

# Association between Soluble ST2 Basal and Global Longitudinal Strain 2D-Speckle on Tracking Echocardiography with Left Ventricle Remodeling after an Acute Myocardial Infarction

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## Abstract

**Background:** Left ventricle remodeling (LVR) is an important prognosis post acute myocardial infarction (AMI). Soluble ST2 is a novel biomarker for myocardial fibrosis and left ventricular remodeling. Global Longitudinal Strain (GLS) which is a reflection of the longitudinal layer of cardiac muscle can be detected in the early ischemia phase, and has been proven to predict the occurrence of left ventricular remodeling post AMI. **Objective:** To identify the association between soluble ST2 basal and GLS with LVR post AMI. **Method:** This research was conducted from August to December 2015. This is an analytic observational study with one group pretest and post test design. Soluble ST2 and GLS examinations were performed twice (2-5 days after AMI and 12 weeks after therapy). The results were analyzed using Spearman's correlation test. **Result:** The sample size was 45 respondents (82.2% males, average age of  $55.47 \pm 10.13$  years, 84.4% STEMI). There was a strong correlation between high ST2 basal levels with LVR ( $p = 0.0001$   $r = +0.723$ ) and  $\Delta$ ST2 with LVR ( $p = 0.0001$   $r = 0.639$ ). The association of low GLS with LVR was  $p = 0.015$  and  $r = +0.362$ . **Conclusion:** A significant LVR was found post-AMI, the high soluble ST2 basal and low GLS basal may be a factor for predicting LVR.

**Keywords:** Left Ventricle Remodeling, Soluble ST2 basal, GLS, Acute myocardial infarction

## Introduction

Heart disease is the main death leading cause worldwide. In the United States, acute coronary syndromes occur every 34 seconds resulting death in every minute<sup>1</sup>. Indonesia's Health Profile 2009 released by the Health Ministry of the Republic Indonesia reported that in 2008, vascular system disease took the highest place (11.06%) of all death causes in hospitals<sup>2</sup>.

Acute myocardial infarction (AMI) causes myocardial regional damage leading to systolic dysfunction, after an infarction then left ventricular remodeling (LVR) occurs. LVR is associated with high cardiovascular cases including heart failure.

The characteristics are progressive left ventricular dilatation (LVESV)  $>15\%$  or  $>20\%$  (LVEDV). Several epidemiological studies and clinical studies suggested that heart failure was a 30-40% complication of AMI. The incidence of left ventricular systolic dysfunction (LVSD) after myocardial infarction was still poorly documented, but LVSD appeared in 25-60% of AMI, and 50% of patients with LVSD would have heart failure<sup>3,4</sup>.

Echocardiography is an affordable screening tool and can be used to study the regional and global functions of the left ventricle on AMI. Left ventricular ejection fraction (LVEF) measured by Simpson biplane method at the time of hospitalization is a well-known marker for left ventricular global function and predicting short-term or long-term morbidity and mortality of AMI patients. 2D Speckle Tracking Echocardiography (2D-STE) is a new non-invasive method of ultrasonic imaging capable

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of quantitatively and objectively assessing the global and regional function of myocardium in both systolic and diastolic function. This modality is considered more sensitive and accurate in predicting or detecting the presence of coronary heart disease. The change of regional function occurs earlier than the global damage, and can be detected by 2D STE. Examination with 2D STE is done by the per segmental strain and strain rate <sup>5,6</sup>.

Longitudinal strains disturbed earlier at the time of ischemia. Studies in AMI patients found that longitudinal strains were associated with peak level cTt and extensive infarction. Longitudinal strains measurement after reperfusion is a very good predictor of LV remodeling, heart failure and mortality <sup>7,8</sup>. Another study showed a Global Longitudinal Strain (GLS) examination before reperfusion could also predict LV remodeling and complications in STEMI patients <sup>9</sup>.

