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Evaluation of Left Atrial Functions in Diabetic Patients with Coronary Artery Disease: Strain Imaging Study

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Abstract: Background: Diabetes mellitus (DM) and coronary artery disease (CAD) have intimate relationship, which is the most common reason of morbidity and death in diabetic participants. Left ventricular (LV) dysfunction in diabetic participants with CAD was investigated by speckle-tracking echocardiography (STE). However, LA function in participants with CAD has not been evaluated with this technique. Objective: To assess left atrial (LA) functions by STE in diabetic patients with coronary artery disease (CAD). Methods: In 50 participants with CAD, two-dimensional strain echocardiographic imaging was done to asses LA function. A control group of twenty healthy people was included. The procedure included both conventional echocardiography and STE. Peak atrial contraction strain (PACS) and peak atrial longitudinal strain (PALS) were measured as strain parameters. Results: PALS and PACS strain were significantly decreased among patient group than control group (18.46±6.41 versus 52.07±7.8%, $P < 0.001$ and 9.92±7.74 versus 20.03±1.35%, $P < 0.001$ respectively). Conclusion: LA strain Parameters is impaired in diabetic patients in comparison with control in spite of normal LV function.

Keywords: Diabetic Patients, Coronary Artery Disease, Left Atrial Functions

1. Introduction

The prevalence of diabetes is advanced and has rapidly considered one of the major common and expensive chronic diseases world-wide in 2010 and that the figure may rise to 7.7% by 2030 [1]. Assessment presented that 6.4% of the global affected by DM [2]. Diabetes affects numerous physiological systems, including the cardiovascular system, with cardiovascular disease becoming the leading cause of death in diabetics. For example, the risk of death from coronary artery disease (CAD) is two to four times higher in diabetics than in non-diabetic people [3]. Cardiovascular disease is the leading cause of morbidity and mortality in diabetic people (CVD). Factors that raise the risk of cardiovascular disease (CVD) include being overweight, having high blood pressure, and having dyslipidemia. Participants with diabetes are at an increased risk of having a heart attack or stroke. Additionally, there are biological ways linked with DM that elevate risks of CVD in diabetic participants include: oxidative stress, increased coagulates endothelial dysfunction and autonomic neuropathy [4]. When compared to euglycemic control individuals with CAD and CAD individuals with regulated diabetes, LA functions were reduced in CAD individuals with non-controlled diabetes. [5]. In diabetic patients, LA expansion on echocardiography has previously been described. [6]. DM is a predisposing factor for atrial fibrillation (AF), and hyperglycemia is linked to AF through numerous ways. [7]. Speckle-track echocardiography (STE) is a novel non-invasive ultrasound imaging technology that enables the determination of global and regional function of myocardium independent of insonation angle and heart translational movements [8]. However, the STE approach was originally developed for the unique purpose of assessing LV function, numerous subsequent studies have shown that it can also be used to assess other cardiac chambers, like the LA [9]. The atrial longitudinal strain, which is derived through the application of STE to analyze myocardial deformation in atrial chambers, is the primary variable relevant for functional investigation of the LA, and it has a high level of reproducibility and feasibility [10]. Therefore,

we performed a cross section study to determine LA functions, by STE in diabetic individuals with CAD.

2. Patients and Methods

A cross section study was conducted on 70 subjects at Menoufia University Hospital, and they were divided into two groups: the first group included 50 diabetic participants with CAD diagnosed by coronary angiography, and the second group included 50 non-diabetic participants with CAD diagnosed by coronary angiography (CA). The second group consisted of 20 healthy volunteers of similar age and sex who served as a control group. All participants were admitted after a thorough history and physical examination, and samples were collected predominantly between October 2020 and August 2021.

2.1. Ethical Consideration

After describing the study's purpose, patients signed a written informed consent form. All methods were carried out in accordance with the ethical guidelines set forth by the institutional research committee. The Medical Research Ethics Committee of Menoufia University's Faculty of Medicine approved the study. Patients having an LVEF of less than 50%, AF, chronic liver disease, chronic kidney illness, restrictive and hypertrophic cardiomyopathy, and restrictive and hypertrophic cardiomyopathy were all excluded from the study.

