CARDIOLOGIE TUNISIENNE

ARTICLE ORIGINAL

# Soluble suppression of tumorigenicity2 : Correlation with left ventricular longitudinal global strain in myocardial infarction

# Suppression soluble de la tumorigénicité2 dans l'infarctus de myocarde: Corrélation avec le strain global longitudinal ventriculaire gauche

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## Summary

**Introduction :** Cardiac remodelling occurring after a myocardial infarction (MI) in response to ischemia and necrosis can be assessed by transthoracic echocardiography (TTE) using global longitudinal strain (GLS). In the other hand, soluble ST2, a marker of myocardial fibrosis, increases to cardiac remodelling.

We aimed to assess the relationship between sSt2 levels and left ventricle GLS in the acute phase of MI.

**Methods:** This was a cross-sectional, single-center study carried out over a period of 6 months in the cardiology department of Habib Thameur Hospital. Comprehensive TEE with 2 D strain analysis and sST2 quantification was performed in patients admitted for MI.

**Results :** Twenty-two patients were included. Mean age was 63±12 years and gender ratio 3.4.

Mean soluble ST2 level was of 165±97 ng/ml with extremes ranging from 21 to 250ng/ml. Mean ejection fraction by Simpson biplane was 46±10% (28 to 66%). Mean left ventricular GLS was -12±3% by both operators. There was no correlation between increased sST2 levels and decreased left ventricle GLS values in patients with MI (r1=-0.179; p1=0.424) by the first and (r2=-0.242; p2=0.343) the second operator. Correlation between increased sST2 levels and decreased left ventricular function was (r=-0.21; p=0.089). Correlation between increased sST2 and increased wall motion score index was (r=0.3; p=0.089).

**Conclusion :** In our study, increased sST2 levels were not correlated with the impairment of GLS in the acute phase of MI.

## Keywords

Infarctus, échocardiographie, contractilité myocardique, biomarqueurs

## Résumé

**Introduction** : Le remodelage cardiaque survenant après un infarctus de myocarde (IDM) peut être évalué par l'échographie cardiaque transthoracique (ETT) en étudiant le strain global longitudinal (SGL).

Le ST2 soluble, marqueur de fibrose myocardique, augmente en réponse au remodelage cardiaque.

L'objectif de notre travail était de déterminer la corrélation entre le sST2 et le SGL lors de l'IDM.

**Méthode** : Il s'agissait d'une étude transversale, monocentrique évaluative de recueil prospectif, réalisée sur une durée de 6 mois dans le service de cardiologie de l'hôpital Habib Thameur. Les patients admis pour IDM ont eu une ETT avec une étude du SGL et un dosage du ST2 soluble.

**Résultats** : Vingt-deux patients ont été inclus. L'âge moyen était de 63±12 ans et le genre ratio de 3,4.
La valeur moyenne du sST2 était 165 ±97 ng/ml (21 et 250 ng/ml).
La fraction d'éjection (FE) moyenne en Simpson biplan était de 46±10% (28 à 66%).
Le SGL moyen calculé par les deux opérateurs indépendants était de -12±3% (r=0,9, p=0,0001).
La corrélation entre l'augmentation des valeurs du sST2 et l'altération du SGL mesurée par le premier opérateur était de r1=-0,179 ; p1=0,424 et de r2=-0,242 ; p2=0,343 pour le deuxième.

La corrélation entre l'élévation du sST2 et l'altération de la FE était de r=-0,21 ; p=0,089 et celle entre le sST2 et l'élévation du score de contractilité régionale de r=0,3 ; p=0,089.

**Conclusion** : L'élévation du ST2 soluble n'était pas corrélée à l'altération du SGL dans l'IDM.

## Mots-clés

Soluble suppression of tumorigenicity2; Global longitudinal strain; acute myocardial infarct; Post-infarct remodeling.

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## INTRODUCTION

Myocardial infarction (MI) is one of the world's leading causes of morbidity and mortality, despite current advances in invasive and pharmacological treatment (1).

It triggers cardiac remodelling and cellular architectural changes due to myocardial ischemia, necrosis, inflammatory process and oxidative phenomena, leading to changes in size and geometry and the impairement of left ventricular function (2).

