*Unpublished manuscript submitted 13th of august 2016:*

**REDUCED INFLAMMATORY RESPONSE USING TRANSCATHETER AORTIC VALVE REPLACEMENT AS COMPARED TO CONVENTIONAL SURGERY**

*Karoline KH Fiane1, Gry Dahle2, Kjell-Arne Rein2, Bjørn Bendz3, Lars Aaberge3, Per Steinar Halvorsen1, Michael Abdelnoor4, Tom Eirik Mollnes5,6,7,8, Erik Fosse1,8*

*1The Intervention centre, Oslo University Hospital, Oslo, Norway*

*2Department of Cardiothoracic Surgery, Oslo University Hospital, Oslo, Norway*

*3Department of Cardiology, Oslo University Hospital, Oslo, Norway*

*4Department of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway*

*5Department of Immunology, Oslo University Hospital, and K.G. Jebsen IRC, University of Oslo, Oslo, Norway*

*6Reserach Laboratory, Nordland Hospital, Bodø, and K.G. Jebsen TREC, University of Tromsø, Bodø, Norway*

*7Centre of Molecular Inflammation Research, Norwegian University of Science and Technology, Trondheim, Norway*

*8Faculty of Medicine, Oslo University, Oslo, Norway*

Correspondence address:

Prof. Erik Fosse, The Intervention Centre, Oslo University Hospital, POB 4950 Nydalen, 0424 Oslo, Norway

email: erik.fosse@medisin.uio.no

Total word count: 4947

**ABSTRACT**

**Objective:** To compare inflammatory response during transcatheter aortic valve implantation with surgical aortic valve replacement.

**Methods**: Twenty consecutive patients admitted for transcatheter implantation either by a transfemoral (n=9), transaortal (n=9) or transapical (n=2) approach were compared with eighteen consecutive patients admitted for surgical replacement. Blood samples per- and postoperatively were analysed for troponin-T and the following inflammatory markers representing activation of complement, granulocytes, lymphocytes and cytokines: C3bc, terminal complement complex, myeloperoxidase, macrophage inflammatory protein-1β, monocyte chemo-attractant peptide-1, eotaxin and IL-6.

All markers were measured at defined time points and the areas under the curve were compared.

**Results:** Activation of complement, granulocytes and lymphocytes were significantly lower in the transcatheter group as compared to the surgical group (<0.01). There was significant elevation in the levels of IL-6 and troponin-T in both groups with no statistical difference. There was no significant difference in clinical outcomes between the two groups.

**Conclusion:** The inflammatory response in the transcatheter group was significantly lower than in the surgical group. This implies a reduced systemic inflammatory response in the TAVI group which might have implications for postoperative complications.

**Key words: inflammation, TAVI, aortic stenosis, SIRS**

**INTRODUCTION**

Aortic stenosis is a common cardiac disease in the western world, with a prevalence of about 5 % in the population above the age of 74 (1). The common treatment has been surgical aortic valve replacement (SAVR) (2), which involves cardiopulmonary bypass (CPB) and open heart surgery. In patients ≥80 years with severe aortic stenosis the 2-year survival rate with SAVR is 78 %, compared to 40 % without SAVR (3).

Open-heart surgery induces a systemic inflammatory response, which includes complement- and granulocyte activation, as well as cytokine release. The main inflammatory response and particularly activation of the complement cascade is attributed to the use of CPB (4). Studies of beating heart coronary surgery have revealed an activation of granulocytes, but no complement activation (5). It is well known that complement and granulocyte activation may cause an unwanted response that in some cases will lead to the development of systemic inflammatory response syndrome (SIRS) and organ failure (6). Also, studies comparing off-pump and on-pump coronary artery surgery suggest that surgical trauma by itself play a role in the systemic inflammatory activation (7).

In 2002 transcatheter aortic valve implantation (TAVI) was introduced as an alternative treatment for patients with severe aortic stenosis at high risk or with contraindications for open surgery (8). TAVI represents a minor surgical trauma and does not involve extracorporeal circulation. However, it involves prolonged catheter procedures and the use of contrast media. The catheter manipulation in the aorta may also release arteriosclerotic plaques. Development of SIRS has been described in TAVI-patients and is a predictor for mortality in these patients (9).

As TAVI has been associated with SIRS, it is highly relevant to study the inflammatory response during insertion of the valve, and compare with the response during SAVR. Thus, the aim of the present study was to measure the inflammatory response as expressed by complement- and granulocyte activation as well as cytokine release in patients undergoing TAVI compared to SAVR, based on the hypothesis that TAVI-patients will have a lower systemic inflammatory response.

