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Original Article

Assessment of Left Ventricular Systolic Function by Speckle Tracking in Diabetic Patients Receiving Direct Acting Antiviral Drugs for Chronic HCV

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ABSTRACT

Background: Diabetes mellitus [DM] is a well-known risk factor for cardiovascular disease. The co-existence of DM and microvascular abnormalities could lead to hypertrophy of left ventricle [LV] with diastolic and/or systolic dysfunction. However, early stages of the disease are asymptomatic due to its chronic nature and the effective control of diabetes.

Aim of the Work: This clinical cohort aimed to assess left ventricular systolic function in DM patients, receiving direct acting antiviral [DAA] drugs for chronic hepatitis-C virus by speckle tracking.

Patients and Methods: This clinical cohort included 90 patients who were divided into three equal groups. Patients were recruited from Hepatology Outpatient Clinic of Kafr El-Shaikh University hospital, who were sent to the cardiovascular department for evaluation. Patients were evaluated just before, one month and three months after starting therapy.

Result: No one in control group had diastolic dysfunction compared to 10.0% and 16.7% in DAAs and Non-DAAs groups, respectively. Conventional echocardiography returned statistically non-significant difference except significant increase of LVESD, IVST and LVPWT in study groups than control groups. However, the difference between DAAs and Non-DAAs groups was statistically non-significant. The basic strain parameters returned significant lower values at different windows in control than study groups. The strains were reduced in the follow up visits [first and third months] in DAAs groups, but not significantly reduced in non-DAAs group. Acute myocardial infarction was reported among one patient in non-DAAs group compared to none in DAAs group.

Conclusion: The speckle tracking is a useful tool for early detection of subclinical left ventricular dysfunction in HCV diabetic patients and could be used for following up of response DAA treatment. DAAs therapy is associated with improvement, not of HCV disease, but also of cardiac dysfunction.

Keywords: Diabetes Mellitus; Left Ventricle; Hepatitis C Virus; Echocardiography; Direct anti-viral drugs

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Diabetes mellitus [DM] is a well-known risk factor for cardiovascular diseases. The coexistence of DM and microvascular changes could lead to hypertrophy of the left ventricle [LV] and diastolic or systolic dysfunction. However, in the early duration of the disease, the patient is usually asymptomatic due to chronic nature of DM, especially if associated with strict control. Echocardiography could detect non-specific abnormalities of the left ventricle function. However, conventional echocardiography usually does not recognize subclinical changes [1].

Chronic hepatitis C virus [HCV] infection is a common infection worldwide, as it affects > 3% of total populations. It could be associated with or lead to a significant complication such as liver cirrhosis or hepatocellular carcinoma [2].

In addition, HCV infection is endemic in Egypt, with the highest prevalence rate in all over the world. In 2015, a National Egyptian survey was completed, and the prevalence of HCV was 7.0% in populations aged 15-59 years [3].

The treatment of HCV included peg interferon-alfa and ribavirin [RBV]. However, its efficacy is limited and associated with higher rate of side effects. New drugs included direct acting antivirals [DAAs] drugs with higher efficacy and safety profile especially on the myocardium [4].

DAAs target specific non-structural proteins of the hepatitis-C virus and so, lead to interruption of viral replication and thus eradicate infection. DAAs composed of various categories according to their therapeutic target and mechanism of action. The first is nonstructural proteins 3/4A [NS3/4A] protease inhibitors [PIs] [e.g., Glecaprevir, Paritaprevir, Voxilaprevir, Galexos, Grazoprevir, and Sunvepra]. The second is Nucleoside and Nucleotide NS5B polymerase inhibitors [NPIs] [e.g., Sofosbuvir]. The third is NS5B non-nucleoside polymerase inhibitors [NNPIs] [e.g., Dasabuvir], and the fourth is NS5A inhibitors [e.g., Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, Velpatasvir Ombitasvir, and Pibrentasvir] [5].

