Interleukin-1 Receptor-Related Protein ST2 and Mitral Valve Repair Outcome in Patients with Chronic Degenerative Mitral Regurgitation

Antonella Galeone[1,2] Arrigo Lessana[2] Elisa Mascolo[3] Francesca Di Serio[3] Nicola Marraudino[1] Francois Laborde[2] Domenico Paparella[1]

[1] Division of Cardiac Surgery, Department of Emergency and Organ Transplant, University "Aldo Moro" of Bari, Italy
[2] Department of Cardiac Surgery, Institut Mutualiste Montsouris, Paris, France
[3] Department of Clinical Pathology, Policlinico Hospital, Bari, Italy

Address for correspondence Antonella Galeone, MD, PhD, piazza Giulio Cesare 11, 70124 Bari, Italy (e-mail: a.galeone@email.it).

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Abstract

Background ST2 is a member of the interleukin-1 receptor family that is markedly upregulated in cultured cardiomyocytes subjected to mechanical strain. Serum soluble ST2 (sST2) levels can be detected in patients with acute myocardial infarction and severe chronic heart failure. This study sought to assess for the first time the activation of the ST2 pathway in patients with severe chronic degenerative mitral regurgitation.

Materials and Methods Serum sST2 levels were measured in 20 patients scheduled for mitral valve (MV) repair at baseline, at the end of the intervention, on postoperative day 1, at hospital discharge, and after 6 months. Patients also underwent measurement of N-terminal pro-brain natriuretic peptide and echocardiographic evaluation at each time point.

Results At baseline, sST2 was detected in 10 (50%) patients (mean value, 60 $\pm$ 74 pg/mL; range, 0–234 pg/mL; median, 8 pg/mL). MV repair was performed successfully in all patients. Cardiac surgery with cardiopulmonary bypass was associated with a rapid and transient increase in sST2 levels. Patients with baseline higher versus lower sST2 levels ($\geq$ 8 vs. $<$ 8 pg/mL) had significantly higher levels of sST2 on postoperative day 1 (1,050 $\pm$ 593 vs. 440 $\pm$ 312 pg/mL; $p = 0.009$). At follow-up, patients with preoperative sST2 $\geq$ 8 pg/mL had significantly higher ejection fraction (EF) (64.7 $\pm$ 5.8 vs. 57.6 $\pm$ 5.9; $p = 0.03$) and lower left ventricular end-diastolic diameter (LVEDD) (50.6 $\pm$ 5.8 vs. 56 $\pm$ 4.2; $p = 0.03$) compared with patients with preoperative sST2 $<$ 8 pg/mL.

Conclusion Preoperative ST2 activation, evidenced by the presence of serum sST2 levels, is present in half of the patients with chronic degenerative mitral regurgitation and is associated with higher levels of EF and lower levels of LVEDD after MV repair.

Keywords
- ST2
- mitral valve regurgitation
- mitral valve repair

Introduction

ST2 is a peptide belonging to the interleukin-1 (IL-1) receptor family that is mainly present in two isoforms that are generated by alternative splicing: the first is bound to the membrane (ST2 ligand [ST2L]) and the second is in the soluble (sST2) form, which is characterized by loss of the transmembrane and the intracellular domains.[1] Originally described as a soluble protein in lipopolysaccharide-stimulated fibroblasts,[2] ST2 was recently found to be markedly upregulated

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in cultured rat cardiomyocytes subjected to mechanical strain.[3] The functional ligand for ST2L is IL-33 that is also produced in response to stretch by cardiac fibroblast and has a cardioprotective role in the setting of myocyte stretch and injury.[4] Soluble ST2 has been shown to bind to IL-33 and function as a decoy receptor to prevent IL-33 from binding to and signaling through ST2L; therefore, increased serum levels of sST2 can serve to limit the systemic biological effects of IL-33, resulting in inadequate cardioprotection from IL-33, with a heightened risk for adverse remodelling and ventricular dysfunction. Soluble ST2 concentrations are elevated and associated with an adverse outcome in patients with acute myocardial infarction (AMI) and heart failure.[5–8] The role of ST2 in the setting of degenerative mitral regurgitation (MR) has not yet been evaluated. Therefore, the aim of our study was to evaluate the activation of ST2 in patients with severe chronic degenerative MR scheduled for mitral valve (MV) surgery by measuring serum sST2 levels. The perioperative trend of N-terminal pro-brain natriuretic peptide (NT-proBNP) was also measured.