2.2. Methods

All selected participants involved in this trial underwent to full data taking involving age, gender, smoking, height, weight, and BMI, also, clinical examination and laboratory investigation involving serum glycosylated hemoglobin (HbA1c) and lipid profile (total cholesterol, TG, LDL, HDL).

2.2.1. Standard 12-lead Electrocardiogram

A twelve-lead ECG was conducted on all participants using a MAC 3500 resting ECG analysis equipment (GE Healthcare, Milwaukee, WI, USA) with a paper speed of 25 mm/s and a 1 mm/mv standardization.

2.2.2. Coronary Angiography

All individuals of group I underwent cardiac catheterization for CA. Usual views of CA were taken. Coronary angiograms were saved on DICOM-formatted compact CDs. Significant coronary lesions were identified by appearance of stenosis of ≥ 50% diameter decrease.

2.2.3. Resting Echocardiography

The individuals underwent a transthoracic echocardiogram (VIVID E9 machine; GE Healthcare, Chicago, IL, USA). Following the traditional parasternal and apical imaging views, the mean of three successive heartbeats was evaluated. As usual, measurements in 2D and M-mode were taken. The left ventricular ejection fraction was measured using the biplane discs approach (the modified Simpson's rule) (LVEF). Both 2D and conventional Doppler variables were recorded according to the American Society of Echocardiography's recommendations [11]. The biplane area-length approach was used to determine the LA volume in apical four and two chamber views at end systole (LAV). By dividing LAV by body surface area, the left atrial volume index (LAVI) was obtained. LAVI of less than 34 ml/m2 was considered excessive. The American Society of Echocardiography's recommendations were followed for registering all of the 2D and standard Doppler variables [12]. Doppler echocardiography was used to measure trans-mitral early diastolic velocity (E-wave), late diastolic velocity (A-wave), E/A ratio, and deceleration duration in the apical four chamber sight. A pulsed-wave tissue Doppler velocity study was performed on apical images captured at > 100 frames per second. The peak early diastolic velocity (e') was measured using a 2-mm pulsed Doppler sample inserted in the lateral and septal mitral annuli. E/e' was determined.

2.2.4. Speckle Tracking Echocardiography

Longitudinal strain and strain rate acquisition images: Apical four and two chamber views were obtained using traditional 2D grey scale echocardiography with ECG monitoring. Three consecutive cardiac cycles were recorded and averaged, with frame rates ranging from 60 to 80 frames per second.

2.2.5. Left Atrium Strain

The surface of the endocardium of every LA wall, septal, lateral wall (A4C view), anterior and inferior walls (A2C view) was manually traced using a point-and-click approach, and the surface of epicardium was then automatically created by the computer. After manual tracing, the software automatically divides each wall into three halves (basal, mid, and apical). The LA fills up during the reservoir phase, extends itself, increasing atrial strain, and reaches a positive peak near the conclusion of atrial filling before the mitral valve opens; this peak is referred to as peak atrial longitudinal strain (PALS). The LA quickly empties and shortens after the mitral valve is opened. According to the diastasis phase, the strain decreased to a plateau after a second positive peak, but one that was lower than the first, in the period preceding atrial contraction. Peak atrial contraction strain (PACS) is the name given to the second peak, which occurs right before the P wave on the surface ECG. Finally, after the contraction of the atrium, there is a negative peak (Post A, which occurs after the P wave on the surface ECG). In each LA wall, the contraction LA systolic index (CSI) was determined using the equation CSI=(PALS/PACS) *100. [11-13] (Figures 1-2).

