Automated Assessment of Myocardial Viability After Acute Myocardial Infarction by Global Longitudinal Peak Strain on Low-Dose Dobutamine Stress Echocardiography

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Background: Low-dose dobutamine stress echocardiography (DSE) assesses myocardial viability at the early stage of acute myocardial infarction (AMI), but its assessment is subjective and variable. Automated function image (AFI) determines global longitudinal peak strain (GLPS) based on tissue tracking technique. The ability of GLPS obtained by AFI during dobutamine stress to assess myocardial viability after AMI was investigated.

Methods and Results: Low-dose DSE at day 3 in 23 consecutive patients with AMI was performed using Vivid 7 (GE Healthcare). Segmental longitudinal peak strain with AFI and obtained GLPS was analyzed. Wall motion score index (WMSI) by echocardiography 1 month later was determined. In 18 patients, left ventriculography was also performed at 3.2±1.5 months later to obtain left ventricular ejection fraction (LVEF) and regional wall motion (RWM, SD/chord). GLPS was improved during dobutamine infusion at 10 μg·kg⁻¹·min⁻¹ (~12.9±3.5% to −15.2±3.6%, P=0.0004). GLPS during dobutamine stress showed good correlations with follow-up WMSI (R=0.47, P=0.02), with peak CK-MB (R=0.52, P=0.01), with RWM (R=−0.48, P=0.04), and with LVEF (R=−0.54, P=0.02), whereas GLPS at baseline showed no correlations with them. Averaged segmental peak strain at baseline and during stress were correlated with follow-up WMSI (R=0.50 and 0.43, respectively), but not with LVEF.

Conclusions: GLPS during dobutamine stress determined by AFI is a promising, objective index to assess myocardial viability on the early stage of AMI. (Circ J 2010; 74: 2158–2165)

Key Words: Acute myocardial infarction; Echocardiography; Myocardial contraction; Stress

Infarct size and myocardial viability are prognostic factors for major cardiac events after acute myocardial infarction (AMI),¹,² and their early assessment is important for the risk stratification.³⁻⁵ Low-dose dobutamine stress echocardiography (DSE) can be safely performed to assess myocardial viability on the early stage of AMI, and predicts functional and clinical prognosis.⁶⁻⁸ The accuracy of DSE, however, depends on image quality and the experience of the readers. Several quantitative imaging methods have been introduced to overcome these limitations.⁹⁻¹¹ Strain imaging based on tissue Doppler imaging is one of these methods to evaluate wall motion during stress quantitatively.¹² In the experimental model, systolic strain recovers by low-dose dobutamine stress in stunned but viable muscle, but not in infarcted myocardium.¹³ In patients with ischemic cardiomyopathy, strain imaging during low-dose dobutamine stress detects myocardial viability¹⁴ and predicts segmental functional recovery after revascularization¹⁵ more accurately than tissue velocity imaging.

However, tissue Doppler-based strain is substantially influenced by the angle between the ultrasound beam and the myocardial wall,¹⁶,¹⁷ which would limit its clinical use. Two-dimensional (2D) strain based on speckle tracking reliably measures myocardial strain independently from angle of ultrasound beam.¹⁸⁻²¹ 2D-strain accurately detects the changes in contraction during ischemia, dobutamine stress, or modification of hemodynamics.²²⁻²³ Automated function image (AFI) algorithm is a novel method based on 2D strain imag-
ing that enables the simultaneous quantification of myocardial strain in different left ventricular segments; its 3-click method minimizes variability related to a manual tracing of endocardial border required in an usual 2D-strain analysis. Peak longitudinal strain values are presented in a single bull’s-eye summary based on the 17-segment model. AFI also provides global longitudinal peak systolic strain (GLPS) by averaging apical 4-, 2-chamber and long axis views. GLPS assessed by 2D-strain is not only correlated with ejection fraction but also with wall motion score index (WMSI) in patients with ischemic heart disease. In the present study, we verified the feasibility and accuracy of AFI during low-dose DSE to assess myocardial viability on the early stage of AMI.

Methods

Study Population
We enrolled consecutive 25 patients with AMI who underwent successful primary percutaneous coronary intervention (PCI) within 6h after symptom onset. The diagnosis of AMI was based on chest pain prolonged by ≥30min, ST segment elevation of ≥2mm in at least 2 contiguous electrocardiograph leads, and greater than 3-fold increase in serum creatine kinase (CK) concentrations. One patient was excluded because of atrial fibrillation at the time of echocardiographic study, and another because catecholamine was used for the treatment of associated heart failure. Therefore, the final study population consisted of 23 patients. The study protocol was approved by the hospital’s Ethics Committee. One of the investigators obtained the informed consent from each patient before cardiac catheterization.