**MATERIAL AND METHODS**

The study was designed as a prospective cohort study where the inflammatory response in 20 patients undergoing a transfemoral, transapical or transaortic TAVI procedure was compared with the inflammatory response in 18 patients undergoing a standard SAVR procedure. As TAVI was reserved for patients judged as inoperable, randomization was not possible. The patients were thus included following the standard criteria in our hospital after informed consent following approval by the regional ethical committee for South East Norway. Euroscore II was calculated for all patients in order to compare the clinical condition of the patients in both groups. Exclusion criteria were known inflammatory disease and anti-inflammatory treatment. Patients were included in the period from May 2012 to February 2013.

**Surgical techniques**

**TAVI procedure**

All TAVI procedures were performed in general anesthesia with a heart team consisting of cardiac surgeons, a cardiologist and an anesthesiologist. After intravenous induction with fentanyl 1-2 µg/kg and thiopenthone 2-4 mg/kg and oral intubation using intravenous cisatracurium 1.5mg/kg, general anesthesia was continued by sevoflurane in an oxygen/air mixture and intermittent boluses of fentanyl 1-2 µg/kg. Systolic blood-pressure was maintained above 100 mmHg by continuous infusion of norepinephrine 0.03-0.1 μg/kg/min supplemented by ephedrine and crystalloid boluses if needed.

The balloon-expandable Edwards Sapien valve (Edwards Lifesciences LLC, Irvine, CA) and for annuli larger than 27 mm the CoreValve revalving system (CoreValve Inc. Irvine, CA) were used. Positioning of the valve was performed with ultrasound and angiographic guidance in accordance with instructions for use from the manufacturer for both valves. The Sapien valve was deployed under rapid pacing to 180 b/m, and the CoreValve was deployed without rapid pacing.

In nine patients TAVI was introduced by the retrograde approach through a cut down in the femoral artery. In nine patients a transaortal approach was performed through a mini-thoracotomy and introduction of the sheath in the ascending aorta, as described by Dahle and Rein (10). In two patients a transapical approach was performed though a left mini-thoracotomy over the apex of the left ventricle.

**Surgical aortic valve replacement**

Induction and general anesthesia were performed in the same way as for the TAVI procedure, except for during the CPB period. Then infusion of propofol 4 mg/kg was used. After CPB, propofol was continued together with intravenous fentanyl to allow early extubation. All operations were performed in moderate general hypothermia (32oC). The extracorporeal system used in the on-pump group consisted of Quadrox-I oxygenater with integrated tubing, cardiotomy suction and reservoir all coated with the Bioline heparin coating (Maquet, Rastatt, Germany) with a roller pump (Stoeckert Stuttgart, Germany). The circuit was primed with 1100-1300 ml Ringer’s acetate with 10,000 IU Heparin. Immediately before start of extracorporeal circulation heparin (4 mg/ kg body weight) was administered intravenously to achieve a minimum activated clotting time (ACT) of 480 hemochron seconds and cold cardioplegic solution (St Thomas II) was administered in the aortic root. A single right atrial two-stage cannula and a perfusion cannula in the ascending aorta were used for the cardiopulmonary bypass. Bypass was performed with a flow of 2.4 l/min per m2. Mean arterial pressure of more than 50 mm Hg was maintained by infusion of norepinephrine 0.01-0.2 if needed. After aortic cross clamping the native aortic cusps were removed and a Carpentier-Edwards Perimount biological aortic valve (Edwards life science, Irvine, CA, USA) was fixed with interrupted sutures through a transversal aortotomy in all the patients. The heart was carefully vented through the aortic root after removal of the aortic clamp. After end of the cardiopulmonary bypass protamine was administered intravenously to achieve the preoperative ACT levels.

**Blood sampling**

Blood samples, 2 ml, were drawn from the arterial line in tubes with ethylenediaminetetraacetic acid (EDTA) as anticoagulant. The tubes were turned gently 3-4 times to ensure that EDTA and blood was mixed well and kept on ice until centrifugation at 2500*g* for 15 minutes within four hours. Plasma was stored immediately at -70°C until analysis. Blood sampling was performed at defined time points per- and postoperatively (figure 1).

