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Role of Speckle Tracking and Strain Rate in Detection of Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus

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Abstract:

Introduction: Based on the visual identification of anomalies in the endocardial wall motion and the evaluation of left ventricular ejection fraction, the echocardiographic assessment of regional myocardial function is a vital component in the diagnosis and treatment of ischemic heart disease. The aim of our study was to test the value of speckle tracking in detection of coronary artery disease in patients with type 2 diabetes.

Methods: The study was a cross sectional descriptive study conducted on 100 Patients with type 2 diabetes mellitus referred for coronary angiography with normal systolic function, no segmental wall motion abnormality and suspected CAD. They were divided into 2 groups according to coronary angiography results. The first group was patients with normal epicardial coronaries. The second group was patients with coronary artery disease. Speckle tracking was done for both groups and results were compared.

Results: GLS score was statistically lowest in zero affected vessels (-22.9 ± 2.2 , P value $\sim < 0.001$), then became higher with abnormal CA findings (-13.0 ± 3.0 , P value $\sim < 0.001$), with no significant difference between one and two vessels as well as between three and four vessels affected. GLS score at cut point ≥ -19.0 had perfect sensitivity and negative predictive value and almost perfect other characteristics.

Conclusion: GLS had high sensitivity, specificity, and diagnostic accuracy method for detecting advanced CAD in DM patients. So, speckle tracking is a non-invasive method that can be utilized.

Keywords: Speckle-tracking; GLS; CAD; Diabetes Mellitus; Myocardial deformation.

1. Introduction

Diabetes Mellitus still considered as a major health problem worldwide as its prevalence continue to be in the rise particularly in low income countries (1).

In most laboratories, the visual identification of endocardial wall motion abnormalities and the assessment of left ventricular (LV) ejection fraction are the primary means of facilitating the echocardiographic evaluation of regional myocardial function, which is a crucial component in the diagnosis and treatment of ischemic heart disease. However, according to Brian D. Hoit,(2) this method is subjective and operator-dependent, necessitates full sight of the endocardium, and is susceptible to variations in cardiac loading and heart rate.

It has been demonstrated that two-dimensional speckle-tracking echocardiography (2D STE) can be used to quantify left ventricular (LV) longitudinal strain and strain rate. This technique is sensitive in detecting significant CAD, transmural myocardial infarction, and acute or subacute ischaemia (3).

The technique known as speckle-tracking echocardiography (STE) was created lately to measure and characterize cardiac deformation. It gives information not available with any of the currently utilized echocardiographic measurements, such as left ventricular ejection fraction (LVEF), by enabling measurement of the various components of myocardial deformation (4).

The primary goal of STE is to give an objective, quantitative assessment of LV systolic function that can precisely identify minute alterations in myocardial function. It seems that Global Longitudinal Strain (GLS) is the most appropriate parameter for this purpose out of all the cardiac deformation metrics. Compared to the other deformation parameters, it is substantially more sensitive to the early myocardial injury and has greater reproducibility (4).

One of the most promising indications for STE seems to be the identification of myocardial dysfunction in the early, subclinical stage, which could have important diagnostic and therapeutic consequences. In addition to helping distinguish hypertrophic cardiomyopathy from hypertensive heart disease or athletes' heart, impairment of GLS is useful in identifying cardiac involvement in a number of disorders, including diabetes mellitus, obesity, obstructive sleep apnea, and systemic diseases like amyloidosis, Fabry's disease, etc (5).

The ability of strain imaging to evaluate myocardial deformation in diabetes patients to differentiate between normal and ischemic myocardium remains unclear. In this work, we examine the usefulness of speckle tracking in the identification of CAD in type 2 diabetic patients.

Aim of the study

The study aims to assess the role of speckle tracking (a non-invasive technique) in detection of coronary artery disease in patients with type 2 diabetes in comparison to coronary angiography (an invasive technique) to be early treated and improve quality of life.

Patients and methods

This cross sectional descriptive study included 100 patients with type 2 diabetes mellitus & suspected coronary artery disease with no segmental wall motion abnormality in resting echocardiography referred for coronary angiography at Echocardiography Lab. and Catheterization Lab., Cardiology Department - Suez Canal University Hospital.