Study Protocol
We recorded 2D-echocardiogram on admission to determine the risk area. We performed low-dose DSE and AFI study at 3 days after the onset of AMI. Beta-blockers, if administered, were terminated 24h before the AFI study. We obtained standard parasternal long-axis, midventricular short-axis, apical long axis, apical 2- and 4-chamber images with the Vivid 7 ultrasound system (GE Healthcare) using a 3-MHz phased array probe. Grayscale images were obtained at a frame rate ≥50 per s, and the digital loops were subsequently saved onto a hard disk installed on the equipment for the later analysis. Recording of the baseline images, dobutamine was administered intravenously at 5μg·kg⁻¹·min⁻¹ for 3min, and then 10μg·kg⁻¹·min⁻¹ for the next 3min. We repeatedly recorded and stored parasternal and apical images at the peak dose. We performed 2D echocardiography at 1 month later in all patients as the follow-up study, and determined WMSI within the corresponding risk area.

Left ventriculography (LVG) was performed in 18 patients (78.3%) at a mean of 3.2±1.5 months later. We measured left ventricular ejection fraction (LVEF) by the biapical Simpson’s rule. Regional wall motion (RWM, SD/chord) within the culprit artery territory was analyzed using the centerline method. We did not perform LVG in other patients because of renal failure (3 patients) or requirement of additional coronary intervention (2 patients).

Analysis of Echocardiography Data
An experienced echocardiographer analyzed echocardiography at baseline, during 10μg·kg⁻¹·min⁻¹ of dobutamine infusion, and in the follow-up study. We divided left ventricle wall into myocardial segments based on a 17-segment model endorsed by American Society of Echocardiography. The risk area was defined as myocardial segments showing abnormal wall motion in echocardiogram on admission. We scored wall motion in each segment as 0=normal, 1=hypokinesis, 2=dyskinesis. WMSI was calculated as an averaged segmental score within the risk area.

We qualified the segmental and global left ventricular longitudinal strain in the baseline and the peak-dose images by AFI technique, using EchoPAC PC software (version 7.0.0, GE Healthcare). At first, the end-systolic frame was defined in the apical long-axis view. The closure of the aortic valve was marked, and the AFI software measured the time interval between the R-wave and aortic valve closure, which was used as a reference for the other view loops. We manually defined the mitral annulus and left ventricular apex with 3 index points at the end-systolic frame in each apical images. AFI algorithm automatically traced 3 concentric lines on the endocardial border, mid-myocardial layer, and epicardial border, and followed the endocardium from this single frame throughout the cardiac cycle. If the automated tracking would be inappropriate, we could manually adjust the region of interest. The left ventricle in each apical image is divided in to 6 segments, and the tracking quality for each segment is validated by the operator. Then, the AFI algorithm tracks the percent of wall thinning and shortening in a set of 3 longitudinal 2D-image planes. The peak systolic longitudinal strain for each segment is displayed based on a 17-segment model for each plane, and the results of all 3 planes were combined in a single bull’s-eye summary. GLPS was automatically calculated as an averaged value of peak longitudinal strain in all 3 image planes (apical 2-, 4-chamber and long axis views). We also calculated an averaged value of peak systolic strain in segments within the risk area, which was defined according to the standard coronary anatomy.

Reproducibility of Data
We determined intraobserver and interobserver variability of GLPS by measuring all baseline GLPS twice by the same observer and by 2 independent observers, respectively. Intraobserver and interobserver variabilities of GLPS were 3.1±3.0% and 5.4±3.6% (absolute difference), respectively.

Statistics
All data are expressed as mean±standard deviation (SD). We made comparisons by one-way ANOVA for continuous variables, and significance of difference was calculated with Tukey’s HSD test for factor analysis. To investigate the interaction between factors, we performed analysis of covariance (ANCOVA). To evaluate the ability of AFI to detect myocardial viability, we performed receiver-operator curve (ROC) analysis, in which we defined the viable lesion as WMSI <2 at the follow-up study. Because of the limited number of the study subjects, the relationships between GLPS and other parameters were examined with the bootstrap resampling analysis to calculate the 95% confidence interval (CI) of the correlation coefficient (R). Differences were considered significant at P<0.05 (2-sided). All statistical analysis was performed with R (R Foundation for Statistical Computing).

