46.7%)	31 (44.3%)	
Age (years)			
Mean±SD	44.30±7.91	46.44±8.05	>0.05
Range	18-55	30-59	
BMI [wt/(ht)^2]			
Mean±SD	23.57±2.10	24.46±2.40	>0.05
Range	18-29	19-30	
Smoker			
No	18 (60%)	45 (64.3%)	>0.05
Yes	12 (40%)	25 (35.7%)	

There was no statistically significant difference between control and patient groups according to hemodynamic data except for heart rate. **(Table 2**).

Table (2): Comparison between patients and control according to hemodynamic data

Parameters \ Groups	Control (n=30)	Patient (n=70)	p-value
SBP (mmHg)			
Mean±SD	121.00±6.35	123.29±7.84	>0.05
Range	110-130	110-140	
DBP (mmHg)			
Mean±SD	83.33±8.98	81.64±6.85	>0.05
Range	70-100	70-95	
Heart rate			
Mean±SD	61.17±3.90	59.30±4.20	<0.05
Range	68-79	54-70	

There wasa statistically significant difference between control and patient groups according to Hemoglobin A1C. **(Table 3**).

Table (3): Comparison between patients and control according to HBA1C

Parameters \ Groups	Control (n=30)	Patient (n=70)	p-value
HBA1C			
Mean±SD	4.75±0.70	8.62±1.75	<0.001
Range	3.5-6.1	6.5-11.5	

There was no statistically significant difference between control and patient groups according to conventional echo **(Table 4**).

Table (4): Comparison between patients and control according to conventional echo

Groups / Conventional Echo	Control (n=30)	Patient (n=70)	p-value
Aortic Dimensions Mean±SD Range	 28.20±3.53 21-34	 29.51±3.29 23-39	>0.05
LAD Mean±SD Range	 35.57±6.02 26-56	 37.21±3.63 27-42	>0.05
LV EDD Mean±SD Range	 48.81±5.01 40-54.2	 51.01±6.99 40-58	>0.05
LV ESD Mean±SD Range	 31.33±4.83 24-34.9	 33.26±5.25 24-45	>0.05
LVEDV Mean±SD Range	107.70±12.25 80-145	110.23±13.39 94-153	>0.05
LVESV Mean±SD Range	 46.10±8.25 29-57	 43.07±7.57 31-56	>0.05
LVEF Mean±SD Range	 57.51±4.61 50.3-68.2	 59.77±6.62 50-72	>0.05

There was a statistically significant difference between control and patient groups according to speckle. **(Table 5**).

Table (5): Comparison between patients and control according to speckle

Groups / Speckle	**Control (n=30)**	**Patient (n=70)**	**p-value**
AP3% Mean±SD Range	 -20.47±1.57 -23- -17	 -16.54±2.28 -23- -12.5	<0.001
AP2% Mean±SD Range	 -20.37±1.43 -23- -18	 -16.87±5.02 -23- - 20	<0.001
AP4% Mean±SD Range	 -20.83±1.66 -24- -18	 -17.38±2.22 -22- -13	<0.001
LV GLSS% Mean±SD Range	 -20.62±1.31 -23- -18	 -16.92±2.23 -22- -13	<0.001

There was a statistically significant difference between retinopathy positive (+ve) and retinopathy negative (-ve) groups according to disease of duration, HbA1C, insulin use and oral anti diabetic. **(Table 6**).

Table (6): Comparison between patients and control according to Retinopathy +ve and Retinopathy -ve according to disease of duration, HbA1C, insulin use and oral anti diabetic

Fundus exam / Parameters	R+ve (n=43)	R-ve (n=27)	P value
Disease of duration	17.28±3.87	6.93±2.07	<0.001
HbA1C	9.65±1.28	6.99±1.00	<0.001
Insulin use	36 (83.7%)	3 (11.1%)	<0.001
Oral Anti Diabetic	7 (16.3%)	24 (88.9%)	<0.001

There was statistically significant difference between patient (Retinopathy +ve and Retinopathy -ve) and control groups according to speckle. **(Table 7**).

Table (7): Comparison between patients and control according to Retinopathy +ve and Retinopathy -ve and control according to speckle

Fundus Exam / Speckle	Control (n=30)	R+ve (n=43)	R-ve (n=27)	P value
AP3%	-20.47±1.57	-15.24±1.57	-18.59±1.62	<0.001
AP2%	-20.37±1.43	-16.06±1.56	-18.17±7.75	<0.001
AP4%	-20.83±1.66	-16.04±1.52	-19.52±1.25	<0.001
LV GLSS%	-20.62±1.31	-15.57±1.44	-19.07±1.44	<0.001

There was statistically significant decrease mean of retinopathy +ve (proliferative R and non-proliferative R) subgroups compared to control group according to LV GLSS%, while 2D LVEF% insignificant difference. **(Table 8**).

