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Predictors of LV Recovery after Proximal Left Anterior Descending Artery Stenting

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ABSTRACT

Background: The presence of proximal left anterior descending artery (LAD) stenosis is an important independent predictor of mortality & major adverse cardiovascular events (MACE). Speckle tracking is highly sensitive for the detection of subclinical impact of both ischemia and revascularization on global and regional myocardial function.

Objective: The study aims to assess global and regional left ventricular strain, in patients with significant proximal left anterior descending coronary artery stenosis, before and after percutaneous revascularization, and its relation with MACE.

Methods: A total of 53 patients were admitted to Mansoura University's Cardiovascular Department between December 2017 and November 2018 for elective proximal left anterior descending artery (LAD) stenting. 2D echocardiography and speckle tracking were done before and one month after percutaneous coronary intervention (PCI), assessing left ventricular ejection fraction (LVEF). Global Longitudinal Strain (GLS), mean LAD territorial strain & left ventricular (LV) function with clinical follow-up for cardiovascular MACE after one year.

Results: There was presenting significant impaired GLS and mean LAD strain even with normal EF (median -13.5 /-11.9) respectively with significant recovery The mean LAD territorial strain one month after PCI than GLS, with p-value <0.001/ <0.01 respectively. However, GLS recovery was found to be the most valuable predictor for the occurrence of MACE one-year follow-up (p-value: 0.019).

Conclusion: GLS & mean LAD territorial strain provided a more precise objective quantification of successful global and regional recovery of LV function after proximal LAD revascularization & predictor for MACE.

Keywords: Proximal LAD stenosis, GLS, mean LAD territorial strain, LV recovery.

INTRODUCTION

Proximal left anterior descending coronary artery stenosis (P-LAD) is known to be a high-risk lesion due to long-term morbidity and decreased survival as compared to distal lesions or other territories [(1)].

Proximal LAD stenosis alone is a significant predictor of cardiac deaths because its related myocardial infarction is commonly fatal [(2)], moreover autopsy for 86% of acute myocardial infarction deaths were related to proximal LAD culprit [(3)].

Stable coronary artery disease with high-grade proximal LAD lesions is at higher risk for LV dysfunction with poor prognosis owing to the large area of involved myocardium that considers an early invasive approach than conservative medical therapy [(4)].

Percutaneous revascularization of proximal LAD lesions has managed to improve short- and long-term physical activity and quality of life in comparison with the medical conservative strategy [(5)].

The proximal LAD stenting is a challenging high-risk procedure due to concern about the left main artery or major side branches injury. Therefore, coronary artery bypass grafting (CABG) is usually considered, even in patients with a sole P-LAD lesion [(4)].

The 2011 American Heart Association/American College of Cardiology (AHA/ACC) and 2012 AHA/ACC stable angina guidelines both reported the superiority of surgical strategy with LIMA graft in P-LAD lesions (>70% stenosis) (indication IIa, level of evidence B), to PCI (class IIb, level of evidence B) regards survival rate [(6)].

While, the latest European Society of Cardiology ESC/European Association of Cardio-Thoracic Society guidelines on myocardial revascularization recommend a “heart team” discussion in both chronic and acute coronary syndromes with proximal LAD stenosis >50% with a class I recommendation and level of evidence A to both, PCI and CABG [(7)].

The choice between conservative therapy, PCI, or CABG for P-LAD stenosis should depend on the cost-benefit ratios of these treatment strategies, comparing the possible complications (e.g., stroke, bleeding, renal insufficiency, arrhythmias, or sepsis) with the refinement of the quality of life, in addition to long-term freedom from MACE as mortality, infarction, or repeat revascularization [(8)].

Kinnaird *et al.* [(9)] reported no differences between surgical LIMA graft or percutaneous DES implantation for isolated P-LAD stenosis as regards deaths, myocardial infarction, and cerebrovascular events; however, there was a significant decline in repeat revascularization rated in CABG patients.

