**A Pilot Study to Predict Future Cardiovascular Events by Novel Four-dimensional Echocardiography Global Area Strain in ST-Elevation Myocardial Infarction Patients Managed by Primary Percutaneous Coronary Intervention**

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**Abstract**

**Context:** Four-dimensional speckle-tracking echocardiography (4D-STE) is ideal to accurately assess myocardial deformation. The novel 4D global area strain (GAS) uses global longitudinal and global circumferential strains (GCSs) to detect subtle changes in myocardium. **Aims:** The aim of this study was to determine the predictive value of 4D strain echocardiography for major adverse cardiovascular events (MACEs) in ST-elevation acute myocardial infarction (STEMI) patients after successful reperfusion by primary percutaneous coronary intervention (PCI).

**Settings and Design:** This was a longitudinal study at a single center. **Patients and Methods:** We enrolled 170 patients who underwent successful primary PCI. Each patient was evaluated with 2D echocardiography and 4D echocardiography with 4D strain parameters and followed up over a year for the occurrence of MACE. **Statistical Analysis Used:** Chi-square test, independent t-tests, and multivariate logistic regression analysis were used. **Results:** Over 1 year of follow-up, 32 MACE were recorded. Patients with MACE were more likely to have had percutaneous transluminal coronary angioplasty done during the index primary PCI intervention, multivessel coronary artery disease, higher left ventricular end-diastolic and end-systolic dimensions (left ventricle end diastolic dimension (LVEDD) and left ventricle end systolic dimension (LVEDD), respectively), lower 2D left ventricular ejection fraction (LVEF), higher baseline heart rate, higher end-diastolic and end-systolic volumes, lower 3D-LVEF, higher 4D global longitudinal strain, 4D-GCS, 4D-GAS, and lower 4D global radial strain (4D-GRS) ($P < 0.005$ for all parameters). The most powerful predictor for MACE among our study population is 4D-GAS, with the best cutoff value of $4D$-GAS >−17 ($P = 0.008$; odds ratio = 20.668; confidence interval = 2.227–191.827). **Conclusions:** The novel 4D-GAS echocardiography predicts adverse clinical events in STEMI patients managed by successful primary PCI.

**Keywords:** Four-dimensional global area strain, four-dimensional strain echocardiography, major adverse cardiovascular events

**INTRODUCTION**

ST-elevation myocardial infarction (STEMI) is the most serious complication of coronary artery disease (CAD). Primary percutaneous coronary intervention (PCI) performed by an experienced team in an acute setting is the recommended reperfusion strategy.[1] Remodeling of the left ventricle (LV) after an acute myocardial infarction (AMI) involves changes that affect LV structure and function.[2] Left ventricular ejection fraction (LVEF) is used to assess and predict clinical outcomes after AMI,[3] but its correlation with intrinsic myocardial contractility is limited by load dependency and complex LV geometry.[4] Because strain analysis by speckle-tracking technology accurately assesses the deformation of each myocardial segment, it correlates to myocardial performance.[5]

Recently, four-dimensional (4D) echocardiography has been developed to overcome the limitations of 2D speckle-tracking echocardiography (STE) using LV longitudinal, diastolic and end-systolic dimensions, lower 3D-LVEF, higher baseline heart rate, higher end-diastolic and end-systolic volumes, lower 3D-LVEF, higher 4D global longitudinal strain, 4D-GCS, 4D-GAS, and lower 4D global radial strain (4D-GRS) ($P < 0.005$ for all parameters). The most powerful predictor for MACE among our study population is 4D-GAS, with the best cutoff value of $4D$-GAS >−17 ($P = 0.008$; odds ratio = 20.668; confidence interval = 2.227–191.827). **Conclusions:** The novel 4D-GAS echocardiography predicts adverse clinical events in STEMI patients managed by successful primary PCI.
circumferential, radial, and areal strains acquired in real time.\cite{6} 4D echocardiography is able to measure strain dynamics in every myocardial segment using a 3D reconstruction of the LV and color mapping throughout the cardiac cycle.\cite{7,8}

This study evaluates the role of 4D global area strain (4D-GAS) in predicting the clinical outcomes of patients who underwent successful revascularization of STEMI by primary PCI.

