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ORIGINAL ARTICLE

# Soluble ST2 Protein in Cardiac Surgery: A Possible Negative Feedback Loop To Prevent Uncontrolled Inflammatory Reactions

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## SUMMARY

***Background:*** **Recent reports have demonstrated that cardiopulmonary bypass (CBP) utilization leads to a TH2 cytokine bias in patients undergoing coronary artery bypass grafting (CABG) operation. The relation of soluble ST2 and secretion of IL-10, markers of TH2 T-cell activation, and IL-13 in relation to immunoglobulin isotope production is not known in patients undergoing On- versus Off-pump (CABG) procedure.**
***Methods:*** **30 patients were prospectively included in the study (On- vs Off-pump CABG, each n=15). Serum samples were obtained prior to, and 30min, 60 min and 24hrs after operation. ELISA was utilized to detect sST2 and IL-10, IL-13 and immunoglobulin isotype production.**
***Results:*** **In both cohorts we could demonstrate a significant rise of ST2 24 hours after the CABG procedure. In the On-pump group ST2 levels (pg/ml) before the operation, at 30 and 60 minutes and after 24 hours were 115.3±25, 71.2±15, 114.1±26 and 4231.9±520, respectively. In the Off-pump group they were 200.3±109, 91.2±20, 137±29 and 4144.9±488 (both, p<0.0001, p<0.0001, respectively). IL-10 (pg/ml) levels rose from preoperative values of 6.2±1.6 in the On-pump group and 7.91±1.8 in the Off-pump group to 33.14±8.7 and 13.72±3 after 60 minutes (p 0.0189, p 0.0397, respectively). IL-13 levels and immunoglobulin production did not change significantly within the study period irrespective of the operation procedure used.**
***Conclusion:*** **In conclusion, our results demonstrate that sST2 and IL-10, markers of TH2 cytokine producing cells, are increased in CABG operation, irrespective of the procedure selected, and settles a longstanding controversy concerning the shift from Th1 to Th2 cells.**
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## KEY WORDS

Cardiopulmonary bypass, off-pump, on-pump, IL-10, IL-13, ST2, immunoglobuline, TH1, TH2

## INTRODUCTION

Cardiopulmonary bypass (CBP) induces a well described systemic inflammatory response syndrome (SIRS). A number of patients have organ dysfunction, which may delay postoperative recovery and may influence morbidity and mortality. The release of a variety of inflammatory mediators has been implicated in the pathogenesis of SIRS during CBP [1,2]. The immunological cascade of CBP leads to lymphopenia in vivo and altered T-lymphocyte subpopulations [3,4,5]. The particular type of immune response is determined by differentiation of precursor T helper (TH0) cells into Th1 or Th2 subsets, which is dependent upon local cytokine concentration. Th1 cells produce interferon γ (INFg) and Th2 cells produce IL-4, 5 and 10. The latter cytokine was reported to have immunsuppressive capacity [6]. Recent reports have demonstrated that CBP utilization leads to a Th2 cytokine bias in patients undergoing CABG operation [7].

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**Table1: Patient Demographics**