Additionally, **Kapoor *et al.*** [(10)] reported that CABG was Superior to PCI as regards symptom relief and repeat revascularization with no differences as regards death, stroke, or MI.

However, studies on newer-generation DES compared with first-generation DES for P-LAD reported that; at >3 years follow-up, death rates declined by 35%, cardiac death and infarctions decreased by 30%, and instant thrombosis reduced by >50% [(11)].

Despite being the most commonly used tool in daily clinical practice for the evaluation of LV function, echocardiographic LVEF has many limitations such as intra- and inter-observer variability, affected by preload

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conditions, and its detection of early subclinical LV dysfunction is low [12].

Echocardiography strain imaging is introduced as a part of routine clinical practice nowadays for the detection of subclinical impact of both ischemia and revascularization on global and regional myocardial function, not only for research purposes [13], but the regional strain is relatively more variable than GLS [14].

Restoration of coronary flow by successful coronary stenting is correlated with remarkable recovery of both territorial and global LV function with better clinical endpoint [15].

In the same way, Ahmed, 2020 stated that restoring the coronary blood flow in patients with angina pectoris is associated with improvement in global and regional myocardial function as LV GLS & EF [16].

So, our study aims to measure & compare changes in LV function LVEF, global and regional left ventricular strain, in patients with significant p-LAD artery narrowing, before and one month after PCI, and their relations to 1-year MACE.

PATIENTS AND METHODS

This study was a descriptive prospective study and was conducted on 53 patients with chronic coronary syndrome who were candidates for elective percutaneous coronary stenting of significant proximal LAD stenosis at the cardiovascular department, specialized medicine hospital, Mansoura University, from December 2017 to November 2018.

Patients undergoing primary PCI in the setting of acute coronary syndrome, non-stentable lesions, those with severe primary valvular heart disease or myocardial disease affecting myocardial function, all were excluded

All Patients were subjected to the following after informed consent:

A. Pre-stenting Assessment:

1) History taking with focusing on risk factors for CAD, angina Canadian Cardiovascular Society (CCS), New York Heart Association (NYHA) grade, past history of previous MI, coronary angioplasty, or bypass grafts.

2) Clinical examination with specific focus on Herat rate, Rhythm & Blood pressure & signs of HF.

3) Standard 12- lead surface ECG interpretation focusing on heart rhythm, and ST-T wave changes.

4) Two-Dimensional conventional transthoracic Echo:

- Standard M-mode, 2D, and Doppler images were obtained using a commercially available system (Vivid 9, General Electric-Vingmed, and Horton, Norway) according to the recent American Society of Echocardiography guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults [17].

- Assessment of resting LV dimensions, LV end-diastolic dimensions (LVIDd), LV end-systolic dimensions (LVISd), and overall systolic/diastolic function by Fractional shortening (FS) & Ejection Fraction (EF) that was automatically obtained by Teichholz formula, trans-mitral pulsed wave Doppler to assess E/A ratio and any valvular abnormality.

- Assessment of any resting segmental wall motion abnormality (RSWMA).

5) Two D speckle tracking echocardiography:

Speckle tracking echocardiography was performed according to the consensus document of the EACVI/ASE Industry Task Force to standardize deformation imaging [18]**:**

1. GLS: the system automatically calculates GLS by quantification of the mean value of longitudinal peak systolic strain of the 17 segments. Current 2015 American Society of Echocardiography guidelines suggested a GLS value above (- 20% ± SD 2%), is likely to be normal [19-21].