Results
Patient Characteristics
Among the 23 study patients (mean age, 61±12 years; range 38 to 77 years), 20 patients (86.9%) were male. The culprit
artery was the left anterior descending artery in 11 patients, the left circumflex artery in 4 patients and the right coronary artery in 8 patients. The mean time from the symptomatic onset to coronary reperfusion was 3.5±2.3 h, and peak CK-MB concentration was 193±157 IU/L. Dyslipidemia was diagnosed in 16 patients (69.6%), diabetes mellitus in 6 patients (26.1%), hypertension in 14 patients (60.9%), and 11 patients (47.8%) were current smokers. Two patients had a history of previous myocardial infarction.

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WMSI within area at risk in the study group was 2.3±0.7 at the baseline study, and significantly decreased to 1.4±1.0 during dobutamine infusion (P<0.0001). WMSI recovered to 1.4±0.9 at the follow-up study. Whereas both WMSI at baseline and during dobutamine infusion showed good correlations with that at the follow-up, WMSI during dobutamine infusion showed a better correlation (R=0.84 (95% CI, 0.65 to 0.93), P<0.00001) than WMSI at baseline (R=0.68 (0.37 to 0.85), P=0.0003). Both WMSI values were also significantly correlated with RWM in the 18 patients who underwent LVG (baseline; R=–0.53 (–0.81 to –0.10), P=0.02, dobutamine; R=–0.70 (–0.88 to –0.35), P=0.001). LVEF in LVG was significantly associated with WMSI during dobutamine infusion (R=–0.53 (–0.80 to –0.08), P=0.02) but not with that at baseline (R=–0.44 (–0.75 to 0.03) P=0.07).

Figure 1. Automated function image (AFI) during dobutamine stress and left ventriculography (LVG) at the follow-up study in a patient with anterior wall acute myocardial infarction (AMI). Peak longitudinal strain in each myocardial segment was assessed and demonstrated in a bull's eye's map by AFI in a patient with anterior wall AMI. Reduction of peak longitudinal strain was observed within anterior wall area on 3 days after onset of AMI (Upper left). Strain within the risk area was improved to almost normal during 10 μg·kg⁻¹·min⁻¹ of dobutamine infusion except in a small apical area (Lower left). Global longitudinal peak systolic strain improved from –7.7 to –12.1% during dobutamine stress. Almost no asynergy was observed in LVG performed 3 months later (Right). Peak creatine kinase (CK) and CK-MB values in this case were only 632 and 46 IU/ml, respectively.
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infusion. Peak CK and CK-MB in this case were 9,340 and 313 IU/L, respectively.

AFI analysis was successfully performed in all study patients. The mean frame rate of the obtained images was 58.8±2.9 fps. GLPS was –12.9±3.5% at baseline in the study patients, and it was improved to –15.2±3.6% during dobutamine infusion at 10 μg·kg⁻¹·min⁻¹ (P=0.0004) (Figure 3). No significant relationship was observed between WMSI and GLPS at baseline (R=0.27 (95%CI –0.16 to 0.61), P=0.21). GLPS during dobutamine stress showed significant correlation with WMSI during stress (R=0.52 (0.14 to 0.77), P=0.01). GLPS during stress also showed a correlation with follow-up WMSI (R=0.47 (0.08 to 0.74), P=0.02), while there was no significant relationship between GLPS at baseline and WMSI in the follow-up study (R=0.25 (–0.18 to 0.60), P=0.25) (Figure 4). To investigate whether the differences in the culprit lesions had an effect on this relationship, we performed analysis of covariance (ANCOVA). Because of the limited number of the patients, the culprit lesions were divided into anterior- and non-anterior wall and used as covariate. Interaction between GLPS during stress and culprit lesions was not significant (P=0.30), indicating GLPS during stress was correlated with follow-up WMSI regardless of culprit lesions. ROC analysis demonstrated that the optimal cut-off value
of GLPS during stress for detecting WMSI <2 was −15.2%. Using this cut-off value, GLPS detected WMSI <2 with 69.2% of sensitivity and 66.7% of specificity (AUC = 0.76).