**Patients and Methods**

**Patient selection**

Patients who presented to our hospital with acute STEMI from December 2015 to March 2017 were enrolled to the study. The diagnosis and treatment of patients with STEMI were carried out according to the European Society of Cardiology guidelines of 2012 on the diagnosis and management of STEMI.\cite{9} All enrolled patients had a successful primary PCI (restoration of thrombolysis in myocardial infarction III flow and myocardial blush grade II–III) in the occluded vessel and its territory. Patients with multivessel disease (64 patients, 37.6%) underwent PCI to the significant lesions in later sessions. All patients underwent 2D echocardiography and 4D strain echocardiography within 48 h after revascularization. Patients with atrial fibrillation, LVEF below 40%, cardiogenic shock, or moderate-to-severe valve disease were excluded. The patients were divided into two groups, according to the presence of major adverse cardiovascular event (MACE). Group I was made up of 32 patients who experienced MACE in the follow-up period, whereas Group II included 138 patients who did not experience MACE in the follow-up period.

**Ethics**

The study was approved by the university hospital research ethics committee, and all patients provided written informed consent. The study followed the principles of the Helsinki Declaration of 1975, as revised in 2000.

**Echocardiography**

**Conventional two-dimensional echocardiography**

Echocardiography was performed using Vivid E9 Ultrasound (GE Healthcare Vingmed ultrasound AS) equipped with a 2.5 MHZ transducer gated with ECG. The patient was positioned in the left lateral decubitus and was allowed to breathe normally. We measured left ventricular end-systolic volume (ml), left ventricular end-diastolic volume (ml), LVEF (%), using biplane Simpson’s method), and the wall motion score index (WMSI) through apical four-chamber, apical two-chamber, and apical long-axis views.\cite{10}

**Four-dimensional strain echocardiography**

Real-time, 4D, full-volume images were obtained using a 4V-D transducer probe (manufacturer details) set at a frequency of 1.5–40 MHZ, a frame rate >25/s, and in apical four-chamber view. The multiple cardiac cycle mode was used to ensure the inclusion of the whole LV cavity and its walls in the total volume of the image. The patient was instructed to hold his or her breath during 3–4 cardiac cycles in order to avoid stitching artifacts on the images.\cite{11}

EchoPAC software version BTII, 4D Auto LVQ (GE Vingmed Ultrasound AS), was used to perform data analysis on all 4D data sets. For semi-automated endocardial surface detection, the software automatically generated tracking of the endocardium and the epicardium. Endocardial mesh was used to measure the LVESV, LVEDV, and LVEF. The endocardial and epicardial web framework was used to measure the weight of the LV and the strain of the segmental and the whole LV. The software provides the following standard 4D echocardiographic parameter values: 4D LVEF, 4D LVESV and LVEDV, 4D stroke volume, cardiac output, and end-diastolic and end-systolic mass. In addition, the software provides peak systolic values of longitudinal, radial, and circumferential strains of each of the 17 LV segments, as well as the mean values of the global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), and the GAS.

All echocardiographic measurements were analyzed by two independent operators without knowledge of the patient’s clinical status or coronary angiography. The average value of three cycles was calculated and used in our analyses. Agreement between the two operators was acceptable (coefficient of variation = 8.5%).

**Follow-up**

All candidates were followed up for 1 year in an outpatient setting and by telephone. The follow-up end point was the occurrence of MACE, defined as cardiac death, cerebrovascular stroke, ventricular arrhythmias (nonsustained or sustained ventricular tachycardia), myocardial infarction, a need for repeated revascularization, and heart failure requiring hospitalization.

**Statistical analysis**

All descriptive data were expressed as mean ± standard deviation. Baseline clinical parameters and echocardiography parameters were compared using Chi-square tests and independent t-tests. Multivariate logistic regression analysis was performed for clinical and echocardiographic parameters. The coefficient of variation was used to assess interobserver variability. Statistical significance was set at P < 0.005.

**Results**

A total of 171 patients were enrolled in our study. One patient was lost to follow-up due to death from bladder cancer. Thirty-two patients had reported MACE: 16 patients developed heart failure, 6 patients had recurrent MI and ventricular arrhythmia, 9 patients had repeated revascularization, and one patient had a nonfatal cerebrovascular stroke. Six patients experienced cardiac death [Table 1].

