PROGNOSTIC VALUE OF CIRCUMFLEX ARTERY MOTION AS A MEASUREMENT OF LEFT VENTRICULAR LONG-AXIS SYSTOLIC FUNCTION IN PATIENTS TREATED WITH PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Background: Accurate assessment of LV systolic function during primary PCI can help to optimize reperfusion strategies and has many prognostic implications. Circumflex artery motion (CAM) can be measured during primary PCI to reflect LV long-axis function which is an accurate indicator of LV systolic function.

Aim of the work: to test the validity of CAM as a measurement of LV long-axis systolic function in anterior STEMI patients treated with primary PCI and to determine its prognostic value.

Patients and Methods: CAM was measured using coronary angiography during primary PCI in 50 STEMI patients. Echocardioghraphic (M-mode, tissue Doppler and speckle-tracking) assessment of LV long-axis systolic function was performed within 24 hours after primary PCI. Follow-up echocardiography was scheduled after 6 months. Reverse remodeling was defined as a reduction >10% in LV end-systolic volume by the end of follow-up period.

Results: Strong correlation was found between CAM and echocardiographic parameters of LV long-axis systolic function (p for each < 0.001) as well as LVEF (r= 0.845, p< 0.001) 24 hours after successful primary PCI. Patients were dichotomized according to the median value of CAM (median CAM: 13.9 mm). Supra-median CAM was associated with higher LVEF (56.0±7.4 vs. 42.6±3.6, p<0.001), lower peak troponin (6.43±2.6 vs. 11.13±2.78 ug/L, p<0.001) and lower incidence of composite major adverse cardiac events (3.8% vs. 45.8%, p=0.001). A CAM cutoff value of 10.8 mm (sensitivity 96% and specificity 100%) accurately predicted reverse remodeling at 6 months.

Conclusion: CAM measured at the time of primary PCI can predict LV systolic function loss, adverse clinical outcome and reverse remodeling in STEMI patients. Thus it can gauge the choice of reperfusion strategy and adjunctive therapy.

Key Words: CAM (circumflex artery motion), LV long-axis systolic function, primary PCI.

INTRODUCTION

Since the time of Leonardo da Vinci, the importance of Left ventricular (LV) long-axis function has been described (1). During a single cardiac cycle, shortening, thickening, and torsion of the LV occur (2). Shortening is mediated by movement of the atrio-ventricular plane (AVP) toward the apex; the latter is relatively fixed (3). Without this long-axis shortening, normal sarcomere contraction would lead to an ejection fraction of less than 30% (4). Depressed LV long-axis function correlates with severity and prognosis of many cardiovascular diseases and it is an early indicator of subclinical systolic dysfunction (5). Being mediated by subendocardial fibers, LV long-axis function is affected early in ST elevation myocardial infarction (STEMI) and recovers early with successful reperfusion (6, 7).

When performed rapidly by an experienced team, primary PCI restores epicardial as well as myocardial perfusion (8), limits infarct size, reverses LV dysfunction and reduces mortality (9). At time of performing primary PCI, prediction of reverse remodeling is of utmost importance because it helps optimizing therapeutic strategies, e.g. the use of glycoprotein (GP) IIb/IIIareceptor inhibitors; thrombectomy and total revascularization are justified in patients with low potential of reverse remodeling. Reverse remodeling after primary PCI occurs more likely with effective microvascular circulation within the infarct zone (10, 11), small infarct size (12), restoration of normal LV mechanics and synchronicity (13, 14) and short ischemic time (10, 15).

Studies in patients with STEMI found that LV long-axis function accurately predicts final infarct size (16), microvascular perfusion (17), extent of myocardial viability (18) and LV remodeling and major adverse cardiac events (MACE), such as congestive heart failure and death (19).

As one part of the circumflex (Cx) artery runs in the AV groove, this part is assumed to represent the AVP. Cx artery motion (CAM) (20) can be used to measure LV long-axis function at time of primary PCI. This allows rapid patient triage on the catheterization table without neither prolonging the door-to-balloon time nor the need of "in-lab" echocardiography machine.