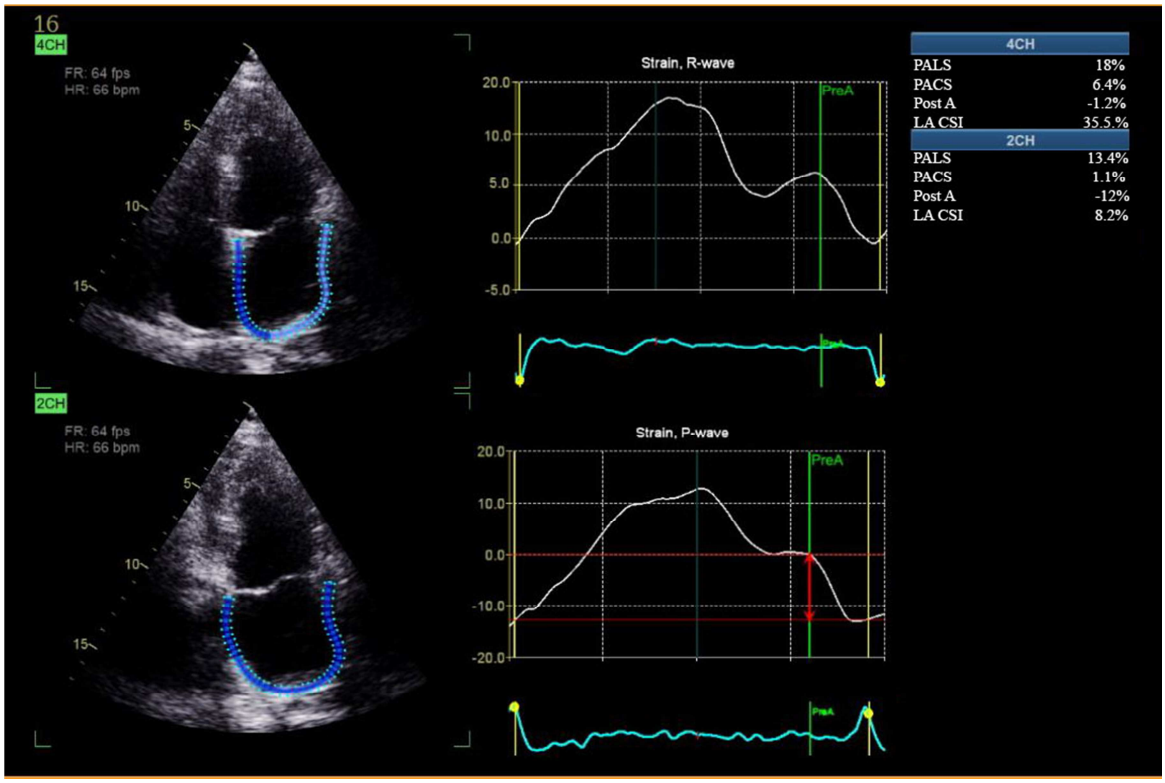

Figure 1. *Apical 4 chamber view, Apical 2 chamber view shows strain curve and strain numeric values walls of LA in a diabetic patient with CAD. A cardiac cycle is tracked, the septal, lateral, inferior wall of LA is divided into 3 segments (basal, mid and apical) that are color coded, and strain curve is obtained. (PALS) in 4CH and 2CH views are 18% and 13.4% respectively, and PACS in 4CH and 2CH views are 6.4% and 1.1% respectively. The post-A which is the peak negative value after atrial contraction is -1.2 and -12% in 4CH and 2CH respectively.*