Cardiac Doppler echography reveals these abnormalities by assessing global and segmental systolic and diastolic function. In addition, global longitudinal strain (GLS) has been identified as a predictive factor for cardiac remodelling following acute coronary syndrome (3) .

On the other hand, numerous biological markers increase in response to remodelling and inflammation (BNP, NTproBNP, CRP, Chromogranin...) and serve as prognostic markers (4).

ST2 (Suppression of Tumorigenicity 2) is a protein belonging to the interleukin receptor family. It is part of this new generation of cardiovascular biomarkers. The soluble form of ST2 (sST2) acts as a decoy for interleukin-33, preventing it from exerting its cardio protective effect by inhibiting myocardial fibrosis and ventricular remodelling (5).

It has been recognized as a prognostic marker in heart failure. Its role in ischemic cardiomyopathy is still under investigation (6).

The aim of our study was to investigate the relationship between sST2 levels and left ventricular (LV) GLS values in MI.

## METHODS

This was a single center cross-sectional evaluative study conducted in the cardiology department of Habib Thameur Hospital over a 6-month period from April to October 2016.

Inclusion criteria were age over 18 years, admission for uncomplicated acute MI defined according to European Society of Cardiology guidelines as any ACS accompanied by an increase in troponins (T or I)(7) , sST2 sampling and cardiac echocardiography performed within 72 hours of admission and oral patient consent for study participation.

In contrast, patients admitted for complicated ACS or semi-recent MI, patients with atrial fibrillation, complete left bundle branch block or ventricular hyperexcitability, and patients who refused to participate in the study were not included in our study.

Also, we excluded patients who developed atrial fibrillation or atrial flutter during hospitalization, as well as patients whose ultrasound images were not optimal for myocardial strain analysis.

Included patients had clinical examination and underwent transthoracic echocardiography (TTE) within the first 72 hours of hospitalization. This exam, combined with a simultaneous eletrocardiogram (ECG) (standard DII lead), was performed using a General Electric Vivid 9 Dimension imaging system (GE Vingmed Ultrasound AS) with a 3.5MHz transducer in accordance with the recommendations of the American Society of Echocardiography (8). Left ventricular ejection fraction (LVEF) was assessed using the volume method in apical 4- and 2-chamber view. Left ventricular diameters in systole and diastole were measured in two-dimensional parasternal long axis.

Visual assessment of the kinetics of the 17 LV segments was performed using apical 4,2 and 3-cavity sections. Calculation of the wall motion score index (WMSI) was based on a 16-segment model comprising 6 basal, 6 mid-ventricular and 4 apical segments identified on parasternal long-axis and short-axis slices and 4 and 2-cavity slices. A score is assigned to each segment according to its contractility and thickening as follows: 1 'normokinetic'; 2 'hypokinetic'; 3 'akinetic'; 4 'dyskinetic'. The resultant of the sum of the scores assigned to each segment divided by the number of segments visualized represents the WMSI(9) .

GLS analysis was performed post-processing echocardiographic examinations using General Electric's EchoPac software (EchoPac PC version 112, GE Vingmed). GLS was carried out on the apical 4-chamber view, 2-chamber and 3- chamber views. For all patients, two different operators performed

the study of left ventricular myocardial deformation by speckle tracking using the automatic function imaging (AFI) mode.

The sST2 measurement was performed on plasma collected on EDTA anticoagulant using the Aspect Reader™ system (Critical Diagnostics) immunodiagnostic assay. The technique used (Aspect-Plus ST2® assay) is standardized and suitable for routine use providing a rapid result (20 minutes) and low sample volume uptake (35µl).

The analytical sensitivity of the technique is set at 12,5ng/ml. The upper limit of linearity is 250ng/ml. In self-reported healthy individuals, interquartile ST2 values range from 15 to 25 ng/ml.A concentration of 35 ng/ml corresponds to 90-95% of the normal population (10).

In patients diagnosed with ACS or heart failure and ST2 concentrations > 35 ng/ml, the risk of adverse events such as hospitalization or death within one year is higher than in patients with ST2 concentrations below this value. As ST2 concentrations increase the risk of mortality also increases (11).