Biomarkers become an important thing in improving the accuracy of diagnosis and providing disease information therefore it can determine the appropriate treatment options <sup>10</sup>. The soluble ST2 (Interleukin 1 like receptor) is part of IL-1 receptor (IL-1R) consisting of ST2 transmembrane (ST2L) and dissolved (sST2). The soluble ST2 has no transmembrane or intracellular domains and is thought to have a function as a bait receptor neutralizing IL-33, known as the ligand of ST2 transmembrane. IL-33 has a function of inhibiting hypertrophy effect on cardiomyocytes and otherwise on the soluble ST2 giving excessive intracardiac pressure on marmots. The data showed that cardiac protection role was from IL-33/ST2 signal pathway <sup>4</sup>.

SST2 biomarkers for myocardial fibrosis had been included in the ACC/AHA guideline for monitoring heart failure patients <sup>11</sup>. Increased soluble ST2 in AMI patients suggested that a good myocardium acquired additional hemodynamic pressure as compensation for the necrotic area. An increase of baseline sST2 >35 µg/L was an independent predictor of mortality, sudden death and heart failure within 30 days and demonstrated sST2 biomarker's role in providing prognostic information of acute coronary syndromes patients. SST2 role studies in ST Elevation Myocardial Infarction (STEMI) patients showed an increase of initial SST2 level indicating mortality risk and heart failure in patients treated with both fibrinolysis and percutaneous coronary intervention (PCI) <sup>12,13</sup>.

## Method

Respondents in this study were AMI patients who underwent treatment at ICCU and inpatient unit Dr. Soetomo General Hospital Surabaya, Indonesia. The respondents should meet the inclusion criteria: >18 years, meet AMI criteria and without heart failure symptom (Killip I), given AMI standard therapy (revascularization with PCI or thrombolytic, or medicamentally with anticoagulant, antiplatelet, β-blocker, ACE- I or ARB and Statin) and exclusion criteria: AMI patients with Killip >I, had previous AMI and heart failure, sepsis patients, hepatic cirrhosis, anemia, acute stroke, malignancy, valvular heart disease, arrhythmia and not in critical condition. The respondents were willing to fill in informed consent

This research was conducted from August to December 2015. Selected patients were recorded and followed up. Records included: identity, diagnosis, additional examination results. Follow up included: echocardiography and soluble ST2 levels. The data were analyzed in accordance with the independent and dependent variables to enforce the hypothesis. Statistical analysis used was spearman correlation test with  $\alpha = 0.05$  using computer program SPSS version 21.0 (SPSS, Inc., Chicago, IL).

## Results

The sample size was 45 people, 37 men (82.2%). The youngest was 36 years and the oldest was 80 years and the most subjects by age category was 51-60 years as many as 14 people (31.1%). The highest risk factors of AMI were 43 dyslipidemia (93.3%), 33 smoking (73.3%), 19 diabetes (42.2%), and 9 CHD (20%). The most common type of AMI was STEMI 38 people (84.4%). Then the most therapy given was conservative of 17 people (37.7%), PPCI of 12 people (26.7%), thrombolytic of 10 people (23.3%) and PCI of 6 people (13.3%). All patients were given ASA therapy at home, Clopidogrel and Statin (100%), while those who received Ace Inhibitor were 36 people (80%) and Beta blockers were 21 people (46.7%; Table 1).

**Table 1. Descriptive Data**

Variables		Mean	Mean (SD)
Age (year)	31-40	3 (6.7)	55.47 ± 10.13
	41-50	12 (26.7)	
	51-60	14 (31.1)	
	61-70	13 (28.8)	
	71-80	3 (6.7)	
Sex	Male	37 (82.2)	
	Female	8 (17.8)	
Risk Factors	Hypertension	28 (62.2)	
	Smoking	33 (73.3)	
	Dyslipidemia	19 (42.2)	
	Diabetes	42 (93.3)	
	CHD	9 (20.0)	
Diagnosis	STEMI	38 (84.4)	
	NSTEMI	7 (15.6)	
Therapy	PPCI	12 (26.7)	
	Thrombolytic	10 (22.3)	
	PCI	6 (13.3)	
	Conservative	17 (37.7)	
Medication at Home	ASA	45 (100)	
	Clopidogrel	45 (100)	
	ACEI/ARB	36 (80)	
	Beta Blocker	21 (46.7)	
	Statin	45 (100)	