Materials and Methods

The study was approved by the local institutional human research committee and conducted according to the ethical guidelines and principles of the international Helsinki declaration. After informed consent, 20 patients with severe chronic degenerative MR scheduled for MV surgery were prospectively enrolled in the study. The following exclusion criteria were applied: MR due to rheumatic disease, associated coronary artery disease, mitral stenosis, aortic valve disease, previous valve or coronary surgery, cardiomyopathies, pericardial disease. The degree of MR was graded semiquantitatively from color-flow Doppler in the conventional parasternal long-axis and apical four-chamber images.

Surgical Procedures

Surgery was performed through a median sternotomy; cardiopulmonary bypass (CPB) was instituted between the ascending aorta and superior and inferior vena cava. Myocardial protection was achieved with antegrade, or combined antegrade and retrograde cold blood high potassium cardioplegia. MV repair was performed by using the following techniques: quadrangular resection, folding, artificial (Gore-Tex, W.L. Gore and associates Inc., Medical Products Division, Flagstaff, Arizona, United States) chordae insertion and commissuroplasty. Mitral ring annuloplasty was performed in all cases. Additional procedures included tricuspid valve annuloplasty and atrial fibrillation ablation.

Laboratory Assays

Blood samples were collected from all patients at baseline during induction (T0), immediately after the end of intervention (T1), on postoperative day 1 (T2), at hospital discharge (T3) and after 6 months (T4). Samples were centrifuged and the serum was stored at −80°C until assayed. Soluble ST2 was measured by a sandwich double monoclonal antibody ELISA method (Medical & Biological Laboratories Co, Ltd). Briefly serum samples were incubated in microwells coated with antihuman ST2 antibody. After washing, peroxidase-conjugated antihuman ST2 antibody was added into the microwell and incubated. After a second wash, the peroxidase substrate was added, and the optical density at 450 nm was determined. NT-proBNP was measured by means of Dimension clinical chemistry system (Siemens AG, Munich, Germany), a one-step enzyme immunoassay based on the "sandwich" principle.

Follow-Up

Clinical and echocardiographic evaluations were performed before hospital discharge and 6 months after intervention. Follow-up was complete in all cases.

Statistical Analysis

The data are given as mean values ± standard deviation (SD); categorical variables are described as number and percentages. The continuous variables were compared using nonparametric Mann-Whitney U test (between-group comparisons) or Wilcoxon test (within-group comparisons). Categorical data were tested with the Fisher exact test. The linear correlation was assessed by using Pearson coefficient. The analyses were made using Statistica 6.1 software (StatSoft Inc., Tulsa, Oklahoma, United States), and p values < 0.05 were considered statistically significant.

Results

At baseline, sST2 was detected in 10 (50%) patients and the mean concentration of sST2 was 60 ± 74 pg/mL (range, 0–234 pg/mL; median, 8 pg/mL). Patients' characteristics as a whole and according to median sST2 at T0 are shown in ►**Table 1**. Preoperatively, NT-proBNP was elevated (> 300 pg/mL) in seven (35%) patients and the mean concentration of NT-proBNP was 309 ± 333 pg/mL (range, 14–1,249 pg/mL; median, 207 pg/mL). Mean preoperative C-reactive protein (CRP) was 1.93 ± 0.94 mg/L in patients with preoperative sST2 < 8 pg/mL and 1.52 ± 0.79 mg/L in patients with preoperative sST2 ≥ 8 pg/mL and the difference was not statistically significant. Patients with preoperative sST2 ≥ 8 pg/mL had lower left ventricular end-systolic diameter (34.44 ± 4.5 vs. 39.1 ± 3; $p < 0.05$) compared with patients with preoperative sST2 < 8 pg/mL. Preoperative sST2 was not correlated with any other clinical or echocardiographic variable or with NT-proBNP serum levels. MV repair was performed successfully in all patients; the mean size of the annular ring was 35 ± 3 mm. The mean CPB and aortic cross-clamp times were 92.3 ± 18.5 and 72.3 ± 14.2 minute in patients with preoperative sST2 < 8 pg/mL and 85.9 ± 17.3 and 65.6 ± 17.2 minute in patients with preoperative sST2 > 8 pg/mL and the difference was not statistically significant. Soluble ST2 levels increased rapidly and transiently after the intervention and reached a peak at T2; additionally sST2 levels were significantly elevated at T2 compared with baseline (746 ± 564 vs. 60 ± 74 pg/mL; $p < 0.001$). Similarly, NT-proBNP levels rose at T2 and were significantly elevated compared with baseline (1,368 ± 988 vs. 309 ± 333 pg/mL; $p < 0.001$). Patients with preoperative