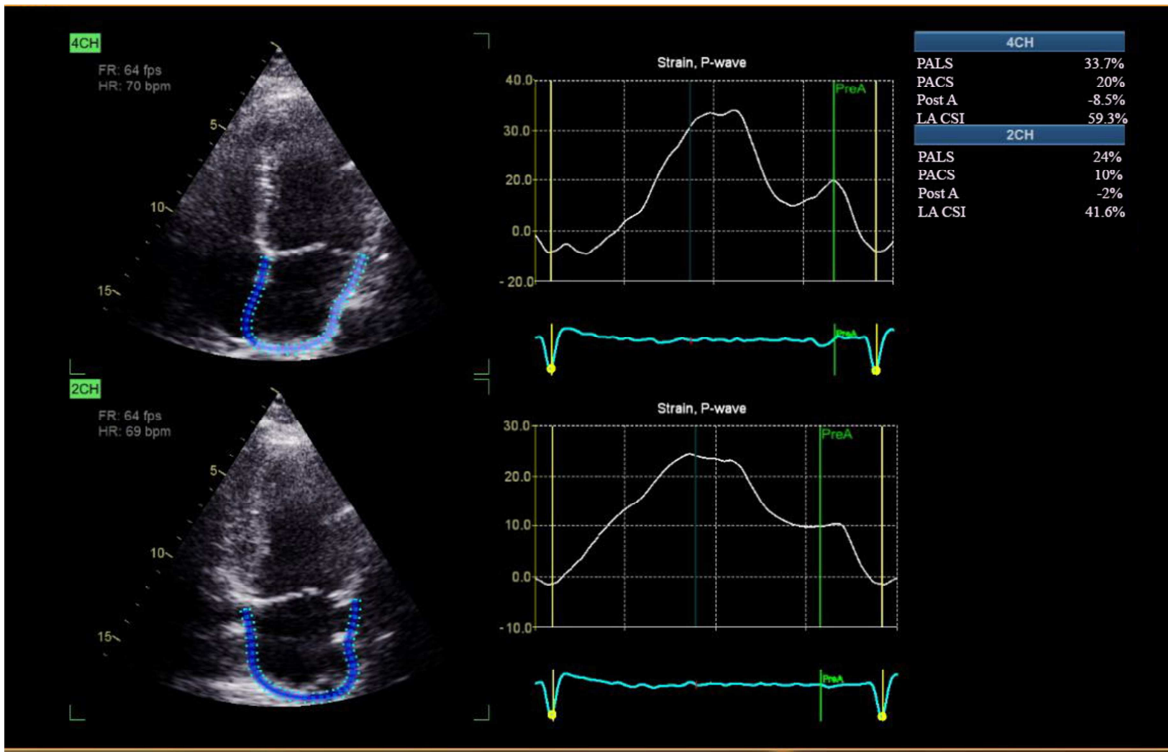

Figure 2. *Apical 4 chamber view, Apical 2 chamber view shows strain curve and strain numeric values walls of LA in a healthy subjects. A cardiac cycle is tracked, the septal, lateral, inferior walls of LA are divided into 3 segments (basal, mid and apical) that are color coded, and strain curve is obtained. PALS in 4CH and 2CH views are 33.7% and 24% respectively, and (PACS) in 4CH and 2CH views are 20% and 10% respectively. The post-A which is the peak negative value after atrial contraction is -8.5 and -2% in 4CH and 2CH respectively.*

2.3. Statistical Analysis

Using IBM personal computer and statistical application SPSS version 22 (Armonk, NY: IBM Corp, 2013), data were collected, arranged, and statistically analyzed. Percentage (%), mean (x), and standard deviation (SD) were descriptive statistics, whereas chi-square test ($\chi 2$), Student t test (t), Mann-Whitney test, and Spearman's correlation (r) were analytic statistics. A two tailed P value < 0.05 was considered statistically significant.

3. Results

Smoking and diabetes types were significantly higher between both groups. BMI, HbA1C%, triglycerides, and LDL were significantly increased among the participants' group than the control group ($p < 0.05$). (Table 1)

LA diameter, mitral A and E/e' ratio were significantly increased in patients' group than the control group. While, Average GLS, mitral E/A ratio and mitral E average were significantly decreased among participant group than control group ($p < 0.05$). There were insignificantly different between the studied groups according to LVEF ($p > 0.05$) (Table 2).

PALS %, PACS%, post A %, septal E and lateral E were significantly increased in control group (52.07±7.08, 20.03±1.35, 1.60±1.35, 11.47±2.17 and 13.73±2.15) respectively than patient group ($p < 0.05$). Also, there was an insignificantly difference between the studied groups regarding LA.CSI % ($p > 0.05$) (Table 3).

A significant positive correlation between PALS with HbA1c%, e' (septal, lateral, and average), while there was a significant negative correlation between PALS with LVEF%, E/e' Ratio, and LA volume index ($P < 0.05$). Also, there was a significant positive correlation between PACS with mitral E and A ratio, mitral e' lateral (cm/s), PALS, and LA CSI. While a significant negative correlation between PACS with HbA1c% and LAVI ($P < 0.05$) (Table 4).