The aim of this study is to determine the correlation between CAM and echocardiographic parameters of long-axis as well as global LV systolic function in patients with anterior STEMI and to determine the value of CAM in predicting LV reverse remodeling after successful primary PCI.

PATIENTS AND METHODS

Our study was performed in the faculty of medicine, Zagazig University Hospital, during the period from May 2012 to June 2014. It included 50 patients with first STEMI diagnosed by typical ischemic chest pain lasting more than 30 minutes associated with persistent ST segment elevation >

2mm in two or more of V1 through V6 leads. Duration of chest pain shouldn't exceed 24 hours and the coronary anatomy should suitable for primary PCI of the infarct related artery (IRA). The following patients were not included in the study: history of previous MI , previous revascularization, atrial fibrillation(AF) rhythm, complete left bundle branch block (LBBB) or pacemaker, coexistence of other significant cardiac disorders (valvular lesions, cardiomyopathies), patients without identifiable apical branches of left anterior descending (LAD) artery, patients with totally occluded Cx artery, angiographically unsuccessful PCI defined as antegrade TIMI flow < 3 and/or >30% residual stenosis of the IRA and patients with poor echocrdiographic windows.

All patients were subjected to:

1. **Complete history taking** with emphasis on cardiac risk factors including hypertension, smoking, diabetes mellitus and hypercholesterolemia.
2. **Full clinical assessment** with special attention to hemodynamic parameters.
3. **Electrocardiography (ECG)** on admission and 90 minutes after primary PCI.
4. **Laboratory work-up** including creatine kinase-myocardial band (CK-MB) and troponin I on admission and serially every 24hours after the PCI procedure to determine the peak concentration for each marker.
5. **Coronary angiography and primary PCI:** Cannulation and contrast injection were done in the left and right coronary systems using suitable catheters before fixing the culprit lesion in LAD. Balloon predilatation, thrombectomy, stenting technique, and administration of glycoprotein IIb/IIIa receptor inhibitors were left to the operator's discretion. All patients were loaded with dual anti-platelets and were effectively anticoagulated.
6. **Assessment of CAM:**

The measurement was made in right anterior oblique (RAO) 30 degree projection both at end-diastole and end-systole. The amplitude of CAM was calculated as the difference between these two distances. For each patient 2 measurements were taken:

i- The first measurement from a proximal point on the horizontal part of the Cx artery and the most apical part of LAD artery.

ii- The second measurement from a distal point on the horizontal part of the Cx artery and the same apical part of LAD artery. The mean of the 2 measurements were taken to represent CAM (**Figure 1**).

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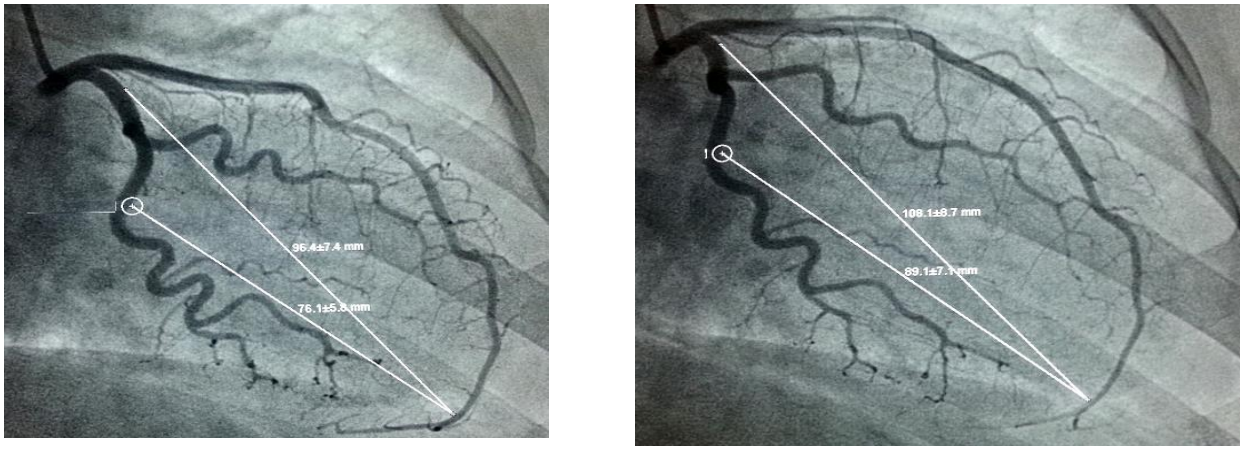