The potential cardiac side effects of DAAs in a retrospective study of 34 patients were cardiac dysfunction among 14 patients [41.2%]; six patients had reduced [<30.0%] left ventricle ejection fraction, and eight had LVEF 30–50%; 11 patients need hospitalization. These side effects lead to clinical withdrawal of BMS-986094 [6].

For accurate assessment of global and regional myocardial deformation, the speckle tracking echocardiography [STE] had been emerged as an accurate technique on the quantitative basis [7, 8].

STE assessment of myocardial deformation allows the identification of subclinical left ventricular dysfunction in diseases appeared normal by conventional echocardiography [9].

The rationale of the current work based on the above truth, where speckle tracking could be used to elucidate the subclinical myocardial dysfunction. This allows early intervention and prevention of development of clinical cardiac dysfunction. This protects our patients, improve their quality of life, and reduce the total healthcare cost.

THE AIM OF THE WORK

This study aimed to evaluate the role of speckle tracking in assessment of left ventricular systolic function in diabetic patients, receiving direct acting antiviral [DAA] drugs for chronic hepatitis-C virus infection.

PATIENTS AND METHODS

The current study was designed as an observational, prospective, clinical trial that included 90 patients who were divided into three equal groups [each group composed of 30 patients].

The first group included 30 healthy persons as a control group. The second group included 30 diabetic patients with chronic HCV who received direct acting antiviral drugs. The third group was 30 diabetic patients with chronic HCV with no antiviral treatment [they refused administration of any antiviral drugs and just accepted tonics and liver support].

All patients were recruited from Hepatology Outpatient Clinic of Kafr El-Shaikh University hospital who referred to cardiovascular department of the same hospital for evaluation. The inclusion criteria were adult diabetic patients with chronic hepatitis C virus [HCV] starting direct acting antivirals [DAA] for the first time. On the other side, the exclusion criteria were cardiomyopathy, myocardial infarction within the last three months, and relapse of earlier antiviral therapy.

Ethical considerations:

The study protocol was approved by the local research and ethics committee of Kafr El Shaikh Faculty of Medicine, and an informed consent was signed by every patient. Patient's rights to withdraw at any time without any harm were guaranteed; and the study had been completed

according to research ethics code declared at Helsinki.

Patients were evaluated just before inclusion, at one and three months after starting therapy by the following: full medical history stressing on cardiac symptoms, full clinical examination, and Investigations [Electrocardiography, Conventional two-dimensional and M-Mode Echocardiography-Doppler and Speckle tracking]. The standard 12 leads ECG was done for all patients and controls to detect cardiac rhythm, chamber enlargement and to exclude ischemic changes. The conventional, tissue Doppler and two-dimensional speckle tracking echocardiography were performed using S5-1 probe of Philips Epic 7c machine.

All echocardiographic examinations were performed according to the recommendations of American Society of Echocardiography [ASE] and European Association of Cardiovascular Imaging [EACVI].

By conventional echocardiography, left ventricular diameters and wall thicknesses were measured in the left parasternal long axis view at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. On the remote side, the speckle tracking is an offline technique that applied to previously acquired 2D images. Longitudinal strain was measured using software on 2D gray-scale images of LV from standard apical four-chamber, two-chamber and three-chamber views. The peak systolic [PS] global longitudinal strain [GLS] was calculated as the average of the LS of the 17 LV segments obtained from 4-CH, 2-CH, and 3-CH views. Global longitudinal Strain [GLS] was used to detect subclinical left ventricular systolic dysfunction.

Statistical analysis:

Data collected from history, clinical examination, laboratory investigations and outcome measures were coded, entered, and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences [SPSS version 20.0] [IBM®SPSS® Inc., Chicago, Illinois, USA] software for analysis. According to the type of data, qualitative data were represented as frequencies and percentages. However, quantitative continues data were represented by mean \pm standard deviation [SD]. The following tests were used to test differences or associations for significance; Chi square test [X²] for qualitative data and independent groups by one way analysis of variance with post-Hoc least significant differences [LSD] for comparison between two

groups and paired by paired [t] test and repeated ANOVA for comparison over time.