Table (8): Comparison between proliferative R& non proliferative R compared to control group according to LV GLSS%,2D LVEF%

Class of Retinopathy / parameter	Control (n=30)	Proliferative Retinopathy (n=27)	Non proliferative Retinopathy (n=16)	p-value
LV GLSS%	-20.62±1.31	-14.87±1.28a	-16.75±0.75b	<0.001
2D LVEF%	57.51±4.61	58.37±5.77	57.59±4.10	>0.05

a: significant difference with control, b: significant difference with proliferative retinopathy

There was a statistically significant difference between patient retinopathy +ve (proliferative R and non-proliferative R) subgroups according to Disease of duration, HbA1Caccording to Disease of duration, HbA1C, while Insulin use and Oral Anti Diabetic insignificant in patients' group. **(Table 9**).

Table (9): Comparison between proliferative R and non-proliferative R according to Disease of duration, HbA1C, Insulin use, Oral Anti Diabetic

Class of Retinopathy / parameter	Proliferative Retinopathy (n=27)	Non-Proliferative Retinopathy (n=16)	p-value
Disease of duration	18.81±3.53	14.69±2.98	<0.001
HbA1C	10.07±1.24	8.96±1.06	<0.005
Insulin use **Oral Anti Diabetic**	23 (85.2%) 4 (14.8%)	13 (81.3%) 3 (18.8%)	>0.05

DISCUSSION

Our study showed no statistically significant difference between the two groups in terms of Age, sex and smoking. As expected, there was a statistically significant difference in DM and DM retinopathy between the two groups. This is in conformity with the findings of *(Karagöz et al., 2015).*

There was a statistically significant difference between the two groups in terms of Heart Rate. This was confirmatory to *Poanta et al. (2010)* in their study of 58 subjects found that cardiac autonomic neuropathy was associated with LV diastolic dysfunction in patients with type 2 DM, but without clinical manifestation of the heart disease.

Our study found a statistically significant lower global longitudinal strain by 2D speckle tracking in DM group in comparison to the control. This was similar to the findings of *Labombarda et al. (2014)* who found that GLS was significantly lower in the diabetes vs. control group.

On the contrary, *Hensel et al. (2016)* noticed that a paradoxical increase of myocardial performance may occur very early in DM as a sign of impaired mechanical efficiency, this difference could be due to ethnic or geographic differences between the studied group or possibly sample size and the duration of the disease.

There was a statistically significant difference in GLS by 2D STE between the groups with DM retinopathy in comparison with the group with no retinopathy. This finding is similar to *Walraven et al. (2014)* that noticed that there is association between retinopathy and reduced LV EF. Also, it is concordant with *Kurioka et al. (2013)* that concluded that diabetic retinopathy might be associated with LV diastolic dysfunction, development of heart failure, and diabetic cardiomyopathy after that.

However, it is disconcordant with the result of *Karagöz et al. (2015)* that concluded that diabetic patients were found to have lower longitudinal myo¬cardial mechanics compared with healthy control group, unrelated to the presence of retinopathy. This may be due to ethnic or geographic differences among the studied population.

Our study found that the developing of retinopathy is related to the duration of the disease, HbA1C level there was a significant correlation between the presence of retinopathy and duration of the disease& HbA1C level (p value (<0.001,0.005)). It coincides with *Patil et al. (2011)* who concluded that diabetic

patients with retinopathy had higher incidence of LV diastolic dysfunction and it correlated with the duration of diabetes mellitus and HbA1C level in the study subject.

Our study found that the higher grades of retinopathy(proliferative) is associated with higher affection Of LV systolic function assessed by GLS.It is concordant with the result of *Aguilar et al. (2009)* and *Bhargavi (2013)* where parameters of LV systolic function were worsened with increasing severity of retinopathy. It also suggested that retinopathy in an individual with type 2 diabetes mellitus should trigger consideration of further cardiac assessment.

CONCLUSION

The 2D strain method appears to be useful in the detection of LV systolic dysfunction in diabetic patients with diabetic retinopathy. Subclinical left ventricular systolic dysfunction in diabetic patients with diabetic retinopathy is significantly noticed in comparison with those without retinopathy, also, the proliferative retinopathy is associated with markedly affection of LV systolic function comparing with non-proliferative type. Diabetic patients who are detected with retinopathy should also be assessed for asymptomatic cardiac involvement. However, there must be studies with a larger sample size and follow up period to know the natural history of cardiac involvement in diabetic patients and trial studied to detect the benefit for cardiac screening in such individuals, before strong recommendations are suggested.