Figure 1: Method of measurement of circumflex artery motion in end-systole (left) and end-diastole (right). CAM= end-diastolic length-end-systolic length.

7. **Echocardiographic examination:** was done using GE, Vivid E9 machine equipped with a 4 MHz transducer. The following modalities were used:

a- **2-D echocardiography:** to calculate the length of LV long-axis at end-diastole, LV volumes (end-systolic and end-diastolic) and LVEF using the biplane Simpson's technique (22).

b- **M-mode echocardiography:** to measure mitral annular plane systolic excursion (MAPSE). The AVP-fractional shortening was calculated by dividing MAPSE by the length of the LV long-axis (23).

c- **Color-flow Doppler echocardiography:** to assess severity of mitral regurge (MR) semi-quantitatively. According to vena contracta width (the narrowest portion of MR jet downstream from the mitral orifice), MR was characterized as: mild (vena cnotracta width < 3 mm), moderate (vena

contracta width 3-6 mm) and severe (vena contracta width ≥ 7 mm) (24).

d- **Tissue Doppler echocardiography:** Measurements of peak systolic velocity (S') at the septal, lateral, inferior, and anterior mitral annulus were taken separately and averaged (25). The degree of LV long-axis dyssynchrony was measured as the maximum difference between Q-S' intervals from the four sites of mitral annulus. Q-S' intervals represent the time lag between the Q wave in the ECG and peak S' waves (26).

e- **Speckle tracking Echocardiography to measure global long-axis peak strain (GLPS):** From optimal 4-chamber, 2-chamber and 3-chamber views, global longitudinal peak strain (GLPS) is measured using automated function imaging (AFI). Then, the 3 measurements were averaged (3).

8. Follow-up:

All patients were discharged at maximal medical treatment. Clinical evaluation at 2-4-6 months and echocardiographic evaluation at 6 months were done. A > 10% reduction in LVESV at 6 months follow-up was used to define reverse remodeling (27).

Intra-observer and Inter-observer Variabilities:

Inter-observer variability was calculated through evaluating 10 random patients by 2 experienced independent observers blinded to the study. Intra-observer variability was calculated through evaluating 10 patients by the same observer but at 2 different points of time.

Statistical methods:

Kolmogorov–Smirnov test was used to confirm normal distribution of continuous variables which were expressed as mean values ± 1standard deviation. However, variables not normally distributed were expressed as medians (interquartile ranges). Categorical variables were expressed as absolute numbers and frequency percentages. Patients were dichotomized according to median value of CAM. The Pearson χ^2-test, Independent-Samples T-test and Mann-Whitney U-test were used to compare categorical variables, normally distributed continuous variables and skew-distributed continuous variables; respectively. Receiver operating characteristic (ROC) curve was used to define the CAM cutoff value with best accuracy for prediction of reverse remodeling at the end of follow-up period. P value <0.05 was considered significant.

RESULTS

The demographic and angiographic characteristics of the study participants are presented in **Table 1**.