RESULTS

In the current work, studied groups were comparable regarding patient's age and gender. The mean age was 54.6 ± 7.6 , 53.63 ± 6.8 and 53.13 ± 7.5 years in control, DAAs and non-DAAs groups, respectively. Males represented 53.3%, 63.3% and 53.3% of control, DAAs and non-DAAs groups, respectively [Table 1].

The diastolic dysfunction did not differ significantly between studied groups. The diastolic dysfunction was absent in control group, 10% in non-DAAs group and 16.7% in DAAs group. However, it was indeterminate in 0.0%, 6.7% and 10.0% in control, non-DAAs and DAAs groups, respectively. Otherwise, it was normal among 100.0%, 83.3% and 73.3% in control, non-DAAs and DAAs groups, respectively.

Regarding conventional echocardiography, studied groups showed statistically non-significant difference except significant increase of LVESD, IVST and LVPWT in study groups when compared to control group. However, the difference between DAAs and Non-DAAs groups was statistically non-significant. On the other side, each of septal e' and lateral e' were significantly higher among control than study groups. However, average E/e' and LAVI was significantly lower in control than study groups [Table 2].

Regarding strain parameters in the first visit, there was significant difference between study and control groups in the values at A4C, A3C, A2C and global longitudinal strain [GLS]. The control group had the lower values, then DAAs and Non-DAAs groups, respectively [Table 3].

At the first visit [one month after treatment], speckle tracking strains were significantly lower among DAAs than non-DAAs group. The comparable situation was reported at three months [Table 4]. In DAAs group, there was no significant change in strain values from the first to the third visit. However, in non-DAAs group, the A4C, A3C and GLS significantly changed at the third visit when compared to the corresponding values at the first visit [Table 5].

Regarding MI, there were no cases of MI in normal and DAAs groups. However, there was one patient [3.3%] of non-DAAs group. There was no significant difference between studied groups [$p=0.36$].

Table [1]: Comparison between groups, about patient age and gender

		Control [n=30]	DAAs [n=30]	Non- DAAs [n=30]	P
Age		54.6±7.6	53.63±6.8	53.13±7.5	0.734
Sex	Female	14 [46.7%]	11 [36.7%]	14 [46.7%]	0.66
	Male	16 [53.3%]	19 [63.3%]	16 [53.3%]	

Table [2]: Comparison between groups, about conventional echocardiography, and diastolic function parameters

		Control [n=30]	Diabetic group		P
			DAAs [n=30]	Non-DAAs [n=30]	
Conventional Echocardiography parameters	LVEDD [cm]	4.66±0.39	4.92±0.48	4.84±0.36	0.053
	LVESD [cm]	2.86±0.29#	3.11±0.35	3.05±0.32	0.014*
	EF [%]	68.36±3.5	66.06±4.6	67.96±4.6	0.094
	FS [%]	37.53±3.05	35.96±3.8	37.4±4.39	0.212
	IVST [cm]	0.96±0.12#	1.02±0.09	1.02±0.08	0.036*
	LVPWT [cm]	0.97±0.11#	1.02±0.08	1.03±0.07	0.040*
Diastolic Function parameters	E wave	82.9±12.4	84.9±16.3	77.91±21.6	0.273
	A wave	67.67±11.3	67.59±13.01	74.46±13.2	0.057
	E/A ratio	1.26±0.3	1.32±0.4	1.11±0.35	0.120
	Septal e'	10.26±1.9&	8.22±1.77	8.49±1.7	<0.001*
	Lateral e'	12.99±3.12&	11.05±2.16	11.08±1.67	0.002*
	Aver E/e'	7.12±0.98#	9.11±1.75	8.08±2.5	<0.001*
	TR velocity	2.33±0.24	2.2±0.3	2.28±0.36	0.290
	LAVI	27.64±3.7#	29.6±2.3	31.42±1.9	<0.001*

LVEDD: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic volume, EF: ejection fraction, FS: fraction shortening, IVST: interventricular septal thickness, LVPWT, left ventricle posterior wall thickness, TR: Tricuspid, LAVI; Left atrial maximum volume index; *: significant difference between groups; #: significant decrease in control when compared to DAAs or non-DAAs groups.