Data were entered and analyzed using SPSS 25.0 software. We calculated only simple frequencies, taking into account the size of our sample. For quantitative variables, we calculated means and standard deviations, and determined extreme values.

The correlation between two quantitative variables was calculated using the spearman's Rank correlation test. The significance level was set at 0.05.

## RESULTS

A total of 25 patients were included in our study from April 12th to October 20th2016. Then, 3 patients were excluded from the analysis, out of these three, two patients were excluded due to poor acoustic window quality and one patient for atrial fibrillation transition. Thus, the total sample was 22 patients. Their baseline caracteristics are presented in table 1.

Mean sSt2 value was 165±97ng/ml ranging from 21 to 250 ng/ml, 20 patient had an sST2 level higher than 35ng/ml.

Echocardiographic data revealed that : Mean LVEF was 46±10% with extremes ranging from 28 to 66%. LV dysfunction was observed in seven patients.

The WMSI was greater than 1,5 in five patients. No significant valvulopathy was noted in our population.

Mean GLS value calculated separately by two operators was -12±3 in both cases. Correlation between the two measurments was r=0.9, p=0.0001.

Our results demonstrated that there was no significant correlation between sST2 and LV GLS1 and GLS 2 with respectively: r1=-0.179; p1=0.424 and r2=-0.242; p=0.343.

Furthermore, we didn't found correlation between sST2 levels and LVEF values and WMSI values.

**Table 1.** Baseline characteristics of our population.

| Parameters | Population |
|---|---|
| **Age** | 63± 12 YEARS |
| **Sexe ratio** | 3,4 |
| **STEMI** | 16 |
| **Anterior** | 9 |
| **Inferior** | 6 |
| **Lateral** | 2 |
| **NSTEMI** | 6 |
| **Management** | N= |
| **Thrombolysis** | 11 |
| **Primary PCI** | 1 |
| **Difefred PCI** | 11 |
| **CABG** | 1 |
| **Medical Treatment** | 9 |

CABG=coronary arteriel bypass graft; PCI= percutaneous angioplasty; STMI= ST segment elevation myocardial infarction

## DISCUSSION

Our results did not demonstrate any correlation between sST2 and left ventricle GLS in the acute phase of MI.

The main strength of our study lies in being the first study in Tunisia to investigate the relationship between sST2 levels and LV GLS in patient with MI in the acute phase.

The limitations of our study were the small sample size due to the high cost of sST2 measurements and its single center design.

ST2 definition

ST2 is a protein that belongs to the interleukin-1 (IL-1) family. It is a new-generation cardiac biomarker whose mechanism of action is yet to fully elucidated. ST2 exists in two forms:

- ST2 Ligand (ST2L) a membrane receptor expressed on the surface of cardiac cells.
- ST2 soluble (sSt2) a plasma soluble form (5).

This protein has been studied for many years in the context of inflammatory, autoimmune and tumoral disease. Recently, following the identification of interleukin-33 (IL-33) as a functional ligand for ST2, its role has expanded to include cardiovascular disease (12).

The ST2/IL-33 complex appears to be signalling pathway to cardiac remodelling. Once established, the IL-33/ST2L system generates a cascade of protective signalscapable of inhibiting myocardial fibrosis and left ventricular remodelling with consequent cardio-protective effects. The addition of sST2 would remove this inhibition and sSt2, released in excess in serum, acts asa decoy for IL-33, preventing it from binding to ST2L and thus inhibiting the antihypertrophic, antifibrosing antiapoptic cardioprotective effect of the IL-33-ST2L pair. Therefore, it serves as a marker for myocardial fibrosis and ventricular remodelling (12,13).

## *Population Characteristics*

In our series, the mean age of our patients was 63±12 years. The sex ratio was 3.4, indicating a male predominance. These results are in line with those of the Tunisian MI registry, FAST-MI Tunisia, whose study population had a mean age of 60.3 years and a male predominance of 79.8% (14).