Patients > 30 years old with type 2 diabetes mellitus (either recently diagnosed or previously diagnosed with DM on anti-diabetic drugs either Insulin therapy or oral hypoglycemic drugs) referred for coronary angiography with normal systolic function (normal range is 55% to 75%) (6), and no segmental wall motion abnormality and suspected CAD were included in the study. While, patients with poor image quality for 2D-STE, who have resting baseline echocardiography that shows segmental wall motion abnormalities, patients with Bundle branch block, or Pacemaker implantation, with more than mild valvular heart disease, restrictive or Dilated cardiomyopathy, prior myocardial infarction or revascularization or atrial fibrillation or atrial flutter were excluded from the study.

The study population was divided into 2 groups according to coronary angiography results. The first group was patients with normal epicardial coronaries. The second group was patients with coronary artery disease.

The selected patients were subjected to the following:

Complete history taking included: age, gender of the patient, history of smoking, diabetes mellitus, main cardiac symptoms, other endocrinal diseases, history of chronic diseases; hypertension, dyslipidemia, bronchial asthma, history of chronic renal failure, chronic liver disease, history of valvular heart disease, valvular heart disease proved by echocardiography, history of atrial fibrillation and other arrhythmias and history and symptoms of PVD.

Proper examination: height, weight, BMI, Waist circumference, Blood pressure on presentation, ECG, laboratory investigations (Serum creatinine, estimated GFR, BUN, serum electrolytes, HbA_{1c}, lipid profile (Serum cholesterol, LDL-c, HDL-c, Serum triglycerides).

Echocardiographic Assessment: Conventional echocardiographic study was performed using the standard views parasternal long, short axis, apical 2 and 4 chamber views at rest (to assess left atrial diameter, left ventricular end-systolic and end-diastolic diameters, left ventricular fractional shortening percentage, the thickness of the interventricular septum (IVS), and the posterior wall (PW), any valvular lesions) using a commercially available system (Philips Ultrasound field service company, EPIQ 7 Q lab version 10.8.5 machine).

Speckle tracking:

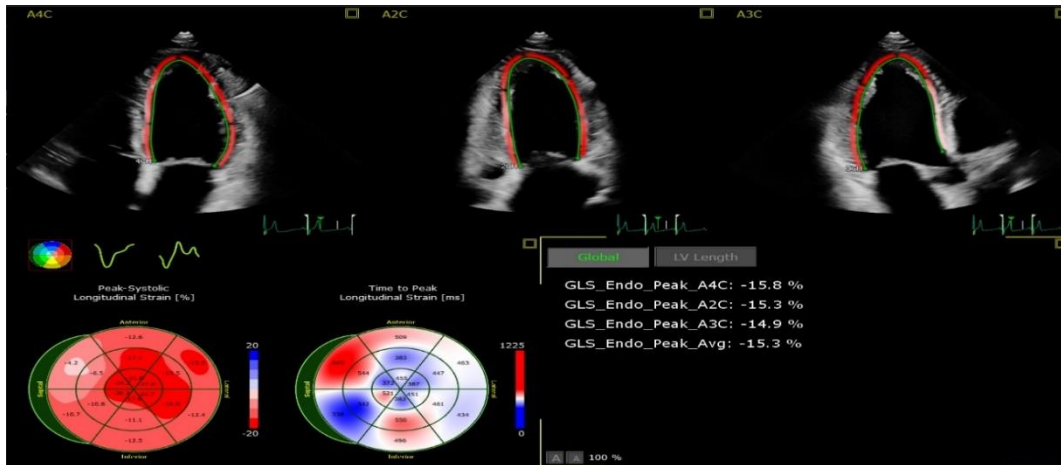


Figure 1: Speckle Tracking & Strain Rate.

- ✓ Images from the apical four-chamber, two-chamber and three-chamber views were required for the measurement of LV longitudinal strain (4).
 - ✓ The gain settings were optimized. The depth was reduced so that the LV occupies most of the image sector. The gray-scale frame-rate was kept between 30 and 70 frames/s.
 - ✓ Minimum three cardiac cycles were acquired for each loop. All the images were acquired in breath-hold to avoid any breathing artifacts.
 - ✓ When the image was opened in the software, the software automatically brought up the end-systolic frame of the cardiac cycle.
 - ✓ In the end-systolic frame, endocardial border was traced manually in its entirety, beginning at one end of the mitral annulus and ending at the other end.
 - ✓ The software then generated a region-of-interest (ROI) to include the entire myocardial thickness. The width of the ROI was manually adjusted as required.
 - ✓ The software then tracked the myocardial speckles frame-by-frame and generated moving images displaying the tracking (4).
 - ✓ The software then divided the LV myocardium into six segments and generated segmental and global longitudinal strain, strain rate, velocity and displacement curves. As the myocardium usually shortens in longitudinal direction during systole, the longitudinal strain and strain rate curves were displayed below the baseline. From these curves, peak-systolic longitudinal strain was recorded for each of the myocardial segments. The value $\sim \geq -18\%$ was considered normal (7).
 - ✓ The same process was repeated with the apical four-chamber and two-chamber images also. The strain values for all the segments were recorded and averaged to obtain the global longitudinal strain (GLS) (4).
 - ✓ All echocardiographic data was interpreted by two independent experts in echocardiography.
- **Coronary angiography:**