Analysis of echocardiographic characteristic difference obtained from not normally data distribution was used by Mann Whitney U Test. There was an increase of LVEDV from  $76 \pm 29.69$  ml/m<sup>2</sup> to  $98.11 \pm 36.84$  ml/m<sup>2</sup> of subjects undergoing LVR compared to non LVR ( $p = 0.003$ ), LVESV was increased from  $40.89$

$\pm 23.89$  ml/m<sup>2</sup> to  $51.96 \pm 26.43$  ml/m<sup>2</sup> ( $p = 0.006$ ) The basal value of soluble ST2 was much higher in LVR  $34$  (12-71) ng/mL ( $p = 0.0001$ ). The basal value of GLS was lower in those with LVR  $-10.0$  (-20-3) compared to non LVR ( $p = 0.017$ ; Table 2).

**Table 2. Table of Echocardiography and Soluble ST2 Characteristics**

Variables	LVR (+) N=27	LVR (-) N=18	P (Mann Withney U test)
Basal LVEF Biplane (%)	52 (26-71)	51 (27-64)	0.437
Basal LVEF Biplane (%)	51 (29-67)	53.5 (28-67)	0.610
Basal Soluble ST2 (ng/mL)	34 (12-71)	13.5 (9-29)	0.0001
Basal Soluble ST2 (ng/mL)	11.55 (2.89-40.89)	9.95 (6.06-33.09)	0.300
Basal GLS	-10.0 (-20--3)	-13.5 (-20--3)	0.017
GLS 12 weeks	-12.0 (-19--4)	-13.5 (-20--6)	0.108
Basal LVEDV (ml/m <sup>2</sup> )	76 ± 29.69	76.06 ± 27.88	0.889
LVEDV 12 weeks (ml/m <sup>2</sup> )	98.11 ± 36.84	67.56 ± 26.26	0.003
Basal LVESV (ml/m <sup>2</sup> )	40.89 ± 23.89	39.28 ± 22.28	0.908
LVESV 12 weeks (ml/m <sup>2</sup> )	51.96 ± 26.43	32.94 ± 15.19	0.006

Based on the type of AMI the most subjects who experienced LVR were patients with NSTEMI (6 people), then inferior STEMI (6 people), anteroseptal STEMI (4 people), broad anterior STEMI, anterior, inferior VR posterior (2 people), and the rest was STEMI inferior and anteroseptal inferior (1 person).

**Table 3. Correlation between basal levels of LVEF biplane and LVR**

Variable	p	r	n
Basal LVEF	0.44	0.117	45

**Table 4. Correlation between basal soluble ST2 and LVR**

Variable	p	r	n
Basal ST2	0.0001	0.723	45

**Table 5. Correlation between Δ soluble ST 12 weeks and LVR**

Variable	p	r	n
Basal ST2	0.001	-0.639	45

**Table 6. Correlation between basal GLS levels and LVR**

Variable	p	r	n
Basal ST2	0.015	0.362	45

Statistical analysis of not normally distributed data using Spearman correlation showed no correlation between LVEF and LVR ( $p = 0.44$ ;  $r = 0.117$ ; Table 3). Statistical analysis using Spearman correlation obtained significant correlation between soluble ST2 and LVR ( $p = 0.0001$ ;  $r = + 0.723$ ; Table 4). It also obtained significant correlation between  $\Delta$  soluble ST2 in 12 weeks with LVR ( $p = 0.001$ ;  $r = 64\%$ ; Table 5). The analysis showed correlation between basal level of GLS with LVR ( $p = 0.015$ ;  $r = + 0.362$ ; Table 6).