**Laboratory analyses**

*Inflammatory markers*

The EDTA plasma samples were examined for the concentration of seven different biomarkers reflecting inflammatory responses. Concentrations of the complement activation products C3bc and the terminal C5b-9 complement complex (TCC) were measured by enzyme-linked immunosorbent assay (ELISA) as described previously (11). The neutrophil release product myeloperoxidase (MPO) was analysed by a commercial ELISA obtained from Hycult Biotech (Uden, The Netherlands). Multiplex technology (Bio-Plex Human Cytokine assay; Bio-Rad Laboratories Inc., Hercules, CA) was used to analyze the cytokines IL-6, eotaxin, MCP-1 and MIP-1β (12). As marker of a myocardial cellular injury troponin T levels were analysed according to the laboratory routine.

*Clinical outcomes*

Postoperative ECG was obtained in 17 patients, and 21 patients was monitored with continuous rhythm surveillance postoperatively. Postoperative echocardiography was only performed in a few patients. Myocardial infarction was defined in accordance with ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction (13).

Postoperative stroke was defined as rapidly developing clinical signs of focal or global in case of coma disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin. Postoperative bleeding and blood product transfusions were recorded in all patients as well as in-hospital, 30 day and one-year mortality.

*Statistical analysis*

As power analysis, the sample size was calculated based on the change in plasma concentration of IL-6 24 hours after procedure as described by Sablotzki et al. (12). The variability of IL-6 after 24 hours off cardiopulmonary bypass was calculated as SD=147 pg/m. We consider a difference between levels of IL-6 at 24 hours of 150 pg/ml a relevant clinical difference between TAVI and SAVR. Taking in consideration a type 1-error of 5 % and a power of 80 %, a total of 32 patients with 16 in each group were needed.

All values were corrected for hemodilution by the formula:

$$value corrected=value Tn∙\frac{Hb (baseline)}{Hb (Tn)}$$

When the measured values of the inflammatory markers were plotted against the frequency by which they appeared, the response did not follow the normal distribution. Hence, non-parametric tests were chosen for statistical analysis. All values are given as median, range and comparison. The difference between baseline and peak value was used to estimate activation within the same group. The area under the curve (AUC) was calculated and used for comparison between the serial measurements of the groups (14), using the Mann-Whitney-U-test to compare mean ranks. The area for one time segment was calculated in the following way:

$$area=\left(\left(t\_{2}-t\_{1}\right)∙y\_{1}\right)+(\left(t\_{2}-t\_{1}\right)∙\frac{y\_{2}-y\_{1}}{2})$$

where y1 and y2 represent the measurements andt1 and t2 represent the time points. The final AUC was then calculated as the sum of segmental areas. All statistical analysis was done by using IBM SPSS Statistics version 24.

**RESULTS**

**Patient characteristics and TAVI performances**

Thirty-six patients, 20 women and 16 men, with a median age of 82 (70-89) were included in the study (table 1). Twelve patients in the TAVI group had previous heart surgery (CABG or SAVR) while none in the SAVR were previously operated in the chest. The median EuroSCORE II was 4.2 (1.1-28.8) and 26 patients were in NYHA class III or higher. The groups did not differ with respect to the preoperative aortic valve area or gradient (table 1).

TAVI was performed transfemorally in 9 patients and transaortally in 9 patients. Six patients received Edwards Sapien, with size 23 (n=1), size 26 (n=2), size 29 (n=3) (median size 26). Twelve patients received CoreValve, size 23 (n=2), size 26 (n=3), size 29 (n=4), size 31 (n=3) (median 29). All patients in the SAVR group received a Perimount, Carpentier Edwards biological valve, size 19 (n=2), size 21 (n=9), size 23 (n=4) and size 25 (n=3) (median size 21), the difference in valve size was not statistically significant.

**Adverse events and clinical outcome**

Myocardial infarction or stroke was not recorded in any of the patients in the two groups. Postoperative bleeding was 735 ml (265-2870) in the SAVR group and 175 ml (0-1440) in the TAVI group (p<0.01) (table 2). There was, however, no significant difference in blood product transfusion between the groups. One patient died within 30 days in each group. In the TAVI group the patient died the first postoperative day. Autopsy revealed a tear in the aortic annulus and mediastinal bleeding resulting in cardiac tamponade. The patient in the SAVR group died after discharge from our hospital. One-year mortality did not differ between the groups.