- Each angiogram was evaluated by an interventional cardiologist who was blinded to the study plan, and the Gensini scoring system was used to determine the severity of CAD.

- This method defines narrowing of the lumen of the coronary arteries as 1 for 1-25% stenosis, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99%, and 32 for total occlusion (8).

- The score was then multiplied by a factor representing the importance of the lesion's location in the coronary artery system.

- For the location scores, 5 points were given for left main lesions; 2.5 for proximal LAD or LCX; 1.5 for mid segment LAD or LCX; 1 for distal segment of LAD or LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches (8).

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data described as mean±SD (standard deviation) as well as minimum and maximum of the range, then compared using independent t-test (two independent groups) and ANOVA test (three independent groups) after being tested for normality using Shapiro-Wilk test. Qualitative data described as number and percentage and compared using Fisher's Exact test. Bonferoni test used for post hoc comparisons. ROC curve was used to evaluate the performance of GLS score to diagnose CA abnormality. Logistic regression used to find out independent risk factors affecting having CA abnormality. The level of significance was taken at p-value <0.050 was significant.

Results

The study included 100 patients with type 2 diabetes mellitus & suspected coronary artery disease with no segmental wall motion abnormality in resting echocardiography referred for coronary angiography. It was found that 12% of cases had normal coronaries and 88% of cases had coronary artery disease.

Table 1: Comparison according to CA abnormality regarding demographic characteristics

Variables		Total (n=100)	CA findings		p-value
			Abnormal (n=88)	Normal (n=12)	
Age (years)	Mean±SD	58.3±8.8	58.9±8.6	54.4±9.7	^0.101
	Range	38.0–77.0	38.0–77.0	38.0–68.0	
BMI (kg/m ²)	Mean±SD	27.9±2.5	28.1±2.4	26.3±2.6	^0.013*
	Range	22.0–36.0	24.0–36.0	22.0–30.0	
Duration of DM (years)	Mean±SD	11.2±7.0	11.6±7.2	7.8±4.4	^0.074
	Range	1.0–30.0	1.0–30.0	1.0–15.0	
Gender	Male	38 (38.0%)	37 (97.4%)	1 (2.6%)	§0.027*

(per row)	Female	62 (62.0%)	51 (82.3%)	11 (17.7%)	
Smoking		17 (17.0%)	16 (18.2%)	1 (8.3%)	§0.685
Hypertension		88 (88.0%)	77 (87.5%)	11 (91.7%)	§0.999
Dyslipidemia		100 (100.0%)	88 (100.0%)	12 (100.0%)	NA
Atrial fibrillation		0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Waist circumference	Mean±SD	94.87±8.2	96.9±8.6	90.4±7.2	0.043*

NA: Not applicable. ^Independent t-test. §Fisher's Exact test. *Significant; BMI: Body mass index.

Table (1) show that: **BMI & waist circumference** were statistically significantly higher in cases with abnormal CA findings. CA abnormality was significantly more frequent in males than in females. Otherwise, no statistically significant differences according to CA abnormality regarding other demographic characteristics.