| | CABG (n=15) | OPCAB (n=15) | p-value |
|---|---|---|---|
| Age (years) | 59.9±2.2 | 58.6±2.6 | 0.712 |
| Sex (%male) | 53.3 | 56.7 | 0.456 |
| Body mass index | 26.8±1.1 | 27.7±0.86 | 0.495 |
| Mean CV risk factors | 1.667±0.2 | 1.667±0.2 | 1 |
| Vessel disease | 2.9±0.1 | 2.7±0.1 | 0.285 |
| NYHA (class) | 3.2±0.1 | 3.1±0.1 | 0.481 |
| EF (%) | 50.1±3.4 | 50.3±1.5 | 0.947 |
| Euroscore | 4.3±0.5 | 3.9±0.6 | 0.696 |
| Average number of grafts | 2.2±0.1 | 2.3±02 | 0.577 |
| Graft type | | | |
| Single | 1 | 2 | |
| Double | 10 | 6 | |
| Triple | 4 | 7 | |
| Aortic clamping time (min) | 61.7±3.0 | | |
| Coronary occlusion time (min) | | 98.2±5.5 | |
| OP time (min) | 223.9±8.7 | 218±11 | 0.686 |
| Creatine kinase after 24 hours (U/L) | 761.2±72.8 | 984.6±302.3 | 0.480 |
| Creatine kinase-MB after 24 hours (U/L) | 46.9±5.2 | 72.1±23.6 | 0.307 |
| Creatine kinase-MB % after 24 hours | 8.4±2.1 | 7.42±1.2 | 0.727 |
| Hemoglobin preoperative (g/dl) | 24.6±8 | 12.8±0.5 | 0.325 |
| Hemoglobin postoperative (g/dl) | 16.9±6.9 | 16.8±5.9 | 0.986 |
| Hemoglobin one day after operation (g/dl) | 17.3±6.9 | 10.9±0.3 | 0.403 |
| Blood loss (ml) | 607.3±54 | 440±66.8 | 0.071 |
| Transfused units | 2.3±0.1 | 1.7±0.1 | 0.211 |
| ICU stay (hours) | 22.4±1.6 | 32.22±9.8 | 0.162 |
| Hospital stay (days) | 6.6±0.3 | 10.3±3 | 0.223 |
| Fluid balance (ml) at 60 min | 2700±91.7 | 575±42.2 | 0.001 |
| Fluid balance (ml) at 24 hours | 2187±157.3 | 1537±137.5 | 0.003 |

Values are mean±s.e.m or percent.
NYHA = New York Heart Assossiation, CABG = coronary artery bypass grafting,
EF = ejection fraction, ICU = intensive care unit;

Other nosological entities, such as asthma and autoimmune diseases have been reported to demonstrate a similar Th2 cell-type immuneactivation and a novel distinct Th2 specific shed product, named T1/ST2, was demonstrated to be elevated [7,8]. The IL-1 receptor-related molecule T1/ST2 has been evidenced to distinguish a subset of CD4+ T-helper cells of the Th2 subtype, characterized by their elevated expression of the cytokines IL-4, IL-5, and IL-13 [9,10]. However, the T1/ST2 receptor is also expressed on cell membranes of mast cells [11] and was originally described as a serum-induced gene in fibroblasts [12]. Alternative transcriptional regulation results in the production of soluble and transmembrane forms of the T1/ST2 protein due to the use of different polyadenylation signals [13,14]. The biological function of the T1/ST2 receptor remains unclear, but its homology with the Toll receptor and other IL-1 family members [15] suggests that it may play a central role in the innate and adaptive immune responses.

Since a Th2 shift was reported in CABG patients we sought to investigate the relationship between IL-10, soluble ST2 secretion and immunoglobulin isotype production in Off- vs On-pump CABG patients in a non randomized, comparative study with no a priori hypothesis.

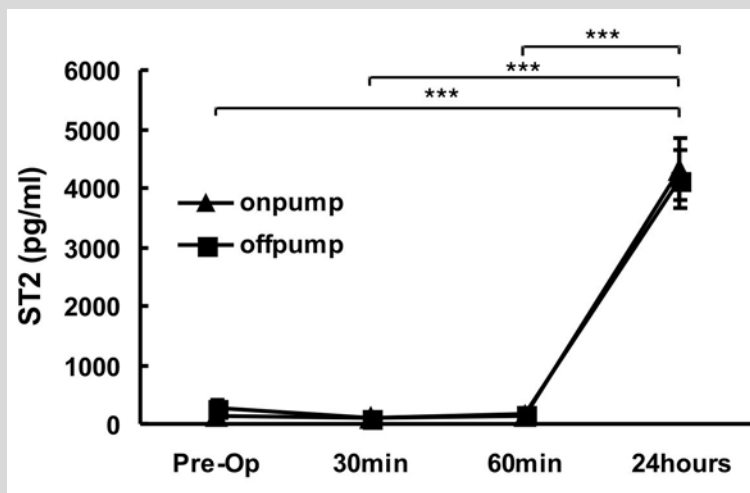


**Figure 1: Serum levels of ST2 (pg/ml) before the CABG procedure, at 30 and 60 minutes, and 24 hours after the operation. The triangles and the squares represent the mean value, the whiskers the standard error of the mean. (*** = p<0.0001)**