**Inflammatory markers**

*Complement*

The median concentration of C3bc increased from a baseline of 11 (8-27) (min-max) arbitrary units (AU)/ml to a peak level of 176 (117-272) AU/ml in the SAVR group (p<0.05), and from 14 (10-33) AU/ml to a peak of 44 (15-162) AU/ml in the TAVI group (p<0.05). In the transfemoral TAVI group the median concentration of C3bc at baseline was 13 (10-18) AU/ml and increased to a peak value of 21 (15-84) AU/ml, and in the transaortal TAVI group the median value at baseline was 15 (10-33) AU/ml and increased to a peak value of 96 (36-162) AU/ml. The area under the curve was 85978 (48276-209296) hrsAU/ml in the SAVR group and 30605 (17824-129801) hrsAU/ml in the TAVI group (p<0.05), indicating a significantly lower C3 activation in the TAVI group (fig. 1). In the transfemoral TAVI group the area under the curve was 22931 (17824-57499) hrsAU/ml in, and in the transaortal TAVI group it was 59972 (26172-129801) (p<0.05), indicating a significantly lower activation of C3 in the transfemoral group.

The median level of TCC increased from 0.5 (0-0.9) AU/ml at baseline to a peak of 4.8 (2.4-9.9) AU/ml in the SAVR group (p<0.05) and from 0.5 (0.4-0.9) AU/ml to 1.0 (0.7-2.8) AU/ml in the TAVI group (p<0.05). In the transfemoral TAVI group the baseline value of TCC was 0.5 (0.4-0.7) AU/ml and increased to 0.9 (0.7-1.6) AU/ml (p<0.05), and in the transaortal TAVI group the value increased from 0.5 (0.4-0.9) AU/ml at baseline to a peak of 1.9 (0.7-2.8) AU/ml (p<0.05). The area under the curve was 2160 (579-3274) hrsAU/ml in the SAVR group, and 1057 (449-2235) hrsAU/ml in the TAVI group (p<0.05), indicating a significantly lower activation of the whole complement cascade in the TAVI group (fig. 1). In the transfemoral TAVI group the area under the curve was 895 (449-1392) hrsAU/ml, and in the transaortal TAVI group it was 1418 (767-2235) hrsAU/ml (p<0.05), indicating a significantly lower activation of the whole complement cascade in the transfemoral group.

*Myeloperoxidase*

The median level of the neutrophil specific protein in the SAVR group increased from a baseline of 11 (8-27) ng/ml to a peak of 176 (117-272) ng/ml (p<0.01), and from a baseline of 19 (11-36) ng/ml to a peak of 107 (28-231) ng/ml in the TAVI group (p<0.01). In the transfemoral TAVI group level of myeloperoxidase was 16 (11-27) ng/ml at baseline and increased to a peak value of 112 (28-231) ng/ml, and in the transaortal TAVI group from 20 (13-36) ng/ml to 98 (81-159) ng/ml (p<0.01). The area under the curve was 84736 (64964-127469) hrsng/ml in the SAVR group and 45415 (22419-89288) hrsng/ml in the TAVI group (p<0.01), indicating a significantly lower neutrophil activation in the TAVI group (fig. 2). In the transfemoral TAVI group the area under the curve was 40663 (25520-88073) hrsng/ml, and in the transaortal TAVI group it was 50168 (22419-89288) hrsng/ml without any significant difference between the two groups.

*Eotaxin*

The median level of eotaxin in the SAVR group increased from a baseline of 19 (nd-59) pg/ml to a peak of 71 (nd-123) pg/ml (p<0.0l), and from a baseline of 19 (nd-56) pg/ml to a peak of 30 (nd-60) pg/mL in the TAVI group (p<0.01). In the transfemoral TAVI group the level of eotaxin was 22 (nd-47) pg/ml at baseline and increased to a peak value of 30 (nd-51) pg/ml (p<0.01), and from 17 (nd-56) pg/ml to 24 (0-60) pg/ml in the transaortal TAVI group (p<0.05). The area under the curve was 39040 (nd-93031) hrspg/ml in the SAVR group and 16883 (nd-54562) hrspg/ml in the TAVI group (p<0.05), indicating a significant lower release of eotaxin in the TAVI group (fig. 2). In the transfemoral TAVI group the area under the curve was 20816 (nd-54562) hrspg/ml, and in the transaortal TAVI group it was 16260 (nd-50433) hrspg/ml without any significant difference between the two groups.