Table 2: Comparison according to CA abnormality regarding laboratory findings

Variables		Total (n=100)	CA findings		p-value
			Abnormal (n=88)	Normal (n=12)	
Total cholesterol (mg/dL)	Mean±SD	172.5±20.6	174.9±19.0	154.7±23.6	^0.001*
	Range	122.0–220.0	136.0–220.0	122.0–210.0	
Triglycerides (mg/dL)	Mean±SD	102.6±30.7	104.3±32.0	90.8±15.3	^0.157
	Range	75.0–312.0	75.0–312.0	75.0–123.0	
LDL (mg/dL)	Mean±SD	88.2±11.8	88.6±11.1	84.9±16.4	^0.463
	Range	63.0–120.0	70.0–120.0	63.0–111.0	
HDL (mg/dL)	Mean±SD	52.5±7.3	52.5±7.5	52.8±5.5	^0.875
	Range	28.0–75.0	28.0–75.0	45.0–66.0	
HbA1c (%)	Mean±SD	7.9±1.6	8.2±1.4	5.7±1.0	^<0.001*
	Range	4.5–11.0	5.2–11.0	4.5–7.5	
Creatinine (mg/dL)	Mean±SD	0.97±0.21	1.0±0.2	1.0±0.2	^0.841
	Range	0.60–1.60	0.6–1.6	0.7–1.5	
BUN (mg/dL)	Mean±SD	17.3±6.7	17.7±6.7	14.0±6.5	^0.075
	Range	5.0–30.0	5.0–30.0	7.5–29.0	

Potassium (mmol/L)	Mean±SD	3.9±0.4	3.9±0.4	4.0±0.4	^0.584
	Range	3.2–5.2	3.2–5.2	3.5–4.6	

^Independent t-test. *Significant

LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, BUN: Blood Urea Nitrogen, HbA1c: Glycated Hemoglobin.

Table (2) show that: **Total cholesterol and HbA1c** were statistically significantly higher in cases with abnormal CA findings. Otherwise, no statistical significant differences according to CA abnormality regarding other laboratory findings.

Table 3: Comparison according to CA abnormality regarding echocardiography findings

Variables		Total (n=100)	CA findings		p-value
			Abnormal (n=88)	Normal (n=12)	
LAD (mm)	Mean±SD	43.9±2.5	44.1±2.3	42.7±3.2	^0.064
	Range	35.0–49.0	39.0–49.0	35.0–47.0	
LVESD (mm)	Mean±SD	31.8±4.0	31.7±4.0	32.4±4.6	^0.574
	Range	25.0–41.0	25.0–41.0	27.0–41.0	
LVEDD (mm)	Mean±SD	48.2±4.6	48.3±4.5	47.2±5.5	^0.417
	Range	38.0–55.0	38.0–55.0	39.0–55.0	
PW (mm)	Mean±SD	8.7±1.1	8.8±1.1	8.2±0.7	^0.077
	Range	7.0–12.0	7.0–12.0	7.0–9.0	
IVS (%)	Mean±SD	8.8±1.1	8.9±1.1	8.2±0.9	^0.043*
	Range	7.0–12.0	7.0–12.0	7.0–9.0	
GLS score	Mean±SD	-14.2±4.3	-13.0±3.0	-22.9±2.2	^<0.001*
	Range	-26.0–4.0	-19.0–4.0	-26.0–19.0	

^Independent t-test. *Significant

LAD: Left Atrial Diameter, LVESD: Left Ventricular End Systolic Diameter, LVEDD: Left Ventricular End Diastolic Diameter, PW: Posterior Wall, IVS: Interventricular Septum, GLS: Global Longitudinal Strain.

Table (3) show that: **IVS and GLS score** were statistically significantly higher in cases with abnormal CA findings. Otherwise, no statistical significant differences according to CA abnormality regarding other echocardiography findings.

Table 4: Coronary angiography findings among the studied cases

Variables		Mean±SD	Range
Gensini score		27.9±27.7	0.0–128.0
		N	%
Findings	Normal	12	12.0%

	Abnormal	88	88.0%
Findings	Normal	12	12.0%
	Cases need PCI	56	63.6%
	Mild CAD	20	22.7%
	Cases need CABG	10	11.4%
	CA ectasia	2	2.2%

Total=100. PCI: Percutaneous Coronary Intervention, CAD: Coronary Artery Disease, CABG: Coronary Artery Bypass Graft.

Table (4) show **coronary angiography findings among the studied cases**; Mean±SD of Genisini score was 27.9±27.7. Minority of cases had normal CA (12.0%), the most frequent abnormality was cases who need PCI (63.6%), followed by patients with mild CAD (22.7%).

Table 5: Comparison according to CA findings regarding GLS score

Conditions	Findings	N	Mean±SD	p-value
Abnormality	Normal	12	-22.9±2.2a	<0.001*
	Abnormal	88	-13.0±3.0	
Pathology	Need PCI	56	-13.0±2.2b	<0.001*
	Mild CAD	20	-14.9±3.0b	
	Need CABG	10	-8.9±2.6c	
	CA ectasia	2	-16.5±0.7b	
Number	0	12	-22.9±2.2a	<0.001*
	1	32	-15.1±1.8b	
	2	26	-13.6±1.7b	
	3	30	-10.3±2.8c	

^ANOVA test with post hoc Bonferroni test, homogenous groups had the same symbol "a,b,c".