Table 1 Baseline and postoperative patients' characteristics. Values are expressed as mean ± SD or percentages

	Overall ($n = 20$)	p	Baseline sST2		p
			< 8 pg/mL ($n = 10$)	≥ 8 pg/mL ($n = 10$)	
Clinical variables					
Age, y	59 ± 14		59 ± 14	58 ± 13	NS
Male gender, *n* (%)	16 (80%)		9 (90%)	7 (70%)	NS
Hypertension, *n* (%)	5 (25%)		3 (30%)	2 (20%)	NS
Diabetes, *n* (%)	0		0	0	
Dyslipidemia, *n* (%)	3 (15%)		0	3 (30%)	NS
Current smoking, *n* (%)	14 (70%)		7 (70%)	7 (70%)	NS
Previous CVA, *n* (%)	1 (5%)		0	1 (10%)	NS
PVD, *n* (%)	0		0	0	
CRF, *n* (%)	1 (5%)		1 (10%)	0	NS
Chronic AF, *n* (%)	3 (15%)		1 (10%)	2 (20%)	NS
Barlow disease, *n* (%)	8 (40%)		3 (33%)	5 (50%)	NS
NYHA class II, *n* (%) III, *n* (%) IV, *n* (%)	2.3 ± 0.6 15 (75%) 4 (20%) 1 (5%)		2.4 ± 0.6 7 (70%) 2 (20%) 1 (10%)	2.2 ± 0.4 8 (80%) 2 (20%) 0	NS NS NS NS
Baseline echocardiographic variables					
EF (%)	65.8 ± 4.1		65.4 ± 4.4	66.1 ± 3.9	NS
LVEDD (mm)	59.8 ± 6		61.4 ± 5	58.1 ± 6.6	NS
LVESD (mm)	36.9 ± 4.4		39.1 ± 3	34.44 ± 4.5	0.03
LA area (cm^2)	32.5 ± 6.3		33.7 ± 6.1	31.22 ± 6.5	NS
ERO $(cm)^2$	48.8 ± 12.4		53.5 ± 14.1	43.7 ± 8.1	NS
RV (mL/beat)	76.1 ± 21.9		83 ± 20.7	62.3 ± 19.5	NS
MR degree	3.8 ± 0.4		4 ± 0	3.6 ± 0.5	NS
Prolapsed segment Anterior Posterior Bileaflet	 1 (5%) 14 (70%) 5 (25%)		 1 (10%) 6 (60%) 3 (30%)	 0 8 (80%) 2 (20%)	 NS NS NS
Flail leaflet	14 (70%)		7 (70%)	7 (70%)	NS
TR degree	0.9 ± 0.6		0.7 ± 0.7	1 ± 0.5	NS
PAP (mmHg)	37.4 ± 9.9		39.2 ± 10.4	35.5 ± 9.6	NS
Follow-up echocardiographic variables					
EF (%)	61.2 ± 6.8	0.013	57.6 ± 5.9	64.7 ± 5.8	0.03
LVEDD (mm)	53.3 ± 5.6	< 0.001	56 ± 4.2	50.6 ± 5.8	0.03
LVESD (mm)	36 ± 5.2	NS	38.2 ± 3.7	33.3 ± 5.7	NS
MR (degree)	0.4 ± 0.6	< 0.001	0.4 ± 0.7	0.4 ± 0.5	NS
PAP (mmHg)	26.3 ± 2.9	< 0.001	26.6 ± 3.7	26.1 ± 2.3	NS
Laboratory variables					
Preoperative CRP (mg/L)	1.7 ± 0.9		1.93 ± 0.94	1.52 ± 0.79	NS
sST2 (pg/mL) T0 T1 T2 T3 T4	 60 103 746 83 80	 – NS < 0.001 NS NS	 0 40 440 100 60	 120 150 1,050 70 100	 – – 0.009 NS NS