2. The mean LAD territorial strain [22]: is calculated by the operator by quantification of the average value of the peak longitudinal systolic strains of the LAD supplied 7 myocardial segments (apex, 3anterior, and 3 anteroseptal segments, numbered 1, 2, 7, 8, 13, 14, and 17) **(Figure 1).**

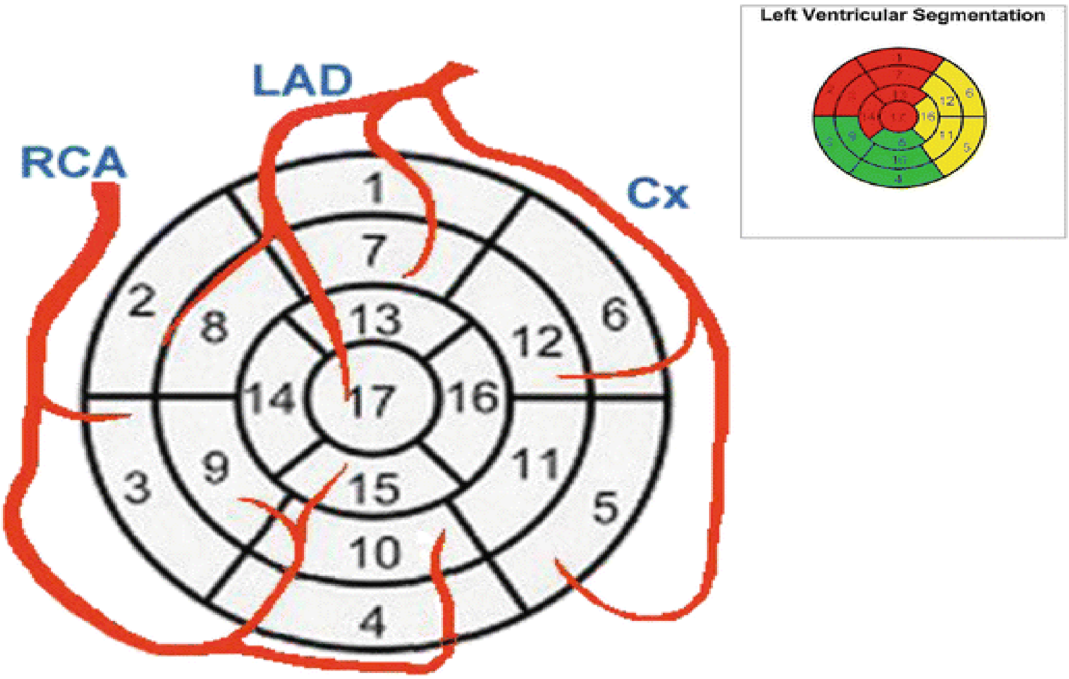

Figure (1): Bull's eye showing segments supplied by LAD (1,2,7,8,13,14,17) and other coronary arteries [18].

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6) Coronary angiography:

Coronary angiography and percutaneous coronary intervention were performed according to the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention [20]. Proximal significant left anterior descending coronary artery lesion was defined as ≥50% narrowing in LAD proximal to the first septal perforator branch. DES implantation to proximal LAD lesions recording Stent type, size, and post-stenting TIMI flow considering TIMI flow III as successful angiographic reperfusion

B. Post-stenting Assessment:

All patients were subjected after one month of LAD stenting to the same pre-stenting examinations & investigations, with a special focus on Transthoracic 2D echo & speckle tracking assessment with a comment on LV recovery that was defined as ≥ 10% improvement from the basal value with clinical follow-up for cardiovascular MACE 1 year after stenting with detection of its predictors.

Ethical considerations:

The study protocol was approved by the Medical Research Ethics Committee, Faculty of Medicine, and Mansoura University (Code No MS/17.11.72). Informed written consent was obtained from each patient in the study after assuring confidentiality. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical data analysis:

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 18 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normality distribution, normally distributed variables were presented as mean ± SD, Paired t-test was used for pre-post comparison, non-parametric variables were presented as Median (Minimum, Maximum) and the Wilxocon sign rank test was used for pre-post comparison. The qualitative variable was presented by number & percent, Chi-square was used for comparison between groups, and P<0.05 was considered statistically significant.

RESULTS

94.3% of patients enrolled in the study were males with only 5.7% females giving significant male predominance. The mean age of the studied group was 54.4 ± 8.01years.

