



Preoperative ST2 but not NT-proBNP is associated with short-term left ventricular remodeling after mitral valve repair for severe symptomatic degenerative mitral valve disease

Antonella Galeone^{1,2} MD, Arrigo Lessana² MD,

Elisa Mascolo³ BSc, Francesca Di Serio³ BSc,

Nicola Marraudino¹ MD, Luigi de Luca Tupputi Schinosa¹ MD,

François Laborde² MD, Domenico Paparella¹ MD

*1*Division of Cardiac Surgery, DETO, 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

Background

- Organic MR induces BNP activation, which reflects the ventricular and atrial consequences of MR
- ST2, an IL-1 receptor family member with transmembrane (ST2L) and soluble (sST2) isoforms, is markedly up-regulated in cultured cardiomyocytes subjected to mechanical strain
- In patients with AMI, elevated sST2 levels are associated with an increased risk of mortality or HF
- In patients with severe chronic NYHA class III to IV HF, the change in sST2 levels is an independent predictor of subsequent mortality or heart transplantation.

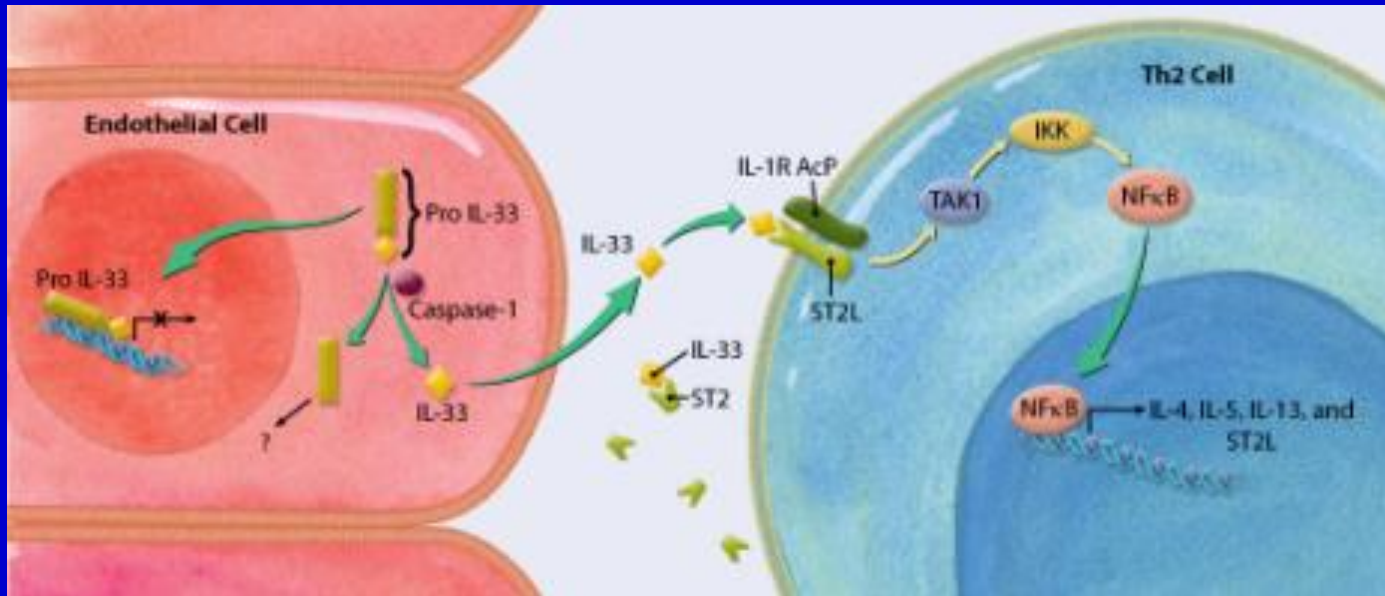
Detaint D. B-Type Natriuretic Peptide in Organic Mitral Regurgitation Determinants and Impact on Outcome. *Circulation*. 2005;111:2391-2397.

Weinberg EO. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation*. 2002;106:2961-2966.

Shimpo M. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation*. 2004;109:2186 -2190.

Weinberg EO. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation*. 2003;107:721-726.