Table (1): Demographic and angiographic characteristics of the whole study group (50 patients):

Variables			No (%)
Age (mean ± SD) (years)			57± 8
Sex		Male	43 (86 %)
		Female	7 (14 %)
Risk factors		Diabetes Mellitus	28 (56 %)
		Hypertension	20 (40 %)
		Current Smoking	19 (38 %)
		Dyslipidemia	10 (20%)
Vital signs		Admission heart rate (beats/min)	92±20
		Admission SBP (mmHg)	135±28
		Admission DBP (mmHg)	83±12
LV failure		NO no(%)	24 (48%)
		Yes no (%)	26 (52%)
		Killip class I	18 (69.2 %)
		Killip class II	4 (15.4%)
		Killip class III	4 (15.4%)
Ischemic time (minutes)			574±336
Peak CK-MB release (ug/L)			153.9±67.02
Peak troponin release (ug/L)			8.69±3.56
CAM (mean±SD) (mm)			14.2±3.9

CAM: circumflex artery motion, **DBP:** diastolic blood pressure, **SBP:** systolic blood pressure; **TIMI:** thrombolysis in myocardial infarction.

Correlation between CAM and echocardiographic measures of LV long-axis function:

Strong correlation was found between CAM and echocardiographic parameters of LV long-axis systolic function (p for each < 0.001) as well as LVEF 24 hours after successful primary PCI (r= 0.845, p< 0.001) **(Figure 2)**.