Smoking was the most prevalent risk factor (64%), followed by dyslipidemia (47.2%), DM (43%), and HTN (39.6%) respectively.

23/53 patients had a previous myocardial infarction (43.3%), among whom 20 patients had a history of anterior STEMI.

The Mean prep-procedural EF was (54.35% ±14.25), and 20 patients had RSWMA in the myocardial walls supplied by LAD.

The percentage of patients with single vessel LAD lesions was 60.4%, compared to 39.6% with multivessel disease. Five patients (9.4%) had total occlusion of LAD (CTO).

Single stent insertion was done in 40 patients, 12 patients had double LAD stents during PCI to proximal LAD, while a single patient had 3 LAD stents. Stent lengths ranged from 20 mm to 38 mm.

In our study, after 1 month of P-LAD stenting, there was significant improvement of the global longitudinal strain (GLS) & mean LAD territorial strain (p< 0.01/p<0.001 respectively), unlike 2D LV EF that showed non-significant improvement (P 0.11).

In our study, it was settled that post-PCI left ventricular function recovery was ≥10% rise in GLS (more negativity) at follow-up.

As regards, 1year follow-up clinical outcome after Prox. LAD stenting; 88.7% had improved angina while 11.3% of patients had post-PCI angina. 7 patients (13.2%) had MACE; 3.8% deaths, 1 patient (1.9%) encountered MI, and the same for life-threatening arrhythmias, and repeated LAD revascularization was done in 5.7% of patients.

Univariate analysis regarding predictors of MACE, pre-stenting GLS (<0.001) was the important one, presence of other associated coronary arterial lesions (*P*<0.036), and chronic total occlusion of LAD (CTO) (P<0.019).

In multivariate analysis, the most independent predictors of higher incidence of MACE were the pre-PCI GLS value (OR:1.824, 95%, CI:1.273- 2.982, *P*:0.043), and the pre-PCI regional LAD mean strain value (OR:1.472, 95% CI:1.251– 1.826, *P*:0.04).

Additionally, GLS recovery was found to be a better predictor for the occurrence of MACE (p-value: 0.019) than mean LAD territorial strain recovery (P-value: 0.11) in one-year follow-up.

Univariate analysis of GLS recovery reported a lower incidence of recovery with multi-vessel disease (*P*=0.031).

However, the multivariate analysis reported that the only independent predictors of poor GLS recovery were lower pre-PCI GLS value and the pre-PCI LAD territorial mean strain value. (Table 2).

Table (1): LV function recovery 1-month post PCI:

Items	Study cases n=53	MACE		Test of significance
Recovery according to GLS				
Recovery	35 (66%)	Yes	1 (2.8%)	FET= 3.708 P= 0.019*
		No	34 (97.2%)	
No recovery	18 (34%)	Yes	6 (33.3%)	
		No	12 (66.7%)	
Recovery a ccording to mean LAD territorial strain				
Recovery	41 (77.4%)	Yes	4 (9.8%)	FET= 1.985 P= 0.116
		No	37 (90.2%)	
No recovery	12 (23.7%)	Yes	3 (25%)	
		No	9 (75%)	

Accordingly, 66% of the study patients encountered recovery of the GLS against 77.4% mean LAD territorial strain recovery (Table 1). It was found that the pre-PCI GLS and pre-PCI regional LAD mean strain values were the most independent predictors of recovery of GLS, and mean LAD territorial strain (Tables 2, 3). Moreover, it was documented that -7.3% was the cut-off point for mean LAD strain recovery with 76% & 42% sensitivity and specificity respectively (Table 4).