Cardiovascular risk factors were dominated by diabetes (n=17), followed by hypertension (n=14) and smoking (n=11).These three risk factors also emerged at the top of the list in the Tunisian registry, but with smoking predominating (64.9%), followed by hypertension (38.6%) and diabetes (36.9%)(14).

## *Cardiac ultrasound findings*

Our results demonstrate that the mean LVEF was 46±10% with extrems ranging from 28 to 66%. The regional contractility score had a mean value of 1.32±0,84 with extrems ranging from 1 to 2.4.This disparity in our results can be attributed to the heterogeneity of the sample which included patients hospitalized for both STEMI and NSTEMI, and on the side by the extent of necrosis, strategy and time of revascularization.

Mean GLS calculated independently by two operators was -12±3%. The normal GLS value according to the American society of echocardiography is -20% with extremes ranging from -17.3 to 21.5 (8). These values are consistent with resultsof other studies carried out in the context of MI.

For instance, in a study by Aniyathodiyil which included 50patients admitted for STEMI and revascularized by primary angioplasty, the mean value of GLS was -12.41±2.95% (15).

## *ST2 and myocardial infarction*

Numerous studies have provided evidence that the sST2 levels increase just one day after MI(11,16,17).

In fact, in a study conducted by Weinberg et al including 69 patients with acute MI, it was found that sST2 levels increased on the first day after the event (16). Antoni et al found similar results in a larger study including 341 patients hospitalized for MI. In fact, they found that the mean SGL value measured on the TTE performed within the first 48 hours of hospitalization was -13.7 ± 3.3% (18). In the current study, we also demonstrated that sST2 values in patients with MI are higher than 35ng/ml, in fact mean value in our series was 165±97ng/ml.

Furthermore, other studies have investigated the prognostic value of sST2. Barbarash et al demonstrated in a series of 88 patients with MI that the risk of complications occuring during hospitalization following MI such as death, arythmia and residual angina was 1.7 times greater in individuals with sST2 above normal (19). Similary, Kohli et al concluded that patients with sST2>35ng/ml had a threefold increased risk of 30-day failure, sudden death and death from any cause (11).

### *sST2, LVEF and WMSI*

Analysis of our study showed the absence of correlation between LVEF and sST2 (r=-0.21 ;p=0.348) in contrast to a previous study carried out in the cardiology departement of Habib Thameur hospital including 74 patients admitted for MI, where a significant correlation was found between sST2 and LVEF (r=-0.401 ;p<0.0001)(20).

On the other hand, the relationship between WMSI and sST2 was also studied in our population. No correlation was found between these two parameters. It should be noted that, up to now, the relationship between sST2 and WMSI has not been evaluated in other studies.

### *sST2 and left ventricle GLS*

The results of our work concluded that there was no correlation between sST2 and left ventricle GLS. It is northway that only one study has investigated the correlation between those two parameters. This was an observational, cross-sectional study conducted by Kusumastuti et al. It included 72 patients hospitalized, in 62 cases dor STEMI and in 10 cases for NSTEMI. This study also found no correlation between sST2 and SGL (r=-0.133, p=0.344) (21).

On the other side, the correlation between sST2 levels and LV GLS has been studied in other pathologies. As an exemple, Yulidia et al conducted a studyinvolving 30 patients admitted for acute cardiac decompensation with LV dysfunction, their results showed a strong correlation ( r=0.99;p=0.0001) between sST2 levels and LV GLS values (22).

The small sample size represents the main limitation that reduces the powerof our results

## CONCLUSION

In our study, there was no correlation between sST2 values and decreased left ventricle GLS values. The relationship between those two parameters is currently not well established.