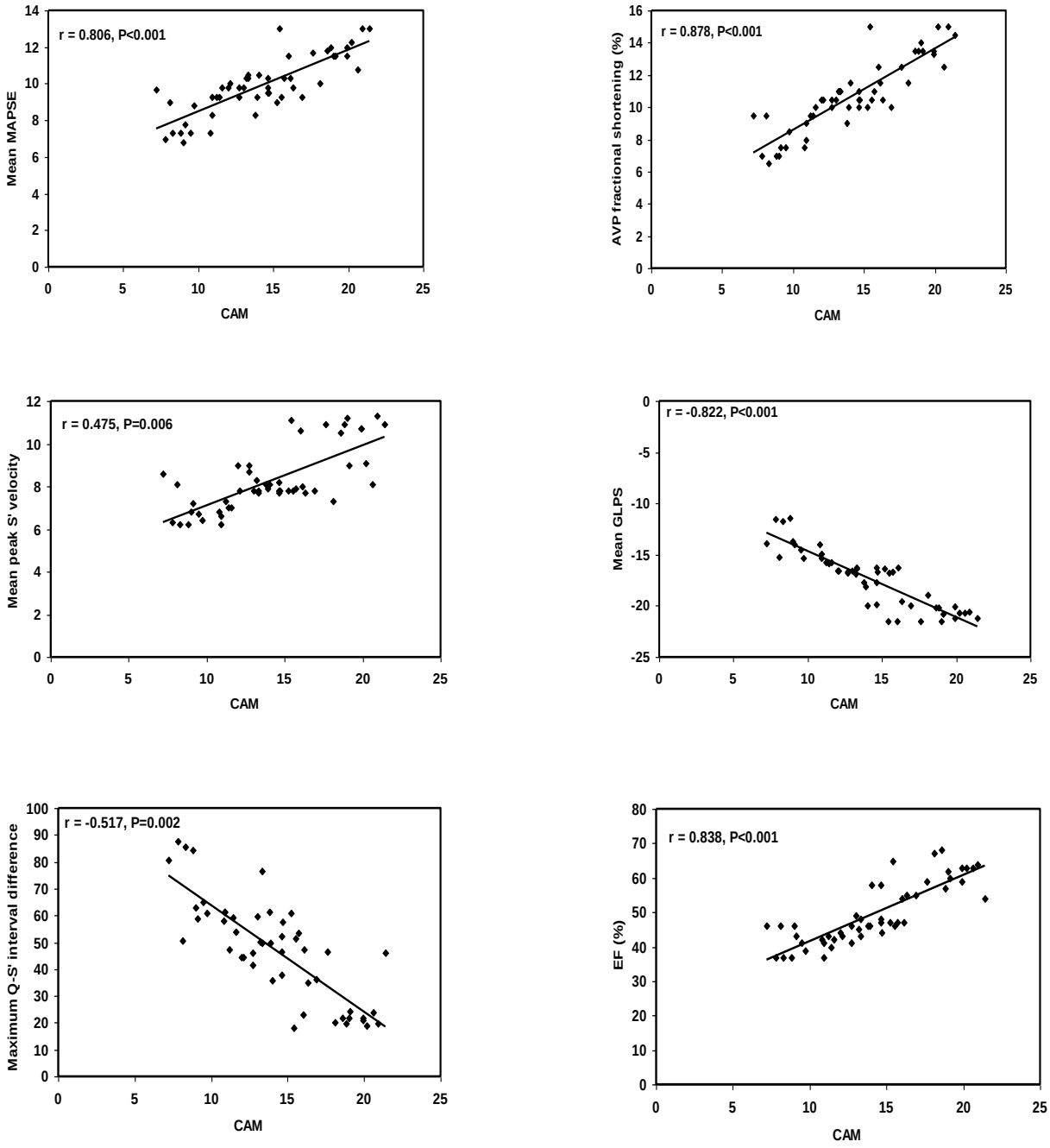

Figure 2: Correlation between CAM and mean MAPSE (r= 8.6, p<0.001), AVP fractional shortening (r= 0.878, p<0.001), mean peak S' velocity (r=0.475, p=0.006), mean GLPS (r=-0.822, p<0.001), LV longitudinal systolic dyssynchrony (r=-0.517, p=0.002) and LVEF (r=0.838, p<0.001). AVP: atrio-ventricular plane, EF: ejection fraction, GLPS: global longitudinal peak strain, MAPSE: mitral annular plane systolic excursion.

Comparison between the 2 CAM groups:

Patients were divided into 2 groups according to median CAM (median CAM: 13.9 mm). **Table 2** shows comparison between the 2 CAM groups according to clinical and angiographic data.

Table (2): Comparison between the two CAM groups:

Variables (Mean ± SD)		Infra-median CAM (n=24)		Supra-median CAM (n=26)		P value
		No	%	No	%	
Age (years)		59.38 ± 7.52		55.5 ± 7.92		0.083
Sex	**Male**	22	91.7 %	21	80.8 %	0.267
	Female	2	8.3 %	5	19.2 %	
Risk Factors	**Diabetes**	18	75 %	10	38.5 %	0.009
	Hypertension	9	3.7 %	11	42.3 %	0.729
	Current smoking	9	3.7 %	10	38.5 %	0.944
	Dyslipidemia	4	16.7 %	6	23.1 %	0.571
Heart rate (beat/min)		102.42 ± 18.82		82.38 ± 15.84		<0.001
SBP (mmHg)		134.58 ± 29.48		134.62 ± 27.45		0.997
DBP (mmHg)		82.5 ± 12.59		83.85 ± 11.34		0.693
Killip class >1		8	47%	0	0%	0.047
Peak CK MB (ug/L)		202.39 ± 48.22		109.19 ± 48.26		<0.001
Peak Treponin (ug/L)		11.13 ± 2.78		6.43 ± 2.6		<0.001
Ischemic time (min)		864.17 ± 195.98		301.15 ± 164.85		<0.001
TIMI 3 after PCI		8	33.3 %	20	76.9 %	0.002
ST segment resolution		12	50%	21	80.8%	0.02
MACE	**Non-fatal MI**	2	8.3 %	0	0 %	0.435
	New CHF	9	37.5 %	1	3.8 %	0.020
	Composite MCE	11	45.8 %	1	3.8 %	0.001

CHF: congestive heart failure, **CK MB:** creatine kinase-myocardial band, **DBP:** diastolic blood pressure, **MACE:** major adverse cardiac events, **MI:** myocardial infarction, **PCI:** percutaneous coronary intervention, **SBP:** systolic blood pressure; **TIMI:** Thrombolysis In Myocardial Infarction.