IL-33/ST2



- IL-33 is expressed by cardiac fibroblasts and it is up-regulated by mechanical strain; IL-33 binds to ST2L and exerts antihypertrophic and antifibrotic effects.
- sST2 acts as a soluble decoy receptor and blocks IL-33 thus preventing its cardioprotective effects.

Schmitz, J. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005;23:479-90.

Sanada S. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest* 2007;117(6):1538-49

Primary end-point

To evaluate the expression and the trend of sST2 and NT-proBNP levels in patients with chronic degenerative MR scheduled for mitral valve surgery

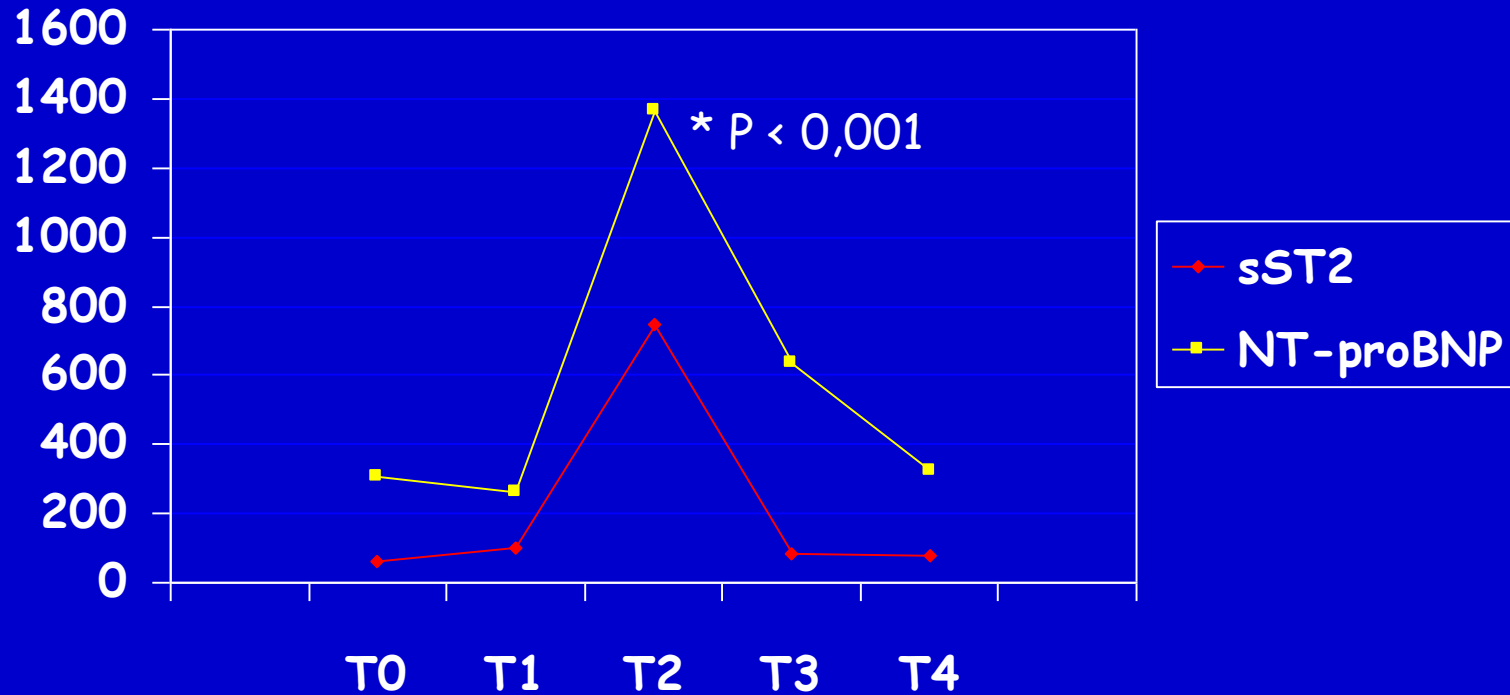
Secondary end-point

To verify the association of sST2 and NT-proBNP levels with clinical and echocardiographic variables

Methods

- Prospective enrollement of 20 patients with chronic degenerative MR scheduled for mitral valve surgery.
- Exclusion criteria:
 - MR due to rheumatic disease,
 - associated coronary artery disease (CAD),
 - mitral stenosis,
 - aortic valve disease,
 - previous valve or coronary surgery,
 - cardiomyopathies,
 - pericardial disease.
- Laboratory assays: sST2 and NT-proBNP
 - T0: at baseline during induction
 - T1: at the end of intervention
 - T2: on post-operative day 1
 - T3: at hospital discharge
 - T4: after 6 months
- Clinical and echocardiographic evaluations
 - baseline
 - 6-months follow-up