There is no significant difference in demographic data, clinical data, risk factors, family history, history of previous
revascularization, laboratory findings, location of myocardial infarction, or pain to balloon time between the two groups [Table 2].

During the PCI procedure, Group I required significantly more percutaneous transluminal coronary angioplasty (68.8% vs. 46.4%; \( P = 0.023 \)). Patients in Group I are more likely to have multivessel CAD (59.4% vs. 32.6%; \( P = 0.005 \)) [Table 2].

As shown in Table 4, 2D echocardiography reveals higher LVEDD \(( P = 0.003 \)), LVESD \(( P = 0.002 \)), lower LVEF \(( P = 0.000 \)), and higher WMSI \(( P = 0.000 \)) in patients in Group I. As shown by 4D echocardiography, patients in Group I have a higher baseline heart rate at presentation \(( P = 0.000 \)), higher end-diastolic volume \(( P = 0.017 \)) and end-systolic volume \(( P = 0.001 \)), lower 3D LVEF \(( P = 0.000 \)), higher GLS \(( P = 0.000 \)), GCS \(( P = 0.000 \)), GAS \(( P = 0.000 \)) and lower GRS \(( P = 0.000 \)).

Multivariate logistic regression analysis for all significant parameters reveals that 4D-GAS is the most powerful predictor for MACE in patients who have STEMIs treated with primary PCI. The best cutoff value of 4D-GAS is found to be 4D-GAS >−17 \(( P = 0.008 \); odds ratio = 20.668; confidence interval = 2.227–91.827). These results are shown in Figure 1 and Table 5.

**DISCUSSION**

LV systolic performance is the cornerstone in the evaluation and follow-up of patients following myocardial infarction, and LVEF is the most used parameter. However, LVEF is limited by load dependency and complex LV structure, rendering myocardial strain analysis to be a more accurate assessment of cardiac function.5 As myocardial strain

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**Table 1: Occurrences of major adverse cardiac events**

| MACE                      | n (%) |
|---------------------------|-------|
| Positive                  | 32 (18.8) |
| Death                     | 6 (3.5)  |
| HF                        | 16 (9.4)  |
| MI or VA                  | 6 (3.5)  |
| Unplanned revascularization | 9 (5.3) |
| Stroke                    | 1 (0.6)  |

HF=Heart failure, MI=Myocardial infarction, VA=Ventricular arrhythmia, MACE=Major adverse cardiovascular events

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**Figure 1:** Best cutoff points for 4D echocardiography strains to detect MACE. The best cutoff value for 4D-GAS to detect MACE was −17 with a sensitivity of 87.5%, a specificity of 92%, a positive predictive value of 71.8%, and a negative predictive value of 96.9%. 4D = Four-dimensional, GAS = global area strain, GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, MACE = major adverse cardiac events

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**Table 2: Demographic data, risk factors, laboratory findings, and angiographic data**

| Parameter                  | Mean±/ SD Group I (n=32) | Mean±/ SD Group II (n=138) | \( P \) |
|----------------------------|--------------------------|-----------------------------|-------|
| Age (years)                | Mean±SD (range) 56.78±9.57 (35-80) | 54.93±9.03 (33-74) | 0.304 |
| Gender (%)                 | Female 12.5               | 14.5                        | 0.771 |
|                           | Male 87.5                 | 85.5                        |       |
| Smoking (%)                | Positive 75.0             | 75.9                        | 0.914 |
| DM (%)                     | Positive 56.3             | 47.8                        | 0.390 |
| HTN (%)                    | Positive 59.4             | 42.8                        | 0.089 |
| Dyslipidemia (%)           | Positive 25.0             | 30.4                        | 0.543 |
| FH of CAD (%)              | Positive 9.4              | 10.1                        | 0.896 |
| Previous revascularization (%) | 12.5                  | 5.1                         | 0.124 |
| Serum creatinine (g/dl)    | Mean±SD (range) 1.16±0.26 (0.6-1.8) | 1.17±0.20 (0.6-1.7) | 0.711 |
| Peak CKT (g/dl)            | Mean±SD (range) 3766.31±1495.15 (750-6300) | 3380.64±1362.18 (200-8000) | 0.158 |
| Peak MB (g/dl)             | Median (IQR) range 424 (290-735.5) (100-1100) | 385 (270-570) (145-3350) | 0.320 |
| Anterior (%)               | Positive 65.6             | 50.7                        | 0.128 |
| Inferior (%)               | Positive 15.6             | 30.4                        | 0.091 |
| Infero-post+lateral (%)    | Positive 15.6             | 12.3                        | 0.616 |
| Lateral (%)                | Positive 3.1              | 4.3                         | 0.754 |
| Posterior (%)              | Positive 0.0              | 2.2                         | 0.400 |
| Pain to balloon (h)        | Median (IQR) range 6 (4-8) (2-24) | 5 (4-7) (1-18) | 0.105 |