Prediction of reverse remodeling at 6 months:

By univariate logistic regression of independent predictors of reverse remodeling (> 10% reduction in LVESV at 6 months follow-up), we found that CAM, AVP fractional shortening at 24 hours, peak troponin and peak CK-MB predicted reverse remodeling with a highly significant value. Age, admission heart rate and blood pressure, use of thrombectomy, successful ST resolution, mean MAPSE at 24 hours, mean peak S' at 24 hours, mean GLPS at 24 hours and LV long-axis systolic synchrony at 24 hours also predicted reverse remodeling with a significant value **(Table 3)**. After multivariate logistic regression, only CAM remained significant **(Table 4)**. To determine a cutoff value for CAM, ROC curve analysis was done (AUC, 0.99; 95% CI 0.88–1.0, P< 0.0001). A cutoff value for CAM of 10.8 mm was found to be predictive with a sensitivity of 96% and a specificity of 100% (**Figure 3**).

Table (4): Univariate logistic regression of potential predictors of reverse remodeling 6 months post-PPCI:

Variables	RC	SE	OR	95% CI	P
Gender (male)	+ 0.747	0.405	2.111	0.955 – 4.666	0.065
Age	+ 0.014	0.006	1.014	1.002 – 1.027	0.027
Heart rate (b/min)	+ 0.008	0.004	1.008	1.001 – 1.016	0.030
SBP (mmHg)	+ 0.007	0.003	1.007	1.001 – 1.013	0.017
DBP (mmHg)	+ 0.012	0.005	1.012	1.002 – 1.021	0.014
LV failure	+ 0.916	0.483	0.058	0.970 – 6.443	0.058
Killip class > I	+ 1.099	1.155	3.000	0.312 – 28.841	0.341
Peak CK MB (ug/L)	- 0.007	0.002	0.993	0.989 – 0.997	**0.001**
Peak Treponin (ug/L)	- 0.108	0.036	0.898	0.837 – 0.898	**0.003**
Ischemic time (min)	+ 0.001	0.000	1.001	1.000 – 1.002	0.109
Thrombectomy	+ 0.847	0.398	2.333	1.069 – 5.095	0.033
CAM	+ 0.110	0.037	1.116	1.038 – 1.200	**0.003**
ST resolution	+ 1.674	0.629	5.332	1.554 – 18.297	0.008
EDV at 24 h	+ 0.005	0.003	1.005	1.000 – 1.010	0.065
ESV at 24 h	+ 0.008	0.005	1.008	0.999 – 1.018	0.089
MR at 24 h (mild)	+ 0.511	0.730	1.667	0.398 – 6.974	0.484
Mean MAPSE at 24 h (cm)	+ 0.126	0.046	1.134	1.037 – 1.241	0.006
AVP fractional shortening at 24 h (%)	+ 0.127	0.045	1.135	1.040 – 1.239	**0.004**
Mean Peak S' at 24 h	+ 0.137	0.053	1.147	1.033 – 1.273	0.010
Q-S' Maximum difference at 24 h	+ 0.005	0.002	1.005	1.001 – 1.009	0.019
Mean GLPS at 24 h	- 0.073	0.027	0.929	0.882 – 0.979	0.006

AVP: atrio-ventricular plane, **CAM:** circumflex artery motion, **CI:** confidence interval,**CK MB:** creatine kinase-myocardial band, **DBP:** diastolic blood pressure, **SBP:** systolic blood pressure, **EDV**: end-diastolic volume, **ESV:** end-systolic volume, **GLPS:** global longitudinal peak strain, **LV:** left ventricle, **MAPSE:** mitral annular plane systolic excursion, **MR:** mitral regurgitation, **OR:** odds ratio, **P value:** significance, **RC:** regression coefficient, **SE:** standard error.

Table (5) Multivariate logistic regression of potential predictors of reverse remodeling 6 months post PCI

Variable	RC	SE	OR	95% CI	P
CAM	+ 1.8535	0.6057	6.3822	1.9469 – 20.9216	0.002

CAM: circumflex artery motion**, CI:** confidence interval, **OR:** odds ratio, **RC:** regression coefficient, **P value:** significance**, SE:** standard error. Constant: - 15.6595.