Peak CK-MB was significantly correlated with GLPS during stress (R = 0.52 (0.12 to 0.77), P = 0.01) but not with that at baseline (R = 0.25 (−0.19 to 0.61), P = 0.26). RWM in LVG was negatively correlated with GLPS during stress (R = −0.48 (−0.77 to −0.02), P = 0.04) but not with that at baseline (R = −0.20 (−0.61 to 0.30), P = 0.43) (Figure 5). GLPS during stress was significantly correlated with LVEF on LVG (R = −0.54 (−0.80 to −0.10), P = 0.02) but GLPS at baseline was not (R = −0.38 (−0.72 to 0.11) P = 0.12).

Averaged segmental peak strain within the risk area was −7.1±4.0% at baseline and −10.9±6.1% during dobutamine infusion. There were significant correlations between WMSI and averaged peak strain at the baseline (R = 0.41 (95%CI, 0.01 to 0.71), P = 0.04) and during DSE (R = 0.43 (0.02 to 0.71) P = 0.04). WMSI at the follow-up study was correlated both with averaged peak strain at baseline (R = 0.50 (0.11 to 0.76), P = 0.01) and with that during stress (R = 0.43 (0.02 to 0.72), P = 0.04) (Figure 6). ROC analysis demonstrated −7.0% was the optimal cut-off point of averaged peak strain at baseline for detecting WMSI <2. It detected WMSI <2 with sensitivity of 71.4% of sensitivity and 77.8% of specificity.

**Figure 4.** Relationship between global longitudinal peak systolic strain (GLPS) and wall motion score index (WMSI) at the follow-up study. While global longitudinal peak systolic strain (GLPS) at baseline showed no significant correlation (R = 0.25, P = 0.25) with follow-up WMSI (Left), there were significant correlation (R = 0.47, P = 0.02) between GLPS during dobutamine infusion and follow-up WMSI (Right). Dotted lines represent 95% confidence interval for the regression line.

**Figure 5.** Relationship between global longitudinal peak systolic strain (GLPS) and regional wall motion (RWM) on the follow-up left ventriculography (LVG). In 18 patients who underwent LVG at 3.2±1.5 months after AMI, GLPS at baseline did not show significant correlations with RWM on LVG (R = −0.20, P = 0.43) (Left). However, GLPS during dobutamine stress was significantly correlated with RWM (R = −0.48, P = 0.04) (Right). Dotted lines represent 95% confidence interval for the regression line.
(AUC=0.79). The optimal cut-off value of averaged peak strain during stress was −8.0%, and it detected WMSI <2 also with 71.4% of sensitivity and 77.8% of specificity (AUC=0.73). Peak CK-MB was correlated with averaged peak strain during stress (R=0.44 (0.03 to 0.73), P=0.04) but not with that at baseline (R=0.42 (−0.01 to 0.72), P=0.06). In 18 patients undergoing LVG, RWM was negatively correlated with averaged peak strain during dobutamine stress (R=−0.56 (−0.82 to −0.13), P=0.01) but not with that at baseline (R=−0.45 (−0.76 to 0.02), P=0.06). LVEF was not significantly correlated averaged peak strain at baseline (R=−0.29, (−0.67 to 0.20), P=0.24) nor during stress (R=−0.43 (−0.75 to 0.05), P=0.08).

Because the number of study patients was limited, we performed the bootstrap resampling analysis to confirm obtained results are robust.56 We tested the relationship between GLPS at baseline or during dobutamine stress and the follow-up WMSI on 1,000 bootstrap sample drawn with replacement from the original datasets. We obtained 95% CI of correlation coefficient (R) value between follow-up WMSI and GLPS during stress as 0.22 to 0.71 (median 0.50). The estimated 95% CI of R-value between GLPS during stress and RWM was 0.38 to 0.77 (median 0.60), and that between GLPS during stress and LVEF was 0.15 to 0.77 (median 0.53). These results indicated that the relationship among these parameters would be true even in the larger group.

**Discussion**

In the present study, we assessed changes in GLPS during low-dose dobutamine stress at day 3 using AFI in consecutive 23 patients with AMI. GLPS during stress was significantly correlated with WMSI at the follow-up study and with peak CK-MB, while GLPS at baseline did not show correlations with them. In 18 patients who underwent LVG at 3.2 months later, GLPS during stress was significantly correlated with LVEF and RWM, while there were no significant correlation between GLPS at baseline and these parameters. These results were confirmed by the bootstrap resampling analysis performed to overcome the limited number of the study patients. WMSI at the follow-up stress was also correlated with an averaged segmental peak strain within the risk area at baseline and during stress. However, their correlation coefficients were similar to that between follow-up WMSI and GLPS during stress, and both averaged strain values were not correlated with LVEF on LVG. The present study demonstrated the feasibility of AFI during low-dose dobutamine stress to assess myocardial viability early after AMI and to predict functional recovery on the convalescent stage.