Table (2): Multivariate analysis of predictors of failure of recovery according to GLS (n=18)

Variables	Multivariate analysis		
	B	95%CI	P-value
EF before	0.019*	0.736	0.427-1.326
Mean LAD territorial strain before	2.112	1.746– 2.837	0.001*
Number of vessels	1.456	1.162-2.546	0.076

Univariate analysis of regional LAD strain recovery reported a lower incidence of recovery with multi-vessel disease (*P*=0.035), and LAD total obstruction (CTO) (0.045). In multivariate analysis, we found that the pre-PCI GLS value (OR: 2.116, 95%, CI:1.857- 2.784, P:0.005), and the pre-PCI mean regional LAD strain value were the only independent predictors of poor LAD segmental strain recovery (Table 3).

Table (3): Multivariate analysis of predictors of failure of recovery according to LAD territorial strain (n=12)

Variables	Multivariate analysis		
	B	95%CI	P-value
GLS before	2.116	1.857- 2.784	0.005*
Number of vessels	0.645	0.308-1.31	0.126
CTO	0.363	0.108- 0.958	0.437

Table (4): Predictive ability of GLS and LAD territorial strain (before treatment) in the prediction of recovery according to LAD territorial strain:

	GLS	LAD territorial strain
AUC	0.545	0.477
Cut off point	-9.6%	-7.3%
Sensitivity	82%	76%
Specificity	46%	42%
PPV	30%	48%
NPV	66%	76%
Accuracy	58%	50%
P	0.645	0.818

DISCUSSION

The ESC revascularization guidelines 2018 stated that revascularization of proximal LAD stenosis in more than 50% of patients with stable angina, is highly recommended IA [(7)] owing to its high morbidity and mortality risk.

Two D speckle tracking analysis has shown to be highly sensitive for the detection of subclinical ischemia & LV dysfunction and the early impact of reperfusion on global and territorial myocardial function [(13)]**.**

A total of 53 patients admitted to Mansoura University Specialized Medicine Hospital between December 2017 and November 2018 for elective stenting of the proximal left anterior descending coronary artery (whether single or multi-vessel), were enrolled for a prospective, non-randomized study.

Two dimensional/Doppler echocardiography and speckle tracking echocardiography were done for all study populations before and 1 month after P-LAD stenting to study LV function parameters (including EF, GLS and mean LAD territorial strain) & LV function recovery using GLS, and regional LAD mean strain. One-year clinical follow-up as regards cardiovascular MACE was done after PCI & their predictors.

In our study, the pre-stenting basal GLS was decreased significantly in patients with proximal LAD significant stenosis even with normal EF (-13.5 as the median), and the LAD strain was lower (-11.9).

In our study, there was a significant improvement of the global longitudinal strain (GLS) one month after PCI (p< 0.01), with no statistically significant improvement of 2D LVEF.

Park *et al.* [(21)] found that there was a significant increase in GLS after revascularization PPCI of LAD.

El Moneum *et al.* [(22)] demonstrated that there were significant increases in GLS after LAD PCI.

Also, **Rifqi *et al.*** [(23)] reported significant improvement of LV function by GLS-Avg (p<0.0001) higher than LV EF improvement (p<0.001), measured by the Simpson method while our study measured LVEF by M-mode.

However, **El Moneum *et al.*** [(22)] demonstrated that there were no significant differences in LVEDV, LVESV, and EF after LAD stenting because these parameters are indirect measurements of myocardial function since they are dependent on preload and afterload.

In the same way, **Gasior *et al.*** [(24)] **and Shehata** [(25)] found that there were no significant changes in LV dimension or LVEF after LAD stenting.

In our study, there was a significant parallel improvement of both average GLS & Mean LAD territorial strain after LAD stenting (P value respectively <0.01, <0.001). However, **Shehata**[(25)] reported significant improvement in the mean LAD territorial strain values (P <0.05) without reporting significant improvement in GLS four months post-PCI in patients with anterior STEMI.

Also, **Park *et al.*** [(21)] **and El Moneum *et al.*** [(22)] documented a significant increase in GLS after percutaneous revascularization of LAD.

Our results agreed with **Becker *et al.*** [(26)] that reported a correlation between GLS and contrast-enhanced MRI measurements of global and territorial scar size.