*Significant

Table (5) show that: **GLS score** was worse (more toward positive) in cases with abnormal CA. **GLS score** was better (more toward negative) in normal CA than .3 other CA findings, becoming worse in those who need PCI, cases with mild CAD and those with CA ectasia with no significant difference between them, and significantly highest & worst in those who need CABG. **GLS score** was statistically lowest in zero affected vessels, then became higher with advancement of number, with no significant difference between one, two and three vessels.

Table 6: Diagnostic characteristics of GLS score in diagnosing abnormal CA findings

Characteristics	Value	95% CI
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AUC	0.999	0.998–1.000
p-value	<0.001*	
Cut point	≥-19.0	
Sensitivity	100.0%	95.9%–100.0%
Specificity	91.7%	61.5%–99.8%
Diagnostic accuracy	99.0%	94.6%–100.0%
Positive predictive value	98.9%	93.9%–100.0%
Negative predictive value	100.0%	71.5%–100.0%

CI: Confidence interval. AUC: Area Under Curve.

Table (6) show that: **GLS score** statistically had significant high diagnostic performance in diagnosing abnormal CA findings; its cut point ≥ -19.0 had perfect sensitivity and negative predictive value and almost perfect other characteristics.

Discussion

According to a number of studies, patients with advanced CAD had substantially less global longitudinal strain, as determined by 2-D STE at rest, than patients without CAD (9).

In this regard, ESC 2019 proposed a new definition of the clinical likelihood of coronary artery disease (CAD) that takes into account data on CVD risk factors (diabetes), changes in the resting electrocardiogram (ECG), left ventricular dysfunction suggestive of ischemia, or coronary calcification. These variables can be used as modifiers to improve the identification of patients with obstructive CAD as opposed to age, sex, and symptoms alone (used for pretest probability (PTP) estimate) (10). The clinical likelihood of CAD is increased by diabetes and/or LV dysfunction suggestive of CAD (early diagnosed by GLS), which leads to a preference for invasive coronary angiography, according to new guidelines released by the European Society of Cardiology (ESC 2019)(11).

We recruited 100 patients with type 2 diabetes mellitus and suspected coronary artery disease without segmental wall motion abnormality in resting echocardiography who were referred for coronary angiography in order to test the usefulness of speckle tracking and strain rate in the detection of coronary artery disease. The patients were divided into two groups: those with normal coronary arteries (without CAD), who enrolled 12 participants, and those with CAD, who enrolled 88 patients: 56 needed PCI, 20 had mild CAD, 10 cases needed CABG, and 2 had CA ectasia.

The Gensini score, a comprehensive score that evaluates the degree and severity of coronary atherosclerotic disease load on angiography, was used to perform this distribution. When calculating scores, mild to moderate stenosis (diameter stenosis $>0\%$) is taken into account. According to reports, there exists a strong correlation between the Gensini score and intravascular ultrasonography measurements of atherosclerotic plaque burden. Consequently, the Gensini score is a suitable scoring tool that has been applied in several research to evaluate the burden of coronary artery atherosclerotic disease (12).

In patients with diabetes mellitus, age is a well-known risk factor for cardiovascular disease (CVD). In this study, we found a significant association between the severity of CAD disease and participant age: 58.9 ± 8.6 years for the CAD group and 54.4 ± 9.7 years for the normal group. There was no statistically significant difference between the groups, which is consistent with other studies that have examined similar topics. Pararajasingam et al., (13) and Alaika et al., (14) also

reported no significant differences between diabetics with and without CAD, but their mean age (67.5) years was higher than ours.

In terms of gender, we discovered a statistically significant greater level of male predominance in the CAD group compared to the normal group. Furthermore, we discovered that male gender is a risk factor for CA abnormalities by the use of logistic regression.

Our results concur with those of Pararajasingam et al. (13) who noted a notable male predominance in the group of patients with complications from DM. Alaika et al. (14) found no statistically significant distinction between the CAD positive and negative groups.

Sex hormones and the receptors they are linked to play a major role in the sex differences that cause disparities in CVD risk factors and outcomes between men and women (15).