Table [3]: Comparison between strain parameters among groups at the first visit

	Control group	Diabetic patients		P
		DAAs [n=30]	Non-DAAs [n=30]	
A4C	-20.93±1.3	-20.06±1.2	-18.56±1.2	<0.001*
A3C	-20.52±1.2	-19.86±1.23	-18.42±1.4	<0.001*
A2C	-21.28±1.5	-19.6±1.01	-18.74±1.2	<0.001*
GLS	-20.91±1.2	-19.8±0.99	-18.55±1.1	<0.001*

Table [4]: Shows comparison between DAAs and non-DAAs groups

		DAAs [n=30]	Non DAAs [n=30]	P
		At one month	A4C	
	A3C	-19.9±1.12	-17.96±1.25	<0.001*
	A2C	-19.6±0.9	-18.67±1.25	0.002*
	GLS	-19.84±0.91	-18.26±0.99	<0.001*
At three months	A4C	-20.02±1.26	-17.78±1.5	<0.001*
	A3C	-19.8±1.18	-17.68±1.6	<0.001*
	A2C	-19.5±0.82	-18.39±1.67	0.002*
	GLS	-19.77±0.94	-17.91±1.42	<0.001*

Table [5] Comparison between strain results before and after antiviral treatment in DAAs and non-DAAs groups.

Group		First visit		Third visit		test	p
DAAs	A4C	-20.06	1.26	-20.02	1.26	-0.51	0.608
	A3C	-19.86	1.23	-19.80	1.18	-0.81	0.423
	A2C	-19.60	1.01	-19.50	.82	-0.86	0.392
	GLS	-19.84	.99	-19.77	.94	-1.07	0.294
Non-DAAs	A4C	-18.56	1.28	-17.78	1.54	-4.096	<0.001*
	A3C	-18.42	1.46	-17.68	1.63	-3.55	0.001*
	A2C	-18.74	1.19	-18.39	1.67	-1.47	0.15
	GLS	-18.55	1.15	-17.91	1.42	-3.63	0.001**

DISCUSSION

The current work aimed to assess left ventricular systolic function in diabetic patients receiving direct acting antiviral [DAA] treatment for chronic HCV by conventional and two-dimensional speckle tracking echocardiography, for early detection of subclinical left ventricular systolic dysfunction in this group of patients before overt clinical diabetic cardiomyopathy ensues.

In our study, diabetic patients had lower significant values of longitudinal strain parameters [AP4C LS, AP2C LS, AP3C LS, GLS] than control group. These results agree with Perticone *et al.* [10] who reported that, HCV, normotensive patients when compared to healthy control have a significant echocardiographic changes and increased cardiac mass. These changes could add to explanation of pathogenic mechanisms of cardiovascular morbidity associated with chronic hepatitis C infection.

There is available evidence that, left ventricular hypertrophy is a powerful predictor of comorbid cardiovascular events, in general populations and in different chronic clinical diseases [11]. Insulin resistance plays a participating role in the development of left ventricular hypertrophy [12]. Earlier studies also revealed that, HCV infection is associated with the development of insulin resistance, through direct interaction between viral products and different signaling pathways of insulin [13, 14]. The eradication of HCV infection induced a significant reduction of insulin resistance and could prevent the development of type-2 diabetes [15, 16]. Early detection of associated cardiovascular abnormalities in HCV infection associated with type-2 diabetes mellitus is crucial for patients' outcome. The concomitant presence of both conditions adds to the risk of morbidity and mortality. In addition, the eradication of HCV infection reduced both the risks of insulin resistance and cardiovascular morbidity. Thus, early initiation of anti-viral therapy is of utmost importance. Additionally, Iorga *et al.* [17] reported that, although chronic HCV infection significantly increased the risk to the development of T2D, the prediction to develop T2D is still under investigation