(*Continued*)

Table 1 (*Continued*)

	Overall ($n = 20$)	p	Baseline sST2		p
			< 8 pg/mL ($n = 10$)	≥ 8 pg/mL ($n = 10$)	
NT-proBNP (pg/mL)					
T0	309	–	309	310	NS
T1	263	NS	291	235	NS
T2	1,368	< 0.001	1,574	1,162	NS
T3	664	NS	703	573	NS
T4	326	NS	478	173	NS

Abbreviations: AF, atrial fibrillation; CRF, chronic renal failure; CRP, C-reactive protein; CVA, cerebrovascular accident; EF, ejection fraction; ERO, effective regurgitant orifice; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PVD, peripheral vascular disease; RV, regurgitant volume; TR, tricuspid regurgitation.

sST2 $\geq$ 8 pg/mL had significantly higher levels of sST2 at T2 compared with patients with preoperative ST2 $<$ 8 pg/mL (1,050 $\pm$ 593 vs. 440 $\pm$ 312 pg/mL; $p = 0.009$; ►**Fig. 1**).

No statistically significant differences were found in perioperative complications, including need for inotropic support and delayed extubation, with respect to preoperative sST2 values.

At T4, sST2 was detected in 13 (65%) patients and the mean concentration of sST2 was 80 $\pm$ 110 pg/mL. In patients with preoperative sST2 $>$ 8 pg/mL, the mean concentration of sST2 at T4 was 100 $\pm$ 123 pg/mL, whereas in patients with preoperative sST2 $<$ 8 pg/mL, the mean concentration was 60 $\pm$ 90 pg/mL, but the difference between the two groups was not statistically significant. Similarly at T4, NT-proBNP levels returned to preoperative values and the mean concentration was 326 $\pm$ 376 pg/mL. Six months after surgery, MR degree decreased from 3.8 $\pm$ 0.4 to 0.4 $\pm$ 0.6 ($p < 0.05$), left ventricular end-diastolic diameter (LVEDD) decreased from 59.8 $\pm$ 6 to 53.3 $\pm$ 5.6 mm ($p < 0.05$) and pulmonary artery pressure decreased from 37.4 $\pm$ 9.9 to 26.3 $\pm$ 2.9 mm Hg ($p < 0.05$). Patients with preoperative sST2 $\geq$ 8 pg/mL had significantly higher EF (64.7 $\pm$ 5.8 vs. 57.6 $\pm$ 5.9; $p = 0.03$) and lower LVEDD (50.6 $\pm$ 5.8 vs. 56 $\pm$ 4.2; $p = 0.03$) at follow-up compared with patients with preoperative sST2 $<$ 8 pg/mL.

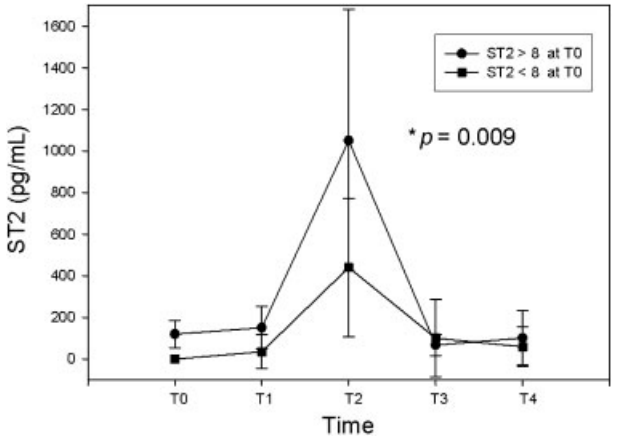

Fig. 1 Serum levels of soluble ST2 (sST2) over time according to baseline sST2 value.