## Discussion

In this study, the incidence of LVR was 27 people (60%), more than in the previous study, probably it caused by the subjects used were all primary PCI and PCI, and aggressive antiremodelling drugs, whereas in this study most of them received conservative therapy because most of the AMI patients came more than 24 hours, thus passing the onset of doing reperfusion either mechanically or pharmacologically<sup>14</sup>. In addition, not all patients wanted to do reperfusion for cost reasons. In the study found 29/93 patients who experienced remodeling (31%)<sup>15</sup>.

An increase of LVEDV >20% from basal or an increase in LVESV >15% from the basal were the criteria used in LVR such as in the previous study<sup>14,16</sup>. LVEDV values after 12 weeks were increased, it was higher in LVR compared to non LVR. This was consistent with previous studies either associated with GLS or soluble ST2 ( $p = 0.003$ ), as well as LVESV after 12 weeks ( $p = 0.006$ ). This was similar to the previous study, there was an increase in LVEDV and LVESV after 90 days on AMI patients treated with PPCI. Basal level of soluble ST2 and GLS were also significant in LVR ( $p = 0.0001$  and  $p = 0.017$  respectively)<sup>14</sup>. In the study there was an increase in LVEDV after 8 weeks from  $36 \pm 6$  to  $56 \pm 22$  with  $p < 0.05$ , and LVESV from  $20 \pm 5$  to  $33 \pm 18$  with  $p < 0.05$ <sup>17</sup>.

NSTEMI and inferior STEMI were the most infarct type of LVR in the study, It was similar with this study, most of them were NSTEMI and inferior STEMI patients<sup>14</sup>. Literature states that infarct areas often experience remodeling if the infarction is widespread or spreading to LAD, but it is also said that diabetes, smoking, and previous infarction also often lead to LVR after AMI<sup>18</sup>.

This study found a significant correlation between basal level soluble ST2 and LVR ( $p = 0.0001$ ;  $r = + 0.723$ ). The previous study found an increase in basal

soluble ST2 was associated with a change in LVEDV after 24 weeks that was measured by Cardiac Magnetic Resonance (CMR) proving that the increase in basal ST2 soluble was associated LVR. In the study basal soluble ST2 was also associated with lower basal LVEF after AMI. Changes in ST2 after 12 weeks ( $\Delta$ ST2) were also associated with  $\Delta$ LVEDV after 24 weeks<sup>15</sup>.

Study of ST2 roles in STEMI patients showed an increased of initial ST2 level indicating mortality and heart failure risk in patients treated with both fibrinolysis and PCI<sup>19</sup>. GLS basal had weak correlation ( $p = 0.015$   $r = + 0.362$ ). This was similar to previous research that obtained a correlation between GLS and LVR<sup>14</sup>. Many studies using STE to predict LVR, either with GLS, torque or circumferential<sup>14,16,19</sup>. STEMI patients treated with PPCI found that the GLS examination at the time before the patient was repatriated was a novel examination to predict the occurrence of LVR. In patients with decreased GLS, LVR was obtained after 3 months and 6 months<sup>20</sup>. A study obtained a low basal GLS  $-11.05 \pm 4.1$  in LVR compared to non LVR  $-15.2 \pm 3.2$  with  $p < 0.001$ <sup>21</sup>. This study only used GLS because of measurement limitation of echocardiography in Dr. Soetomo General Hospital Surabaya.

Generally, longitudinal LV mechanics, which are influenced largely by subendocard region, are the most vulnerable components of global LV mechanics because they are very sensitive to the presence of myocardial disease. Single longitudinal mechanical assessment is more adequate in early myocardial disease or has not shown significant abnormalities. The subendocardium region is the most remote area of perfusion therefore it is susceptible to hypoperfusion and ischaemia<sup>4,5</sup>.

## Conclusion

There was a positive correlation between basal soluble ST2 and LVR after AMI and there was a negative correlation between basal GLS and LVR after AMI.

**Ethical Clearance:** This study protocol was approved by ethical clearance Dr. Soetomo Surabaya, Indonesia teaching hospital research.

**Conflict of Interest:** The author reports no conflict of interest of this work.

**Source of Funding:** This study is done with individual funding.

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