## MATERIAL AND METHODS

### Patient selection

With approval of the Ethics Commitee, 30 consecutive patients with multivessel coronary artery disease undergoing the CABG procedure were studied. Patients were selected for Off-pump CABG only when complete revascularization was technically feasible. There were no differences between the two groups of patients with respect to age, sex, symptoms, or functional class (Table 1).

All patients received a similar balanced anesthetic regimen as described below: medication protocols were similar in both study cohorts (Off- vs On-pump): Premedication: Morph. Sulph.: 0.1 mg/kg im., Midazolam: 0.05-0.1 mg/kg, Atropin sulph.: 0.005mg/kg. Anesthesia: Midazolam: 0.1-0.15 mg/kg, Fentanyl 0.005 mg/kg, Muscle relaxant: Pipecuronium bromide 0.08mg/kg or Atracuronium: 0.5 mg/kg. Maintenance of anesthesia: continuous IV. Propofol infusion 0.07-0.14 mg/kg/min + inhalation of Isoflurane narcotic gas (0.2-1.5 vol%).+ repetitive administration of Fentanyl bolus (0.0025 mg/kg) for pain relief, in order to attain constant muscle relaxation 0.02 mg/kg Pipecuronium bromide or continuous i.v. infusion of Atracurium (0.5 mg/kg/hr) were administered. Heparinization: On-pump group – 3 mg/kg Na-heparin (=300IE/kg), ACT – are determined to be above 600 sec, mild hypothermia (32-34 °C), minute volume 2.5 L/min, Composition of priming solution: 1200-1750 ml cristalloid solution + 1000 IE Na-heparin + 100 ml Mannite (20%solution) + 150 ml Na-bicarbonate solution (4.2%), neutralization with protamine suph.. Heparinization: Off-pump – half of the On-pump dosis = 1.5 mg/kg=150 IE/kg was administered. ACT should be 300 sec during operation. At the end of operation a ACT is always performed and should be below 200 sec. No protamine was administered at the end of the operation.

### Exclusion criteria

Criteria such as infections, redo or emergency operation, malignancies, verified immunological disorders, acute myocardial infarction less than 2 weeks ago and medication with immune-modulating agents such as steroids or antiphlogistics were causes for exclusion from the study.

### Cardiopulmonary Bypass Technique

The extracorporal circuit consisted of a roller pump (Pemco Inc., Cleveland,OH; Stöckert, Munich, Germany) and a membrane oxygenator (Dideco D-703, Modena, IT; Monolyth, Sorin, Saluggia, IT). Standard systemic heparinization with target levels of activated clotting time of greater than 480 seconds was maintained during CPP. The pump flow was set at 2.4 L/min/m$^2$. Patients were cooled to 32 °C during CBP, and they received intermittent antegrade normothermic crystalloid cardioplegia, which was a mixture of graduated doses of potassium-magnesium solution. At the end of CBP the heparin effect was neutralized with equivalent doses of protamine (1000U heparin is antagonized with 1000 U protamine).