Results: laboratory assays



- Baseline sST2: 0-234 pg/ml (median 8 pg/ml)
- Baseline NT-ProBNP: 14-1249 pg/ml (median 207 pg/ml)

Results: Baseline clinical variables

| | Overall (n = 20) | Baseline sST2 | | p | Baseline NT-proBNP | | P |
|-----------------------|---------------------|-----------------------|-----------------------|--------------|-------------------------|-------------------------|----|
| | | < 8 pg/ml (n = 10) | ≥ 8 pg/ml (n = 10) | | < 207 pg/ml (n = 10) | ≥ 207 pg/ml (n = 10) | |
| Age, y | 58,9±13,5 | 59±14 | 58±13 | NS | 59,8±13,7 | 57,9±13,9 | NS |
| Male gender, n (%) | 16 (80%) | 9 (90%) | 7 (70%) | NS | 8 (80%) | 8 (80%) | NS |
| Hypertension, n (%) | 5 (25%) | 3 (30%) | 2 (20%) | NS | 2 (20%) | 3 (30%) | NS |
| Diabetes, n (%) | 0 | 0 | 0 | | 0 | 0 | |
| Dyslipidemia, n (%) | 3 (15%) | 0 | 3 (30%) | NS | 0 | 3 (30%) | NS |
| Smoking, n (%) | 14 (70%) | 7 (70%) | 7 (70%) | NS | 5 (50%) | 9 (90%) | NS |
| Previous CVA, n (%) | 1 (5%) | 0 | 1 (10%) | NS | 0 | 1 (10%) | NS |
| PVD, n (%) | 0 | 0 | 0 | | 0 | 0 | |
| CRF, n (%) | 1 (5%) | 1 (10%) | 0 | NS | 10% | 0 | NS |
| Chronic AF, n (%) | 3 (15%) | 1 (10%) | 2 (20%) | NS | 0 | 3 (30%) | NS |
| Euroscore (additive) | 2,4 ±1,5 | 3,2±1,3 | 1,5±0,9 | 0,009 | 2,6±1,8 | 2,1±0,9 | NS |
| Barlow disease, n (%) | 8 (40%) | 3 (33%) | 5 (50%) | NS | 5(50%) | 3 (33%) | NS |
| NYHA class | 2,3±0,6 | 2,4±0,6 | 2,2±0,4 | NS | 2,5±0,7 | 2,1±0,3 | NS |

Results: Baseline echocardiographic variables

| | Overall (n = 20) | Baseline sST2 | | p | Baseline NT-proBNP | | P |
|--------------------------------|---------------------|-----------------------|-----------------------|-------------|------------------------|------------------------|--------------|
| | | < 8 pg/ml (n = 10) | ≥ 8 pg/ml (n = 10) | | <207 pg/ml (n = 10) | ≥207 pg/ml (n = 10) | |
| EF (%) | 65,8±4,1 | 65,4±4,4 | 66,1±3,9 | NS | 67,6±4,8 | 63,9±2 | 0,025 |
| LVEDD, mm | 59,8± 6 | 61,4±5 | 58,1±6,6 | NS | 59,3±2,6 | 60,2±8,2 | NS |
| LVESD, mm | 36,9±4,4 | 39,1±3 | 34,44±4,5 | 0,03 | 36,3±3,7 | 37,4±5,1 | NS |
| LA area, cm ² | 32,5±6,3 | 33,7±6,1 | 31,22±6,5 | NS | 28,4±3,7 | 36,2±5,9 | 0,005 |
| ERO, cm ² | 48,8±12,4 | 53,5±14,1 | 43,7±8,1 | NS | 49,5±14,6 | 48,1±10,3 | NS |
| RV, ml/beat | 76,1±21,9 | 83±20,7 | 62,3±19,5 | NS | 75,6±26 | 77±13,6 | NS |
| MR degree | 3,8 ±0,4 | 4±0 | 3,6±0,5 | NS | 3,8±0,4 | 3,8±0,4 | NS |
| Prolapsed segment | | | | | | | |
| Anterior | 1 (5%) | 1 (10%) | 0 | NS | 0 | 1 (10%) | NS |
| Posterior | 14 (70%) | 6 (60%) | 8 (80%) | NS | 6 (60%) | 8 (80%) | NS |
| Bileaflet | 5 (25%) | 3 (30%) | 2 (20%) | NS | 4 (40%) | 1 (10%) | NS |
| Flail leaflet | 14 (70%) | 7 (70%) | 7 (70%) | NS | 7 (70%) | 7 (70%) | NS |
| Tricuspid regurgitation degree | 0,9±0,6 | 0,7±0,7 | 1±0,5 | NS | 0,9±0,6 | 0,8±0,6 | NS |
| PAP, mmHg | 37,4±9,9 | 27,25±3,2 | 26,1±2,2 | NS | 33,9±9,2 | 40,8±9,8 | NS |