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إكتشاف الإعتلال الوظيفي للبطين الأيسر في مرضي البول السكري المصحوب بإعتلال الشبكية السكرى بواسطة التتبع النقطي بالموجات فوق الصوتية ثنائية الأبعاد

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خلفيـــة البحـــث: إعـــتلال الشـــبكية هـــو أحـــد مضـــاعفات الأوعيـــة الدمويـــة الدقيقـــة فـــي مرضـــي البـــول الســـكري. وأوضـــحت بعـــض الدراســـات أن إعـــتلال الشـــبكية الســـكري قـــد يـــرتبط بخلـــل وظيفـــي إنبســـاطي بعضـــلة القلـــب و حـــدوث هبـــوط بعضـــلة القلـــب، وإعـــتلال عضلة القلب السكري بعد ذلك.

الهـــدف مـــن البحـــث: الكشـــف عـــن الخلـــل الـــوظيفي الإنقباضـــي للبطـــين الأيســـر عـــن طريـــق تخطـــيط القلـــب ذي التتبـــع النقطـــي ثنـــائي الأبعـــاد للمرضـــى الـــذين يعـــانون مـــن مـــرض البـــول الســـكري المصـــحوب بإعـــتلال الشـــبكية الســـكري و دراســـة مـــدي الإرتباط بين درجة إعتلال الشبكية والخلل الوظيفي الإنقباضي لعضلة القلب.

المرضـــى وطـــرق البحـــث: تضـــمن البحـــث ســـبعين مريضـــا يعـــانون مـــن مـــرض الـــداء الســـكرى، وثلاثـــين شخصـــا آخـــرين كمجموعـــة مقارنـــة ولايعـــانون مـــن مـــرض الـــداء الســـكرى. وقـــد تـــم إجـــراء هـــذا البحـــث فـــى عيـــادة القلـــب بمستشـــفيات جامعـــة الأزهـــر فـــى الفتـــرة مـــن أكتـــوبر 2019 إلـــى ابريـــل 2020، وقـــد تـــم عمـــل تحليـــل الســـكر التراكمـــي لهـــم جميعـــا وعمـــل طريـــق تخطـــيط القلـــب ذي التتبـــع النقطـــي ثنـــائي الأبعـــاد كـــذلك لبيـــان مـــدي الإرتبـــاط بـــين إعـــتلال الشـــبكية الســـكري وخلـــل البطـــين الأيســـر الـــوظيفي الانقباضي.

نتـــائج البحـــث: مقارنـــة بالأصـــحاء تبـــين أن الـــذين يعـــانون مـــن إعـــتلال الشـــبكية بســـبب مـــرض البـــول الســـكري يعـــانون مـــن زيـــادة فـــى معـــدل هبـــوط الوظيفـــة الانقباضـــية للبطين الأيسر وتناسب ذلك طرديا مع زيادة شدة إعتلال الشبكية.

الإســـتنتاج: تخطـــيط القلـــب ثنـــائي الابعـــاد ذي التتبـــع النقطـــي مفيـــد فـــي الكشـــف عـــن الخلـــل الانقباضـــي الـــوظيفي فـــي المرضـــى الـــذين يعـــانون مـــن مـــرض البـــول الســـكري المصـــحوب بـــإعتلال الشـــبكية الســـكري.ويرتبط الخلـــل الانقباضـــي الـــوظيفي البطينـــي الأيســـر فـــي مرضـــى الســـكري الـــذين يعـــانون مـــن إعـــتلال الشـــبكية الســـكري بحقيقـــة أن الـــداء الســـكري يســـبب قصـــور القلـــب حتـــى فـــي غيـــاب مـــرض الشـــريان التـــاجي، ويعتبـــر إعتلال الشـــبكية أحـــد مضـــاعفات الأوعيـــة الدمويـــة الدقيقـــة. ويشـــير وجـــود إعـــتلال الشـــبكية الســـكري إلـــى وجـــود خطـــر زائـــد مـــن هبـــوط الوظيفـــة القلبيـــة وبغـــض النظـــر عـــن عوامـــل الخطـــر المعروفـــة. واتضـــحت محـــددات هبـــوط الوظيفـــة الانقباضـــية للبطين الأيسر مع زيادة شدة إعتلال الشبكية.