DM=Diabetes mellitus, HTN=Hypertension, FH of CAD=Family history of coronary artery disease, CKT=Creatinine kinase total, MB=Myocardial fraction, IQR=Interquartile range
analysis with speckle tracking allows for the evaluation of myocardial deformation (segmental and global), it is a precise assessment of LV systolic function. However, the myocardium cannot be evaluated by 2D-STE; 4D-STE must be used.

4D echocardiography uses longitudinal, circumferential, radial, and areal strains acquired in real time to measure myocardium.\(^\text{[10]}\) It uses a 3D reconstruction of the LV and color mapping to measure strain dynamics in every myocardial segment.\(^\text{[13,19]}\) 4D-GAS is the best 4D strain parameter to detect viable myocardium and microvascular obstruction.\(^\text{[12]}\) It reflects regional changes in endocardial surface area throughout the cardiac cycle and is a faster, more comprehensive, and easily reproduced assessment of myocardial function.\(^\text{[11]}\) In magnetic resonance imaging tagging, area strain has been shown to discriminate normal and ischemic zones better than most other strain indexes.\(^\text{[14]}\) However, limited data exist on the prognostic value of 4D-STE on clinical outcomes after AMI.\(^\text{[15]}\) Our study evaluated the predictive value of 4D echocardiography in the clinical outcomes of patients with STEMI after successful reperfusion by PCI. We found that family history of CAD, history of revascularization, and serum biomarkers are not correlated with the occurrence of MACE. These results are similar to those of Kim et al.,\(^\text{[16]}\) but opposed to those of Tsai et al.,\(^\text{[17]}\) who found a correlation between serum creatinine and MACE in patients with acute coronary syndrome. This may be explained by the exclusion of patients with renal impairment from our study. Our study also found that the location of myocardial infarction is not a statistically significant predictor for MACE. Again, this is in agreement with the results of a study reported by Cai et al.,\(^\text{[12]}\) Cai et al. showed a statistically significant correlation of MACE and anterior MI, but their follow-up period was longer than that in our study.\(^\text{[12]}\)

Several studies have found that LVEF obtained using 4D echocardiography is an independent predictor for MACE\(^\text{[18,19]}\) and

### Table 3: Percutaneous intervention data

| Culprit vessel | Group I, \(n\) (%) | Group II, \(n\) (%) | \(P\) |
|----------------|---------------------|---------------------|------|
| LAD            | 22 (68.8)           | 72 (52.2)           | 0.089|
| RCA            | 7 (21.9)            | 47 (34.1)           | 0.182|
| LCX            | 2 (6.3)             | 9 (6.5)             | 0.956|
| OM             | 1 (3.1)             | 8 (5.8)             | 0.543|
| PDA            | 0 (0.0)             | 1 (0.7)             | 0.629|
| D1             | 0 (0.0)             | 1 (0.7)             | 0.629|

| Lesions        |                  |                     |      |
|----------------|-------------------|---------------------|------|
| Single         | 13 (40.6)         | 93 (67.4)           | 0.005|
| Multiple       | 19 (59.4)         | 45 (32.6)           |      |