Table 1. *Demographic, clinical and laboratory data among the studied groups.*

Variables	Control (N=20)	Patients (N=50)	Test of significance	p value
Age (year)				
Mean ± SD	38.73±4.65	53.19±9.23	t=7.469	< 0.001*
Rang	25-45	35-70		
Gender			X^2=0.627	
Male (N %)	17 (85%)	40 (80%)	0.236	
Female (N %)	3 (15%)	10 (20%)		
Smoking (N %)				
Non-smoker (N %)	13 (65%)	27 (54%)	X^2=0.706	0.401
Smoker (N %)	7 (35%)	23 (46%)		
HTN (N %)	7 (35%)	31 (62%)	X^2=4.197	0.041*
BMI (kg/m^2)				
Mean ± SD	24.73±2.8	25.39±3.48	t=0.718	0.478
Rang	20.83-30.89	19.03-33.22		
HR				
Mean ± SD	83.27±8.84	79.46±12.93	t=1.221	0.230
Rang	70-95	59-105		
HbA1C%				
Mean ± SD	5.26±0.14	4.20±3.78	U=1.697	0.098
Rang	5.00-5.50	0.08-11.00		
Total Cholesterol				
Mean ± SD	215.93±23.34	246±45.55	U=3.128	0.003*
Rang	180-250	143 -412		
Triglycerides				
Mean ± SD	157.4±58.1	238.32±85.75	t=3.931	< 0.001*
Rang	98-310	149 -412		
LDL				
Mean ± SD	118.4±23.27	168.72±31.37	t=6.355	< 0.001*
Rang	90-159	90.00-218		
HDL				
Mean ± SD	50.73±8.04	46.65±9.55	t=1.569	0.127
Rang	37-67	32-75		

DM: Diabetic mellitus, CAD: Coronary Artery Disease, t: Independent t test, BMI: Body mass index HR: Heart rate t: Independent t test, X^2: Chi-square test, HbA1c: Hemoglobin A1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein, X^2: Chi-square test, U: Mann-Whitney U test, CI: Confidence interval, *significant

Table 2. *Conventional echocardiographic parameters among the studied groups.*

Variables	Control (N=20)	Patients (N=50)	p value
Aortic Diameter (cm)			
Mean ± SD	2.83±0.42	2.92±0.34	0.444
Rang	1.8-3.3	2.2-3.7	
LA Diameter (cm)			
Mean ± SD	3.33±0.51	4.3±0.51	< 0.001*
Rang	2.3-4	3.3-5.3	
LA volume indexes			
Mean ± SD	25±2.88	31.73±4.6	< 0.001*
Rang	21-33	22-38	
LVEDD (cm)			
Mean ± SD	5.05±0.44	5.26±0.49	0.145
Rang	4.2-5.8	4.3-6.5	
LVESD (cm)			
Mean ± SD	3.59±0.31	3.43±0.35	0.115
Rang	2.9-4	2.6-4.1	
LVEDV (ml)			
Mean ± SD	95.33±13.71	98.81±12.94	0.408
Rang	70-118	78-126	
LVESV (ml)			
Mean ± SD	37.67±6.3	37.78±6.65	0.953
Rang	28-46	22-54	
LVEF (%)			
Mean ± SD	58.93±4.7	59.65±4.79	0.625
Rang	54-70	52-68	
Mitral E (cm)			
Mean ± SD	74.60±15.05	66.78±13.05	0.092
Rang	52-102	47-92	
Mitral A (cm)			
Mean ± SD	48.27±8.5	56.57±13.18	0.010*
Rang	33-6	35-87	
Mitral E/A ratio			
Mean ± SD	1.51±0.27	1.24±0.48	0.013*
Rang	1-2.1	0.7-2.4	
E (m/s) Average			
Mean ± SD	12.37±2.14	9.2±2.2	< 0.001*
Rang	9-15.5	6-15.5	
E/e' m Ratio			
Mean ± SD	5.86±0.98	7.49±1.82	< 0.001*
Rang	4.2-7.3	4.2-11.8	

LVEDD: LV end diastolic dimension, LVESD: Left ventricular end-diastolic and end-systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: Left Ventricular End Systolic Volume. LVEF: left ventricular ejection fraction GLS: Global Longitudinal Strain E: early trans-mitral flow velocity A: atrial trans-mitral flow velocity, E: Early trans-mitral flow velocity, A: Atrial trans-mitral flow velocity CI: Confidence interval, t: Independent t test, U: Mann-Whitney U test *significant.