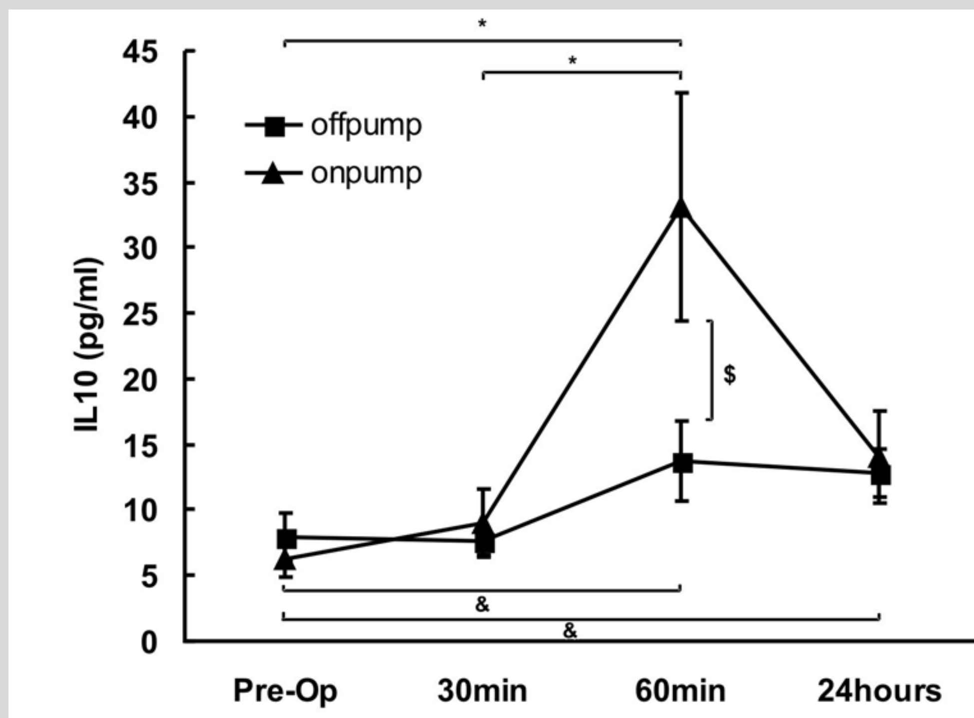


**Figure 2: Serum levels of IL-10 (pg/ml) before the CABG procedure, at 30 and 60 minutes, and at 24 hours after the operation. The triangles and the squares represent the mean value, the whiskers the standard error of the mean. (* = p<0.05 in the On-pump group; $ =p<0.05 in the Off-pump group; &=p<0.05 between the two cohorts)**

**Off-Pump Technique**
Traction sutures were applied to the pericardial edges, displacing the heart anteriorly. For exposure of the left anterior descending coronary artery or its diagonal branches, additional pericardial traction sutures were inserted anteriorly to the left phrenic nerve. To rotate the heart a moist sponge was placed behind its laterodorsal aspect, bringing the coronary artery into the operative field. For exposure of obtuse marginal or right coronary branches, two wet cotton tapes were passed through the transverse sinus with their right ends secured to the surgical drapes. The two loose lengths of tape were then used to lift and rotate the heart toward the surgeon, as well as to stabilize the coronary artery. Patients were heparinized (1 mg/kg) and two thin elastic bands made of rubber were used to temporarily occlude the coronary artery on either side of the anastomosis site. For the exposure and stabilization of the target vessel stabilizers were utilized. (Medtronic, Minneapolis, MN; Genzyme Cooperation, Cambridge, MA))

**Blood samples**
In the CBP group, samples of venous blood were obtained from each patient before the operation, at the beginning and at the end of CBP, and 24 hours after the procedure. In the OPCAB-group blood samples were drawn before the operation, after reperfusion of all grafts, at the end of the operation and 24 hours after the surgical procedure. Serum samples were obtained via centrifugation of the blood tubes and were kept frozen until the specific tests were performed.

**Quantification of serum ST2 levels**
Serum samples were aliquoted and deep frozen. Soluble ST2 levels were measured with a commercial enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA). In brief, serum samples and standards were incubated in 96-well microplates pre-coated with anti-human ST2 antibody. After washing, peroxidase-conjugated anti-human ST2 antibody was added to the microwells and incubated. After another washing the substrate was added, and after adding the stop solution, the optical density was determined at 450nm. The amount of protein in each sample was calculated according to a standard curve of optical density values constructed for known levels of ST2. The sensitivity of the ELISA kit is 25 pg/ml.