Discussion

This study investigated for the first time the role of ST2 in the setting of chronic degenerative MR. In our series, low sST2 levels could be detected in 50% of patients with severe chronic MR and after MV repair the presence of preoperative serum levels of sST2 was associated with higher levels of EF and lower levels of LVEDD.

ST2 is mainly expressed in T-helper type-2 (Th2) cells[9] and the ST2/IL-33 system is primarily involved in inflammatory and autoimmune diseases, such as bronchial asthma,[10] idiopathic pulmonary fibrosis,[11] inflammatory bowel disease,[12] septic shock and trauma,[13] arthritis[14] and warm hepatic ischemia/reperfusion injury.[15] While the lung has been shown to have the highest expression of ST2, other sources include endothelial cells and cardiac myocytes; recently the role of ST2/IL-33 system in cardiovascular diseases has been highlighted. In patients with AMI, serum levels of sST2 are inversely correlated to the EF[5] and predict mortality and congestive heart failure (CHF).[6] In patients with CHF and NYHA, functional class III to IV, sST2 serum levels are correlated to BNP levels and an increase in sST2 levels over time is an independent predictor of subsequent mortality or need for heart transplantation[7]; additionally, increased plasma concentrations of sST2 are predictive of 1-year mortality in patients with acute decompensated CHF.[8] All the above mentioned pulmonary and cardiac diseases are characterized by a strong inflammatory component and elevated serum sST2 levels which represent an important prognostic factor in these diseases. On the contrary, degenerative MR has a distinctive pathophysiology depending primarily on volume overload in the absence of an inflammatory component[16]; thus, the stimulus for ST2 activation is essentially relegated to the myocardial stretch. This could explain why low levels of sST2 were detected in only half of the population study in the preoperative period. Additionally, preoperative CRP levels were normal and there was no difference between the two groups of patients. Conversely, in the early postoperative period sST2 levels rose significantly. Cardiac surgery with CPB leads to a systemic inflammatory response syndrome; surgical stress and CPB represent an acute injury that leads to prompt activation of ST2 pathway and secretion of high

amounts of sST2. Our results go along with the literature indicating that cardiac surgery with CPB induces a rapid and transitory elevation of sST2 with a peak on postoperative day 1.[17] Interestingly, patients with preoperative detectable sST2 levels experienced a bigger increase in sST2 levels after CPB, thus confirming the preoperative activation of the ST2 pathway in these patients.

The echocardiographic control at 6 months after MV repair showed that patients with preoperative detectable sST2 levels had postoperative significantly higher levels of EF and lower levels of LVEDD. Low preoperative sST2 serum levels seem to have a protective role in the context of chronic degenerative MV disease and are associated with a favorable outcome after MV repair, maybe because they allow IL-33/ST2L interaction with cardioprotection. IL-33, a cardiac fibroblast product produced in response to stretch, represents the functional ligand for ST2L and is known to mediate the negative effects of pressure and volume overload on ventricular myocytes; in fact the infusion of this cytokine prevents remodeling when the heart is acutely exposed to pressure overload, and thus has a cardioprotective role in the setting of myocyte stretch and injury.[4] The protective anti-remodeling effect of IL-33 needs the binding to ST2L in the context of left ventricular pressure and volume overload; in fact interruption of the *ST2* gene results in a deleterious phenotype marked by unchecked myocardial hypertrophy, dilation of ventricular chambers, and reduction in EF.[4] Soluble ST2 plays a delicate role as a "decoy" receptor for IL-33; too much sST2 in the context of potential stretch-induced injury to the heart may therefore result in inadequate cardioprotection from IL-33, with a heightened risk for adverse remodeling and ventricular dysfunction. The explanation why patients with detectable preoperative sST2 levels had a better outcome following MV repair may be that in these patients the ST2/IL-33 system is activated as demonstrated by the presence of serum levels of sST2, and low levels of sST2 still allow the interaction between IL-33 and ST2L, thus ensuring cardiac protection. Further studies are required to fully elucidate the role of ST2/IL-33 in the setting of degenerative MV disease.

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