**Myocardial Viability and GLPS During Dobutamine Stress**

Automated assessment of longitudinal peak strain by the AFI algorithm is a highly objective method even comparing to the usual 2D-strain measurement. Although longitudinal peak strain is determined in each myocardial segment, we considered GLPS as an index to select for detecting myocardial viability instead of segmental peak strain values. In the representative AFI images in Figures 1 and 2, blue and red color area are mixed in some segments in the bull’s eye maps, implying that the segmentation based on the 17 segment model does not always correspond to the distribution of infarcted area. Moreover, the risk area must be determined by an operator, and it might be subjective and biased. GLPS is automatically calculated by the AFI algorithm regardless of location of infarction, and it could be a highly objective index. Averaged segmental peak strain values at baseline and during stress were correlated with follow-up WMSI, but their correlations (R=0.50 and 0.43, respectively) were similar to that between WMSI and GLPS during stress (R=0.47). Averaged segmental peak strain detected WMSI <2 with better sensitivity and specificity than GLPS during stress. However, LVEF on the convalescent stage was predicted by GLPS during stress, but not by averaged segmental strain values. Thus, GLPS could reflect both severity of myocardial damage and size of infarcted area, whereas segmental strain only represents the severity of myocardial damage. A previous report demonstrated that GLPS measured early after reperfusion therapy is correlated with infarct size, and that relationship is better than that between infarct transmurality and peak strain in corresponding segments.27 GLPS during dobutamine stress in the present study is associated with CK-MB...
and predicted functional recovery. Infarct size and left ventricular function on the convalescent stage are prognostic factors after AMI, and therefore, GLPS during low-dose dobutamine stress might be useful to predict prognosis after AMI.

Previous studies reported that GLPS showed correlation with WMSI and with LVEF in the control and in patients with ischemic heart disease, although the correlations are weaker in patients with ST-elevation myocardial infarction or with heart failure. In the present study, no significant relationship was observed between WMSI and GLPS at baseline, although GLPS during stress was significantly correlated with WMSI during stress and in the follow-up study. Longitudinal strain is more sensitive to slight changes in contraction than visual assessment, and WMSI by visual assessment might underestimate slight contraction in the stunned myocardium at baseline.

Vartdal et al demonstrated that GLPS measured at 1.5h after reperfusion therapy is correlated with infarct size measured by magnetic resonance imaging in patients with anterior infarction. They did not measure GLPS before reperfusion, therefore, it is not clear whether myocardial strain could be improved so soon after coronary reperfusion. GLPS measured early after reperfusion could reflect not myocardial viability but the size of the area at risk. Microvascular dysfunction could progress during a few days after coronary reperfusion in patients with myocardial infarction, and thus, myocardial viability could not be determined definitively soon after infarction. The present study demonstrated that low-dose dobutamine stress is still required to determine myocardial viability even using the strain imaging.

AIFI technique has made the assessment of longitudinal 2D-strain easier, less time-consuming and more objective than the usual 2D-strain imaging, but it also has some disadvantages. It provides only longitudinal strain, and we did not analyze radial or circumferential strains. In an open-chest animal model, correlation between 2D-strain and myocardial deformation measured by sonomicrometry were best for longitudinal strain both at rest and during dobutamine stress, followed by circumferential and radial strain. Radial strain also had large variability and the resulting unreliability.

Thus, the longitudinal strain could be the most suitable parameter for assessment of contractility in DSE. The present study demonstrated that global- or averaged segmental longitudinal peak strain by AIFI during low-dose dobutamine stress detected myocardial viability after AMI. Further study is required for the accuracy of other 2D-strain parameters to predict viability.

**Study Limitations**

The present study was conducted only in a limited number of patients. Although bootstrap resampling analysis demonstrated that the relationship between GLPS and other parameters would be true even in the larger study group, a larger-scale study is required to confirm the validity of AIFI for assessment of myocardial viability.

AIFI might induce measurement errors that might be overlooked by an operator because of an automated process. To avoid them, we used good quality images for AIFI analysis, and carefully observed and validated tracking of speckles.

We roughly estimated infarct size with creatine kinase-MB values, and defined viability as the recovery of contractile function on the convalescent stage. Positron emission tomography is now recognized as a standard method for assessment of viability, but we could not afford it in the present study.
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