In our study, 66% of the study patients encountered recovery of the GLS against 77.4% mean LAD territorial strain recovery that had the most remarkable recovery percentage.

This was compatible with **Shehata *et al.*** [(27)] that found that 64% of perfused STEMI patients encountered recovery of GLS. Additionally, those recovered patients had shrinking scar sizes reflecting territorial LV function.

In our study, GLS recovery was found to be a better predictor for the occurrence of MACE than mean LAD territorial strain in one-year follow-up. 2.8% of the recovered GLS cases had MACE, compared to 33.3% in the non-recovered group with a P-value: of 0.019. While regarding the recovery of mean regional LAD strain, there was no significant correlation to the occurrence of MACE.

The results of our study confirm the safety & efficacy of percutaneous revascularization of proximal LAD lesions, in the form of a high success rate (98.9%), low rate of recurrent revascularizations (5.7%), less frequent MACE (13.2%), and low mortality (3.8%).

In consistence with our results, **Codner *et al.*** [(28)] documented lower occurrence of MACE (24.6%) & all-cause mortality (24.9%) after proximal LAD stenting.

At 4-year follow-up, patients with P-LAD stenting showed a decline in death rates, stent thrombosis, and MACE to be just as low as non-proximal LAD stenting.

While **Codner *et al.*** [(28)], In multivariate analysis at 1-year follow-up, patients had similar clinical MACE outcomes independent of stenting location of LAD, so proximal LAD stenting was not an independent predictor of target lesion failure (P=0.48).

Also, **Roguin *et al.*** [(30)] stated that the incidence of MACE in P-LAD patients was higher than in non-proximal LAD (7.6% vs. 6.0%; p = 0.020). However, multivariate analysis showed no independent correlation between PCI to P-LAD lesions and clinical outcomes.

The NOBORI-2 trial reported no differences in PCI outcomes using Bioliomus DES between proximal and non-proximal LAD territory[(31)].

In multivariate analysis, we found that the pre-stenting GLS value was one of the independent predictors of a greater incidence of MACE after P-LAD stenting.

This was concordant with **Paul and George**[(32)] who found that pre-stenting GLS was an excellent predictor of LV dysfunction & MACE after LAD primary PCI

Park *et al.* [21] documented that global LV strain was an independent predictor of mortality, congestive heart failure, and myocardial remodeling.

In our study, the pre-PCI GLS value and the pre-PCI mean LAD territorial strain value independently predicted recovery of GLS, and mean LAD territorial strain.

Shehata *et al.* [27] documented that basal GLS values are the most important predictors for LV functional recovery after STEMI reperfusion.

Similarly, **Mollema *et al.*** [33] reported that baseline GLS after acute MI significantly correlated with recovery of LV function after 1-year follow-up.

Shehata *et al.* [25] also reported that better GLS strain values (more negative) correlated with better post-stenting recovery of left ventricular function.

Similar to this study, **Park *et al.*** [21] documented a positive correlation between baseline LVEF% and GLS on one side, and better post-stenting myocardial function recovery on the other side.

In our study, Univariate analysis reported a correlation between multivessel coronary arterial disease and lower incidence of post-PCI GLS recovery (P=0.031).

In concordance with our results, **Ottervanger *et al.*** [34] approved that the presence of multi-vessel coronary stenosis was associated with a limited collateral flow that triggered a poor predictor of left ventricular recovery.

Study Limitations: As regards our study limitations included a small sample volume in one center, short-term follow-up with unequal sex distribution (male 94% of the study population), also Simpson method might be more accurate than LV dimensions qualification for LVEF, lastly Lack of comparison of data acquired by speckle tracking echocardiography with other standard imaging modalities as MRI.

CONCLUSION

GLS & mean LAD territorial strain provided a more precise objective quantification of successful global and regional recovery of LV function after proximal LAD revascularization & predictor for MACE.

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