PTCA=Percutaneous transluminal coronary angioplasty, BMS=Bare metal stent, DES=Drug-eluting stent, LAD=Left anterior descending artery, RCA=Right coronary artery, LCX=Left circumflex artery, OM=Obtuse marginal artery, PDA=Posterior descending artery, D1=First diagonal artery, MACE=Major adverse cardiovascular events

### Table 4: Two-dimensional and four-dimensional echocardiographic parameters

| Parameter          | Group I \((n=32)\) | Group II \((n=138)\) | \(P\) |
|--------------------|---------------------|----------------------|------|
| LVEDD (mm)         | Mean±SD (range)     | 54.66±5.62 (42-64)   | 52.01±4.08 (42-63) | 0.003|
| LVESD (mm)         | Mean±SD (range)     | 40.44±5.31 (29-48)   | 37.34±4.92 (26-49) | 0.002|
| EF%                | Mean±SD (range)     | 45.97±5.03 (37-57)   | 51.20±6.03 (32-65) | 0.000|
| E/A (m/s)          | Mean±SD (range)     | 1.09±0.51 (0.4-2.63) | 0.96±0.34 (0.4-2.1) | 0.073|
| E/e’               | Mean±SD (range)     | 7.44±2.65 (3.33-16.8)| 6.50±2.18 (2.63-12.75)| 0.036|
| WMSI               | Mean±SD (range)     | 2.03±0.36 (1.18-2.5) | 1.73±0.38 (1-2.35) | 0.000|
| HR                 | Mean±SD (range)     | 91.59±15.82 (60-130) | 79.25±14.52 (53-126) | 0.000|
| FRAME RATE         | Mean±SD (range)     | 27.00±0.00 (27-27)   | 27.00±0.00 (27-27) | NA    |
| EDV (ml)           | Mean±SD (range)     | 112.75±19.83 (77-160)| 102.49±22.02 (1.3-157)| 0.017|
| ESV (ml)           | Mean±SD (range)     | 65.72±14.44 (37-95)  | 56.56±13.58 (33-102) | 0.001|
| EF%                | Mean±SD (range)     | 42.41±2.75 (40-51)   | 46.54±4.91 (33-67)  | 0.000|
| LVM                | Median (IQR) (range)| 130 (122-140) (100-153)| 134.5 (125-140) (86-1254)| 0.364|
| GLS                | Median (IQR) (range)| −8 (−8–6) (−13–5)   | −11 (−13–10) (−21–6) | 0.000|
| GCS                | Median (IQR) (range)| −8 (−8.5–6) (−18–4) | −11 (−13–10) (−20–6) | 0.000|
| GAS                | Mean±SD (range)     | 17.84±4.11 (10-30)   | 28.51±5.49 (10-43)  | 0.000|
| Median (IQR) (range)| −13.5 (−15–12) (−18–10) | −20 (−22–18) (−28–15)| 0.000|

HR=Heart rate, EDV=End-diastolic volume, ESV=End-systolic volume, EF=Ejection fraction, LVM=Left ventricular mass, GLS=Global longitudinal strain, GCS=Global circumferential strain, GRS=Global radial strain, GAS=Global area strain, LVEDD=Left ventricular end-diastolic diameter, LVESE=Left ventricular end-systolic diameter, EF=Ejection fraction, WMSI=Wall motion score index
that all 4D echocardiography strains are predictors of MACE.\cite{12,16} In our study, 4D-GAS is the most powerful predictor for MACE when compared with all other significant parameters using multivariate logistic regression analysis. This strain is able to measure the change of the area under the LV myocardial intima and analyze the cardiac function as a whole or as a segment. The systolic reduction in the area is a product of both longitudinal and circumferential shortening, which increases the magnitude of the change and, consequently, the sensitivity of 4D-GAS. This is in accordance with several other studies.\cite{12,16,20}

Our study is not without limitations. It was performed at a single center, included a small number of patients, and had a short follow-up period. Furthermore, 4D-STE is a new technology, and normal strain range values have not yet been established. This technology requires low frame rates, good quality images, a regular cardiac rhythm, and patient cooperation and is more expensive than 2D echocardiography. The intervendor variability has not yet been studied.

**Conclusions**

We found that 4D-GAS can predict MACE in patients with STEMI after successful primary PCI.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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