**Table 2: Serum levels of immunoglobulin isotypes**

| | | preoperative | 60 minutes | 24 hours |
|---|---|---|---|---|
| On-pump | IgG1 (mg/L) | 3107.7±840 | 2934.1±572.6 | 2328±440.2 |
| | IgG2 (mg/L) | 1765.8±237.9 | 2152.1±311 | 2095±356.6 |
| | IgE (mg/l) | 0.50±0.1 | 0.55±0.1 | 0.52±0.21 |
| | IgM (g/L) | 3.72±0.5 | 3.95±0.4 | 3.87±0.6 |
| Off-pump | IgG1 (mg/L) | 4263.8±1208.6 | 4366.2±716 | 2594.3±641 |
| | IgG2 (mg/L) | 2071±356.4 | 2385.2±477 | 2402.7±478.3 |
| | IgE (mg/l) | 0.80±0.3 | 0.46±0.1 | 0.52±0.1 |
| | IgM (g/L) | 3.61±0.3 | 4.19±0.5 | 4.29±0.7 |

**Quantification of interleukin-10**
Circulating serum levels of IL-10 were measured by ELISA (Amersham Pharmacia Biotech, Little Chalfont, UK). The sensitivity of the ELISA is 0.1 pg/mL. The amount of protein in each sample was calculated according to a standard curve of optical density values constructed for known levels of IL-10.

**Detection of immunoglobulins by solid-phase ELISA**
96-well microplates (Nunc Polysorb; Life Technologies) were coated overnight with 100µl/well of BSA as control or with anti-human monoclonal IgE, IgG1, IgG2 or IgM (Sigma, St. Louis, MO, USA) at a dilution of 1:1000. 0.05% Tween/PBS was used for washing. Nonspecific binding was blocked with PBS+1% BSA for one hour at room temperature. Before use, the serum samples were diluted 1:3 for IgE and 1:5 for IgG and IgM with PBS +1% BSA. Each plate was equipped with human IgE, IgG1, IgG2 and IgM as standard and with the diluted sera of 15 septic patients, 13 critically ill patients and 15 healthy controls and was then incubated for 2 hours at room temperature. After another washing step, immunoglobulin binding was quantified by incubating with peroxidase-conjugated rabbit anti-human IgE, IgG or IgM at a dilution of 1:1000 for one hour at room temperature followed by the substrate reaction with 1,2 phenylenediamine. Plates were read at 490nm and specific binding was calculated according to a standard curve of optical density values constructed for known levels of immunoglobulins.

**Quantification of interleukin-13**
Serum samples were aliquoted and deep-frozen (-80 °C) Serum levels of IL-13 were measured with commercial enzyme-linked immunosorbent assay (instant ELISA, Bender Med Systems, Vienna, Austria). Serum samples were incubated in 96-well microplates precoated with monoclonal antibodies (murine) to human IL-13. After washing, TMB substrate solution was added into the microwells and incubated. After adding the stop solution, the optical density was determined at 450 nm. The sensitivity of the ELISA is 1.5 ng/l. The amount of protein in each sample was calculated according to the standard curve of optical density values constructed for known levels of IL-13. (Table 3)

**Statistical analysis**
Results are presented as mean ± SEM if not otherwise stated. After checking for normal distribution paired and unpaired Student's t-test were used to compare the means of the results. Bivariate data in the table were compared using the chi-square test. A P value of $< 0.05$ was considered to be statistically significant.

## RESULTS

**Serum levels of ST2**
Figure 1 demonstrates the course of ST2 values (pg/ml) in the serum of the two cohorts. The levels before the operation and at 30 and 60 minutes were significantly lower than those at 24 hours in both groups ($p<0.0001$). There was no difference between the two cohorts.

**Serum levels of IL-10**
Figure 2 shows the serum levels of IL-10 (pg/ml). In the Off-pump group, the pre-operative levels were significantly lower than those at 60 minutes (p 0.032) and 24 hours (p 0.0397). In the On-pump group, the IL-10 levels preoperative and at 30 minutes were significantly lower than those at 60 minutes (p 0.0189; 0.0477 resp.). At 60 minutes, the IL-10 levels were significantly higher in the On-pump group than in the Off-pump group (p 0.0433).