Table 3. *Strain parameters of LA walls in the studied groups.*

Variables	Control (N=20)	Patient (N=50)	p value
PALS%			
Mean ± SD	52.07±7.08	18.46±6.41	< 0.001*
Rang	20-68	5-33	
PACS%			
Mean ± SD	20.03±1.35	9.92±7.74	< 0.001*
Rang	18-22.1	1-31	
Post A%			
Mean ± SD	1.6±1.35	0.47±0.15	0.006*
Rang	1-6	0.2-0.8	
LA.CSI%			
Mean ± SD	37.82±4.15	48.65±32.05	0.051
Rang	29.2-43.4	4.5-99	
Average GLS (%)			
Mean ± SD	19.52±2.02	16.86±1.68	< 0.001*
Rang	15.-23	14.00-21.6	

PALS**:** Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, Post A: refer to LA longitudinal strain at end of atrial contraction, CSI: Contraction systolic index, representing, in percentual values, the contribution of the LA active contraction to the LV filling phase, E: Early trans-mitral flow velocity, CI: Confidence interval.

Table 4. *Correlation between PALS and PACS with all studied parameters among patients' group.*

Variable	PALS		PACS	
	R	P value	r	P value
Age	0.244	0.145	0.265	0.113
BMI	-0.435	0.007*	-0.197	0.243
HR	0.068	0.691	0.037	0.826
HbA1c%	-0.501	0.036*	-0.614	0.001*
Total Cholesterol	0.014	0.933	0.213	0.025
Triglycerides	-0.085	0.616	0.157	0.354
LDL	0.007	0.968	0.152	0.370
HDL	0.297	0.075	-0.020	0.907
AOD	-0.170	0.315	0.155	0.359
LAD	-0.149	0.380	-0.143	0.400
LVEDD	-0.155	0.361	-0.275	0.099
LVESD	0.168	0.321	0.287	0.085
LVEDV (ml)	-0.008	0.964	0.292	0.079
LVESV (ml)	-0.048	0.779	-0.109	0.519
LVEF %	-0.561	< 0.001*	0.420	0.010*
Average GLS (%)	0.209	0.215	-0.113	0.507
Mitral E	0.623	< 0.001*	0.550	0.001*
Mitral A	0.604	< 0.001*	0.440	0.006*
Mitral E/A ratio	0.025	0.881	0.294	0.077
E m septal (cm/s)	0.466	0.004*	0.293	0.078
E m lateral (cm/s)	0.498	0.002*	0.350	0.030*
E m Average	-0.270	0.106	0.306	0.065
E/E m Ratio	-0.505	0.001*	-0.076	0.654
LA volume index	-0.597	< 0.001*	-0.382	0.020*
PALS	NA	----	0.329	0.047*
PACS	-.181	0.283	NA	----
Post A	-0.223	0.185	0.057	0.738
LA CSI	0.098	0.563	0.882	< 0.001*

BMI: Body mass index HR: Heart rate HbA1c: Hemoglobin A1c, HDL: high-density lipoprotein LDL: low-density lipoprotein AOD: Aortic diameter LAD: Left atrial diameter LVEDD: LV end diastolic dimension, LVESD: Left ventricular end-diastolic and end-systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: Left Ventricular End Systolic Volume. LVEF: left ventricular ejection fraction GLS: Global Longitudinal Strain E: early trans-mitral flow velocity A: atrial trans-mitral flow velocity

4. Discussion

The LA functions as a reservoir during LV systole, a blood route from the lungs to the LV cavity during diastole, a chamber contract action upon atrial electrical stimulation, and a volume sensor for the heart through the production of natriuretic peptides [14-16]. The morphology and function of the heart can be determined via echocardiography. Traditional echocardiographic indices like LA size and Trans mitral Doppler are the most prevalent approaches for assessing atrial size and function. These methods are, however, simple and easy to use, but their sensitivity is limited. 2DSTE strain and strain rate imaging are novel, independent angle techniques for detecting the presence and degree of LA longitudinal deformation in the myocardium, as well as LA function in its whole [17-19]. As a result, we may anticipate that LA reservoir dysfunction, which represents LA diastolic abnormalities, occurs in diabetics with CAD, most likely as a result of LA myocardium ischemia [20]. The capacity to distinguish the severity of DM effects on LA function and size from atrial data is highly influenced by LV compliance during diastole [21]. Ischemia-linked diastolic abnormalities caused by long-term uncontrolled DM impaired LV compliance in CAD patients. [22]