Obesity is linked to coronary artery disease (CAD), atherosclerosis, and cardiac mortality. It has long been recognized as a separate risk factor for CVD. Moreover, studies have demonstrated that BMI and waist circumference are associated with key cardiometabolic risk factors like hypertension and elevated low-density lipoprotein cholesterol (LDL-C), and that overweight and obesity are highly prevalent in T2DM patients with high CV risk (16).

Automated speckle tracking echocardiography (STE) is a new method for measuring and identifying small LV systolic function abnormalities: global longitudinal strain (GLS). The accuracy of GLS, which represents the myocardium's longitudinal contraction, has been verified by comparison with tagged magnetic resonance imaging (10).

The current investigation revealed that GLS scores were considerably lower ($p < 0.001$) in instances with DM and aberrant CA results (-13.0 ± 3.0) compared to the normal group (-22.9 ± 2.2). Additionally, GLS scores decreased in patients who required PCI (severe CAD).

Our results are in line with those of Alaika et al. (14), who used 2D STE to prospectively examine resting echocardiographic features, followed by stress echocardiography and coronary angiography data in 34 diabetic individuals who did not have resting regional wall motion abnormalities (RWMA). Patients were divided into two groups, CAD (+) and CAD (-), based on the results of stress echocardiography and coronary angiography. It was discovered that the GLS at rest was lower in the CAD (+) group ($-14.2 \% \pm 3.1$) than in the CAD (-) control group ($-17.8 \% \pm 3.1$) ($P = 0.004$).

Our findings align with a systematic analysis by Norum et al. (17), as the overall weighted mean GLS was lower in CAD + patients ($-17.2 \% \pm 2.6$) compared to CAD-patients ($-19.2 \% \pm 2.8$).

With an area under the curve (AUC) of 0.999 and a cut point of ≥ -19.0 , the GLS score demonstrated statistically significant high diagnostic performance in diagnosing abnormal CA findings. It also had nearly perfect other characteristics, such as specificity (91.7%), diagnostic accuracy (99.0%), and positive predictive (98.9%), along with perfect sensitivity (100.0%) and negative predictive value (100.0%).

Since Biering-Sørensen et al. (18) showed that myocardial strain analysis by 2-D STE improves the diagnostic of CAD in a stable angina pectoris, there are an increasing number of consistent reports that validate the use of 2D strain in the identification of various levels of CAD in different conditions. The combination of global longitudinal peak systolic strain and exercise test had a significantly higher AUC (ROC) than the exercise test alone (0.84 versus 0.78; $P = 0.007$).

According to Radwan and Hussein's (19) research, the GLS cut-off for detecting significant CAD was -15.6 percent, with corresponding sensitivity and specificity of 93.1% and 81.8% at AUC 0.88 , $p < 0.000$.

Alaika et al.(14) found that, with a cut-off of -14.5% , GLS at rest had the highest area under the ROC curve (AUC) (AUC 0.78 , sensitivity 61% , specificity 91% , $P=0.009$).

In a prior study, Zuo et al. (20) discovered that CAD patients with DM had significantly lower global and segmental longitudinal strains than those without DM. They also found that the entire cohort had reduced sensitivity and specificity, but the DM patients in particular had lower sensitivity and specificity (61.1% and 52.9%), with a lower cutoff point of GLS at rest (-17.15% vs. -18.35% in patients without DM). AUC = 0.67 ; $P = 0.048$ was the diagnostic accuracy of GLS at rest in DM patients.

Both diabetes mellitus and coronary artery disease may impede longitudinal strain. DM, as opposed to CAD, causes damage to the myocardium by a variety of mechanisms, such as an imbalance in energy metabolism, an excess of calcium within the cell, and the deposition of collagen and fibrosis. Patients with diabetes mellitus may also have cardiac dysfunction due to decreased endothelial progenitor cells and elevated oxidative stress (21).

Even in the absence of coronary artery disease, all of these variables may lead to cardiac contractile dysfunction that can be identified by deformation analysis. There is a synergistic effect of CAD and DM on strain impairment. When comparing patients with CAD and DM alone, those with both conditions together have the worst longitudinal strain.

Conclusion

In conclusion, the current study showed that GLS scores were statistically considerably lower in DM and CAD subjects with Using a GLS cut off value of -19% is suggested as a high sensitivity, specificity, and diagnostic accuracy method for detecting advanced CAD in DM patients. Therefore, instead of using coronary angiography, which is an intrusive procedure, to detect coronary artery disease in individuals with type 2 diabetes and treat it early and enhance quality of life, speckle tracking and GLS are non-invasive methods that can be utilized.

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