Reproducibility: Interobserver and intraobserver agreement for assessment of CAM was 93% and 95%; respectively.

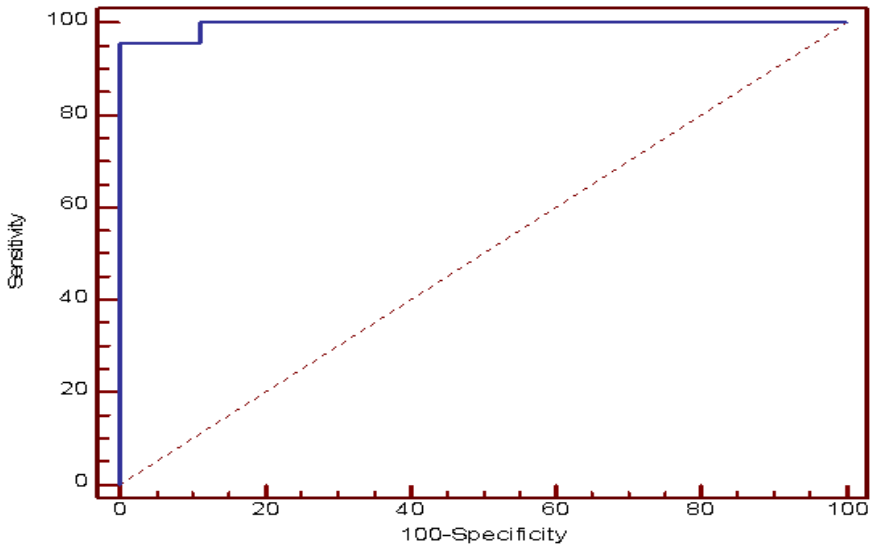

Figure 5: ROC curve of CAM in prediction of reverse remodeling 6 months after primary PCI.

DISCUSSION

Main findings of the current study are (1) there is strong correlation between CAM and echocardiographic (M-mode, tissue Doppler and speckle tracking) parameters of LV long-axis function, (2) CAM was strongly correlated with LVEF 24 hours after successful primary PCI, and (3) A CAM cutoff value of 10.8 mm accurately predicted reverse remodeling 6 months after successful primary PCI.

Correlation between CAM and echocardiographic parameters of LV long-axis function:

In the current study, we found that CAM was strongly correlated with echocardiographic parameters of long-axis LV function. This can be explained by the fact that the first horizontal part of the Cx artery is situated in the AV groove. Consequently, movement of this part can reflect left AVP displacement towards LV apex. **Emilsson K. et al.** (20) used the same technique to measure CAM and demonstrated no difference between CAM and mitral annular motion (MAM) both at the level of the lateral part of the annulus and the mean MAM from the four sites of the annulus.

Correlation between CAM and LVEF:

This study found a significant correlation between CAM and LVEF measured by modified Simpson's method. Furthermore, patients with supra-median CAM tended to have higher LVEF. A similar finding was observed by **Kahari A. et al.** (32) who found a significant correlation between CAM and LVEF estimated by ventriculography. Many studies support the use of echocardiographic parameters of long-axis LV function as surrogates of global LV function (33, 34).

Correlation between CAM and LV long-axis systolic dyssynchrony:

The study found a significant negative correlation between CAM and LV long-axis systolic dyssynchrony measured as the maximum Q-S' interval difference. LV dyssynchrony have been observed in the setting of STEMI despite normal systolic function and normal QRS duration (35). In addition, it was demonstrated that dyssynchrony associated with STEMI was mainly determined by the infarct size measured by MRI (36). **Turan B. et al.** (37) demonstrated that after primary PCI, a maximum Q-S' interval difference of > 56 msec predicts LV remodeling at 6 months with a sensitivity of 73% and a specificity of 84%.