Hemodynamics in the cardiovascular system have traditionally been studied through the lens of LV form and function, with the LA serving as a passive transport chamber. Nowadays, the importance of LA function as a predictor of unfavourable cardiovascular events such as HTN, IHD, AF, valvular heart disease, heart failure, and cardiomyopathy is becoming more widely recognised. As a result, primary LA dysfunction diagnosis adds new dimensions to our understanding of the pathogenesis and treatment of these diseases [23]. By analysing deformation in 2D STE, we were able to determine LA functions.

The main finding of our study was that diabetic patients with CAD have impaired LA function as measured by strain echocardiography. In the patients, BMI, HbA1C percent, total cholesterol, triglycerides, LDL, LA Diameter, mitral A, and Ee' ratio were all significantly higher in the patients' group than the control group. While, mitral E/A ratio, PALS %, PACS%, Post A %, septal E and lateral E were significantly lower in the patients' group than the control group.

LAV was significantly affected by increasing BMI. BMI, total cholesterol, TG, and LDL were all considerably higher in the patient group than in the control group, according to our findings. In terms of HR, HTN, and HDL, there were no significant differences between the groups studied. In a similar vein, Demira et al. [8] discovered that the patient group's TG and total cholesterol were significantly greater

than the control groups. Between the groups, there was no significant difference in HDL, BMI, HR, or HTN. In addition, the study by Aslan et al. [25] found no differences in blood pressure or BMI between the two groups. In the patient group, hyperlipidemia was greater and statistically significant.

LA diameter and E/e' were substantially higher in the sick group than in the control group, according to our findings. The patient group's mitral E/A ratio and mitral e′ , on the other hand, were considerably lower than the control groups. While the size and volume of the LA are within acceptable limits, LA dysfunction may occur in persons diagnosed with diabetes within the preceding six months, and this outcome was mostly associated with BMI and age, according to Demira et al., [8] who reported diastolic dysfunction in diabetic individuals than controls, while the size and volume of the LA are within acceptable limits, LA dysfunction may arise in persons diagnosed with diabetes during the preceding six months, and this outcome was mostly associated with BMI and age... Similar findings were found by Russo et al. [26]. According to Zoppini et al., [24], the length of DM disease was found to be substantially and favourably associated with a bigger LAV and poorer LA function as measured by echocardiography.

The STE findings in our study are in line with Liu Yy et al. [5] who showed reduced PALS and PACS in diabetic patients with CAD. However, this finding was reported only in patients who had dilated LA diameter.

In the same line, the study by Demirağ et al. [8] reported reduction of LA strain in diabetic patients, and this finding was correlated with increasing age. This can be explained by the prevalence of DM elevation over a person's lifetime because of aging, the obesity epidemic, and sedentary lifestyles. Additionally, the occurrence of CVD and morbidity and mortality due to CVD elevation in individuals with DM.

The study by Facchini et al. reported reduced LA function in patients with CAD [28].

The study by liu Yy et al. presented that LA volumes significantly increased in diabetic participants in addition to reduction of LA strain rate [5].

Mondillo et al. [23] showed no difference in LA conduit and pump functions in diabetic individuals with normal LA size and volume and controls. Atas et al., [27] showed that When compared to the control group, people with diabetes exhibited lower reservoir and pump function but similar conduit function. Multiple cardiovascular imaging modalities to assess LA function, small sample sizes, varied baseline features, and varying durations of diabetes in the research populations may have contributed to the predicted contradictory findings with earlier research.

5. Study Limitations

The study's tiny sample size makes it impossible to make fair conclusions or investigate the effects of medicines on LA volume and function. To assess the clinical diagnostic benefit of early LA functional problems in humans, long-term follow-up and large-scale prospective study are necessary. The frame rate and image resolution are a technological barrier for STE. Increased frame rate, on the other hand, reduces scan line density, lowering picture resolution.

6. Conclusion

STE is a non-invasive, reasonably simple, and reliable approach for assessing LA myocardial function in diabetic individuals with CAD. LA reservoir, conduit, and pump functions were severely compromised in individuals with uncontrolled DM.

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