**Serum immunoglobulin levels**
Table 2 shows the mean serum levels of IgG1, IgG2, IgE and IgM. No significant differences could be found

**Table 3: Serum levels of interleukin-13**

| | preoperative ng/l | 30 minutes ng/l | 60 minutes ng/l | 24 hours ng/l |
|---|---|---|---|---|
| On-pump | 8.82±2.39 | 10.40±3.48 | 81.58±74.47 | 8.30±3.62 |
| Off-pump | 4.66±1.13 | 5.02±1.41 | 17.16±9.50 | 3.48±1.02 |

between the different time points and between the two cohorts.

**Serum levels of IL-13**

Table 3 shows the serum levels of IL-13 (ng/l). There was no significant difference between the Off-pump and the On-pump group at 30 minutes, 60 minutes and 24 hours. Preoperative On-pump levels were significantly higher than those in the Off-pump group.

## DISCUSSION

Our study demonstrated that IL-10 showed a significant transient increase in On- vs Off-pump CABG patients within 60 minutes after initiation of CBP. Humoral immunity, as determined by immunoglobulin detection was not increased within 24 hours. Our study showed for the first time that serum ST2 increases approximately 30-fold in CABG patients, irrespective of the selected operation procedure.

The biological role of ST2 is still unclear. ST2 expression was shown to be induced by IL-1b, IL-1a, and TNF-alpha in fibroblasts, in macrophages, in muscle and in the spleen following lipopolysaccharide (LPS) challenge that is comparable to the sepsis/LPS syndrome [16,17]. Thus, macrophages respond to LPS by both, producing cytokines that can induce sST2 expression and by enhancing the expression of a putative sST2 receptor. In a murine BALF model, the kinetic analysis of cytokine and ST2 protein expression demonstrated that ST2 protein levels peaked at 24 hrs and remained at 60% of their maximum level even after 120 hrs, whereas proinflammatory cytokine levels peaked at 6-24 hrs with a rapid decline to baseline levels by 120 hrs post LPS challenge. Based on these findings, it was hypothesized that sST2 protein may downregulate the expression of proinflammatory cytokines. Oshikawa et al. showed that pretreatment with ST2 protein did downregulate protein and gene expression of pro-inflammatory cytokines such as IL-1a, IL-6, and TNF-alpha in LPS-stimulated MH-S cells in vitro [18]. However, the exact mechanism has not been elucidated as yet. With respect to TH1/TH2 T-cell balance it was demonstrated that T1/ST2 can activate AP-1, JNK, p42/p44, and p38 MAP kinase, but it apparently does not activate NF-kB and concurs with conclusions drawn by Kumar et al [21]. Their findings are consistent with a role of T1/ST2 in Th2 cell function since NF-kB has strongly been implicated in Th1 responses. In line with this data, Meisel *et al* have shown that the production of type 2 cytokines precedes the expression of T1/ST2 in Th2 cell polarized in vitro. Most importantly, the finding that cross-linking of T1/ST2 provided a costimulatory signal for Th2 but not Th1 cells and directly induces proliferation and type 2 cytokine production [22]. It was concluded from these data that ST2 may function as an important mediator in this negative feedback loop to prevent uncontrolled inflammatory reactions.

In conclusion, our results demonstrate that sST2, a marker for Th2 cytokine producing cells, is increased in both CABG patients, irrespective of the selected mode of operation. However, immunoglobulin production was not increased within 24 hours and a sequential analysis is warranted. Notable was the rapid secretion of IL-10 within the duration of surgery. This increase was much more pronounced in the On-pump operation. This indicates, that the On-pump procedure is for the patient much more invasive than the Off-pump one. No increase during surgery was seen with IL-13, a cytokine known to be associated with the Th2 cytokine environment. We suggest that the sST2 serum marker has the potential to determine the immune status and the progression in the outcome of patients undergoing CABG and other major surgery [23]. Our study is, however, limited by the unknown variables such as circadian rhythm and half-time of ST2. But the relative significance of increase of soluble ST2 prior compared to 24 hrs post surgery, supports the importance of this novel description and adds an new pathway/explanation in the understanding of postoperative immune compromise after CABG operation.

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