The echocardiographic results of the current study showed both HCV-diabetic groups at inclusion in the study. However, control group had significantly lower left ventricle end systolic diameter, lower thickness of interventricular septum and posterior wall thickness of the left ventricle. Otherwise, no difference was elicited about end diastolic volume, ejection fraction and fraction shortening. Additionally, six out of eight diastolic function parameters

returned non-significant difference between diabetics and healthy controls. On the contrary, the strain parameters by speckle tracking revealed significant changes in diabetic than healthy controls. Additionally, after 3 months treatment regimens, strain parameters revealed significant improvement in DAAs than non-DAAs groups. These results reflected the ability of speckle tracking to detect LV abnormalities and to follow up the response of treatment. Finally, only one patient developed acute coronary syndrome in non-DAAs group, reflecting high safety profile of DAAs.

The idea after speckle tracking based on its ability to measure the displacement of speckles on the two-dimensional images, measures the deformation of the myocardium rather than its volumetric change measured by traditional LVEF determination methods [18]. Potter and Marwick [19] assessed the left ventricular function by echocardiography, included global longitudinal strain, and appreciated its role in the early detection of diastolic or systolic dysfunction. In addition, the early detection of LVD before the onset of cardiac symptoms enables the proper use of drugs at a point, which may slow or prevent disease progression. Adinolfi *et al.* [20] showed that, the risk of cardiovascular incidents [e.g., acute coronary syndrome or TIA] were significantly reduced by DAAs treatment were decreased and annual incidence of HCV was highly reduced. They added DAAs are characterized by a favorable safety profile. Biomy *et al.* [21] confirmed the safety of DAAs in an Egyptian study, where DAAs therapy did not cause any change in QTc interval, in patients with or without liver cirrhosis. Another later study from Egypt confirmed such safety profile [22]. Roguljic *et al.* [23] returned the reduction of cardiovascular risk to an improvement of endothelial function and glucose metabolism. Ibrahim *et al.* [22] concluded that, HCV infection treatment with DAAs used in Egyptians has a good cardiac safety profile. It had no effect on QTc interval, left or right ventricular functions except for a reduction in right ventricle GLS in those with no liver cirrhosis.

On the extreme side, Farrag *et al.* [24] reported cardiotoxic effects of DAAs on the myocardium, in both patients with normal and impaired basic ejection fraction. However, they included 100 patients with impaired and only 20 patients with normal basic ejection fraction. They did not find significant difference when stratifying their patients according to their gender, different chronic disease states [e.g., hypertension, diabetes, ischemic heart disease, and established cardiac medications]. This heterogeneity in their study design could explain the contradictory nature of their results in comparison to the current one.

Conclusion: Diabetes mellitus could be considered as a latent, independent risk factor for cardiac dysfunction, which may progress to heart failure. HCV infection is a systemic disease with extra-hepatic manifestations, which could be detected before the diagnosis of HCV itself. Diabetic groups had significant lower global strain than control group. The speckle tracking is a useful tool for early detection of subclinical left ventricular dysfunction in HCV diabetic patients and could be used for following up of response DAA treatment. DAAs therapy is associated with improvement, not of HCV disease, but also of cardiac dysfunction.

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International Journal

The background of the cover is a light blue gradient. It features a faint, semi-transparent ECG (heart rate) line running across the top and bottom. In the center, there is a globe of the Earth, and a stethoscope is draped over it, with its chest piece on the left and its ear pieces on the right. The overall theme is medical and global.

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