Comparison between the 2 CAM groups:

The current study showed that DM was significantly more prevalent in the group with infra-median CAM. Diabetic cardiomyopathy has been defined as a primary myocardial disease in diabetic patients without significant epicardial CAD, hypertension, or valvular heart disease. It is thought to be mediated by myocardial steatosis, microvascular disease, and myocardial fibrosis (38). These changes are reflected on long-axis function as shown in many studies using both tissue Doppler imaging (39) and speckle-tracking imaging (40).

There was a significant difference between both groups regarding clinical LV failure and Killip class. This is explained by the fact that LV longitudinal function, measured by cardiac magnetic resonance, is the primary contributor to LV function, and accounts for approximately 60% of the SV (41).

Ischemic time was significantly shorter in the group of supra-median CAM, probably reflecting lesser myocardial damage. This is consistent with the negative correlation between ischemic time and GLPS reported by **Bertini M. et al** (42). Longer ischemic time will ultimately lead to larger infarct size and limit reverse remodeling (43). In addition, it will lead to a mature fibrin-rich thrombus which predisposes to distal embolization and decreases microvascular flow (44).

Peak CK-MB and troponin were significantly higher in the group of infra-median CAM. Higher cardiac biomarkers reflect more sizable infarcts, compromised microvascular perfusion, refractory thrombi, a more thrombophilic milieu and longer ischemic time. These factors would negatively impact on long-axis LV function. **Bertini M. et al.** (42) and **Woo J. et al.** (45) reported negative correlation between cardiac biomarkers and GLPS.

After primary PCI, ST segment resolution occurred more in the group of supra-median CAM. ST segment recovery has been shown to be related to cell membrane integrity, myocyte function and tissue level reperfusion (46). Many studies report the strong correlation between ST resolution and long-axis LV function (47, 48).

In the current study, TIMI 3 flow was identified in 8 patients (33.33 %) of infra-median CAM group versus 20 patients (76.9 %) of supra-median CAM group (P value 0.002). This may reflect shorter ischemic time, smaller and less mature thrombus, better microvascular preservation, smaller final infarct size and normalized LV mechanics.

Prediction of reverse remodeling at 6 months:

The current study found that CAM, AVP fractional shortening at 24 hours and peak CK-Mb and troponin level predicted reverse remodeling with a highly significant value. Other echocardiographic parameters of long-axis LV function at 24 hours also predicted reverse remodeling with a significant value. After multivariate logistic regression, only CAM remained significant. A cutoff value for CAM of 10.8 mm was found to be predictive with a sensitivity of 96% and a specificity of 100%.

This may be explained by that long-axis LV function is related to final infarct size (16), microvascular occlusion (17) and extent of myocardial viability (18). Collectively, they determine the contractile recovery of LV function after primary PCI.

Peak troponin and CK-MB could significantly predict LV functional recovery at 6 months. This finding support previous findings that peak troponin level strongly predicts the recovery of LV function even more important than any other clinical measure (49, 50).

Study Limitations:

Our findings are restricted to anterior STEMI patients with culprit lesions in LAD treated with primary PCI. So, these results cannot be extrapolated to right coronary or Cx artery STEMIs. The study included a relatively small number of patients but the 2 CAM groups were matched as regards age, gender and most of risk factors.

The study shows a rather good reproducibility for CAM. In some patients however, this measure cannot be obtained, namely in patients lacking visible branches in the apical region or patients having total occlusion of the proximal horizontal part of the Cx artery. In addition, it still remains to investigate the validity of CAM in patients with AF, LV hypertrophy and LV aneurysm.

CONCLUSION AND CLINICAL IMPLICATIONS

CAM measured at time of primary PCI correlates excellently with LVEF and negates the need for "in-lab" echocardiography machine as well as ventriculography. Is also allows rapid assessment of LV function without prolonging the "door-to-balloon" time. Furthermore, it allows prediction of reverse remodeling at 6 months which helps optimizing therapeutic strategies at time of mechanical reperfusion. Use of GP IIb/IIIa receptor inhibitors, thrombectomy and total revascularization are justified in high-risk patients with lower CAM (< 10.8 mm).

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