Operative Results

| Operative characteristics | |
|---|-----------------|
| MV repair | 20 (100%) |
| Quadrangular resection | 17 (85%) |
| Folding | 16 (80%) |
| Artificial chordae insertion | 7 (35%) |
| Commisuroplasty | 2 (10%) |
| Mitral annular ring size mean \pm SD (mm) | 34,9 \pm 3,2 |
| Tricuspidal ring | 5 (25%) |
| FA Ablation | 3 (15%) |
| CPB time (min) mean \pm SD | 87,2 \pm 19,3 |
| Cross-clamp time (min) mean \pm SD | 67,6 \pm 16,4 |
| Postoperative cTnI peak (ng/ml) | 11,9 \pm 7,2 |

Results: follow-up

| | Baseline | 6-months Follow-up | p |
|-----------------------------|----------|-----------------------|---------|
| Echocardiographic variables | | | |
| EF (%) | 65,8±4,1 | 61,2±6,8 | < 0,05 |
| LVEDD, mm | 59,8±6 | 53,3±5,6 | 0,001 |
| LVESD, mm | 36,9±4,4 | 36±5,2 | NS |
| PAP, mmHg | 37,4±9,9 | 26,3±2,9 | < 0,001 |
| MR degree | 3,8±0,4 | 0,4±0,6 | < 0,001 |
| Laboratory variables | | | |
| ST2, pg/ml | 60 | 80 | NS |
| NT-proBNP, pg/ml | 309,2 | 325,6 | NS |

Results: follow-up

| | Baseline sST2 | | p | Baseline NT-proBNP | | p |
|------------------------------------|----------------------|----------------------|-------------|------------------------|------------------------|----|
| | <8 pg/ml (n = 10) | ≥ 8pg/ml (n = 10) | | <207 pg/ml (n = 10) | ≥207 pg/ml (n = 10) | |
| | 6-months Follow-up | | | 6-months Follow-up | | |
| Echocardiographic variables | | | | | | |
| EF (%) | 57,6±5,9 | 64,7±5,8 | 0,03 | 63,4±7 | 59,1±6,4 | NS |
| LVEDD, mm | 56±4,2 | 50,6±5,8 | 0,03 | 52±4,4 | 54,67±7 | NS |
| LVEDS, mm | 38,2±3,7 | 33,3±5,7 | NS | 34,4±5,2 | 37±5,3 | NS |
| PAP, mmHg | 26,6±3,7 | 26,1±2,3 | NS | 27,1±3,2 | 26±2 | NS |
| MR degree | 0,4±0,7 | 0,4±0,5 | NS | 0,5±0,7 | 0,33±0,5 | NS |
| Laboratory variables | | | | | | |
| ST2, pg/ml | | | | 110 | 60 | NS |
| NT-proBNP, pg/ml | 478,4 | 172,8 | NS | | | |

Conclusions

- Degenerative MR is associated with hormonal activation; patients with baseline higher levels of NT-proBNP have preoperative lower EF and higher LA area
- sST2 is slightly activated in patients with chronic degenerative MR; patients with baseline higher levels of sST2 have preoperative lower LVEDD
- CPB induces an acute and transient increase of both sST2 and NT-proBNP levels with a peak at T2
- At 6-months follow-up after MV repair patients experienced an equal LV remodelling irrespective of preoperative NT-pro-BNP levels, while patients with baseline higher sST2 levels have higher EF and lower LVEDD