Thus, larger-scale studies are needed to validate the relationship between these two parameters

## REFERENCES


1. Les 10 principales causes de mortalité [Internet]. [cited 2023 Jun 27]. Available from: https://www.who.int/fr/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. Azevedo PS, Polegato BF, Minicucci MF, Paiva SAR, Zornoff LAM. Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment. Arq Bras Cardiol. 2016 Jan;106(1):62–9.
3. Tomoaia R, Beyer RS, Simu G, Serban AM, Pop D. Understanding the role of echocardiography in remodeling after acute myocardial infarction and development of heart failure with preserved ejection fraction. Med Ultrason. 2019 Feb 17;21(1):69–76.
4. Salvagno GL, Pavan C. Prognostic biomarkers in acute coronary syndrome. Ann Transl Med. 2016 Jul;4(13):258.
5. Biaggi P, Ammann C, Imperiali M, Hammerer A, Breidthardt T, Maisel A, et al. Soluble ST2 – a new biomarker in heart failure. Cardiovasc Med. 2019 Jan 30;
6. Jenkins WS, Roger VL, Jaffe AS, Weston SA, AbouEzzeddine OF, Jiang R, et al. Prognostic Value of Soluble ST2 after Myocardial Infarction: A Community Perspective. Am J Med. 2017 Sep;130(9):1112.e9-1112.e15.
7. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237–69.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39.e14.
9. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, et al. Strain Echocardiography and Wall Motion Score Index Predicts Final Infarct Size in Patients With Non–ST-Segment–Elevation Myocardial Infarction. Circ Cardiovasc Imaging. 2010 Mar;3(2):187–94.
10. Lu J, Snider JV, Grenache DG. Establishment of reference intervals for soluble ST2 from a United States population. Clin Chim Acta Int J Clin Chem. 2010 Nov 11;411(21–22):1825–6.
11. Kohli P, Bonaca MP, Kakkar R, Kudinova AY, Scirica BM, Sabatine MS, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. Clin Chem. 2012 Jan;58(1):257–66.
12. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov. 2008 Oct;7(10):827–40.
13. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie ANJ, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest. 2007 Jun;117(6):1538–49.
14. Addad F, Gouider J, Boughzela E, Kamoun S, Boujenah R, Haouala H, et al. Prise en charge de l'infarctus du myocarde en Tunisie : résultats préliminaires du registre FAST-MI Tunisie de la Société tunisienne de cardiologie et de chirurgie cardiovasculaire. Ann Cardiol Angéiologie. 2015 Dec 1;64(6):439–45.

15. Aniyathodiyil. Speckle-Tracking echocardiography to assess global and regional left ventricular function in acute myocardial infarction [Internet]. [cited 2023 Jun 28]. Available from: https://www.jiaecho.org/article.asp?issn=2543-1463;year=2017;volume=1;issue=3;spage=177;epage=184;aulast=Aniyathodiyil
16. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S ichi, Solomon SD, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation. 2002 Dec 3;106(23):2961–6.
17. Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, et al. Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome—There is Meat on the Bone. J Clin Med. 2019 Feb 22;8(2):270.
18. Antoni ML, Mollema SA, Atary JZ, Borleffs CJW, Boersma E, van de Veire NRL, et al. Time course of global left ventricular strain after acute myocardial infarction. Eur Heart J. 2010 Aug;31(16):2006–13.
19. Barbarash O, Gruzdeva O, Uchasova E, Dyleva Y, Belik E, Akbasheva O, et al. Prognostic Value of Soluble ST2 During Hospitalization for ST-Segment Elevation Myocardial Infarction. Ann Lab Med. 2016 Jul;36(4):313–9.
20. Mzoughi K, Chouaieb S, Zairi I, Fredj S, Ben Kilani M, Berriri S, et al. Prognostic value of ST2 in myocardial infarction. Tunis Med. 2019 Feb;97(2):335–43.
21. Kusumastuti D, Taufiq N, Mumpuni H. Correlation between Level of Soluble Suppression of Tumorigenicity-2 (sST2) with Global Longitudinal Strain (GLS) of Left Ventricle in Patients with Acute Myocardial Infarction. ACI Acta Cardiol Indones. 2019 Mar 27;5:62.
22. Yulidia H, Aminuddin M, Pikir B. CORELATION OF GLOBAL LONGITUDINAL STRAIN (GLS) – LEFT VENTRICLE AND SOLUBLE SUPRESSION OF TUMORGENICITY 2 (sST2) IN ACUTE HEART FAILURE WITH SYSTOLIC DYSFUNCTION. Indones J Cardiol. 2019 Sep 11;39.