*MIP-1β*

The median level of the chemokine MIP-1β in the SAVR group increased from a baseline of 50 (32-108) pg/ml to a peak of 859 (370-2523) pg/ml (p<0.01), and from a baseline of 64 (27-156) pg/ml to a peak of 119 (58-820) pg/ml in the TAVI group (p<0.01). In the transfemoral TAVI group the level of MIP-1β was 53 (27-81) pg/ml at baseline and increased to a peak value of 104 (58-320) pg/ml (p<0.05), and from 66 (48-156) pg/ml to 127 (87-820) pg/ml in the transaortal TAVI group (p<0.05). The area under the curve was 361115 (142787-602034) hrspg/ml in the SAVR group and 123970 (42624-480622) in the TAVI group (p<0.01), indicating a significantly lower MIP-1β release in the TAVI group (fig. 3). In the transfemoral TAVI group the area under the curve was 119911 (42624-225157) hrspg/ml, and in the transaortal group it was 128028 (100607-480622) hrspg/ml without significant difference between the two groups.

*MCP-1*

The median level of the chemokine MCP-1 in the SAVR group increased from a baseline of 22 (nd-47) pg/ml to a peak of 183 (67-502) pg/ml (p<0.01), and from a baseline of 26 (nd-57) pg/ml to a peak of 63 (nd-216) pg/ml in the TAVI group. In the transfemoral TAVI group the level of MCP-1 was not detectable (nd-43) pg/ml at baseline and increased to a peak value of 63 (nd-211) pg/ml (p<0.01), and in the transaortal group the baseline value was 32 (nd-57) pg/ml and increased to 63 (27-216) pg/ml (p<0.05). The area under the curve was 104223 (39166-200978) hrspg/ml in the SAVR group and 53770 (nd-148831) hrspg/ml in the TAVI group (p<0.01), indicating a significantly lower MCP-1 release in the TAVI group (fig. 3). In the transfemoral TAVI group the area under the curve was 73122 (nd-128106) hrspg/ml, and in the transaortal TAVI group it was 44107 (934-148831) hrspg/ml without significant difference between the two groups.

*Interleukin-6*

The median level of the proinflammatory cytokine IL-6 in the SAVR group increased from a baseline of 4 (nd-15) pg/ml to a peak of 81 (51-644) pg/ml (p<0.01), and from a baseline of 5 (nd-33) pg/ml to a peak of 98 (19-433) pg/ml in the TAVI group (p<0.01). In the transfemoral TAVI group the level of IL-6 was 5 (nd-33) pg/ml at baseline and increased to a peak value of 95 (19-433) pg/ml (p<0.05), and in the transaortal TAVI group from 5 (2-18) pg/ml at baseline to a peak value of 119 (50-422) pg/ml (p<0.01). The area under the curve was 83407 (46064-453205) hrspg/ml in the SAVR group and 75535 (11951-323081) hrspg/ml in the TAVI group, without any significant difference between the groups (fig. 4). In the transfemoral TAVI group the area under the curve was 68125 (11951-323081) hrspg/ml, and in the transaortal TAVI group it was 91727 (35478-305783) hrspg/ml without significant difference between the two groups.

*Troponin T*

In the SAVR group the median troponin T level increased from a baseline of 19 (10-141) ng/ml to a peak of 299 (190-1370) ng/ml (p<0.01), and from baseline 28 (0-67) ng/ml to 303 (54-2592) ng/ml in the TAVI group (p<0.01). In the transfemoral TAVI group the median level of troponin T was 30 (11-50) pg/ml at baseline and increased to a peak value of 253 (61-2592) pg/ml (p=0.058), and in the transaortal TAVI group from 24 (0-67) pg/ml at baseline to a peak value of 325 (54-1639) pg/ml (p<0.05). The area under the curve was 402539 (230158-1540000) hrsng/ml in the SAVR group, and 372648 (62523-1430000) hrsng/ml in the TAVI group, without any significant difference between the groups (fig 4). In the transfemoral TAVI group the area under the curve was 298800 (64916-1410000) hrspg/ml, and in the transaortal TAVI group it was 369231 (66956-1220000) hrspg/ml without significant difference between the groups.

**DISCUSSION**

There was a higher total generation of the two complement markers C3bc and TCC and the granulocyte enzyme myeloperoxidase in the SAVR group compared to the TAVI. This is consistent with previous studies on inflammatory markers during cardiac surgery (4), demonstrating that the extracorporeal system is a strong activator of complement and subsequently of the neutrophils. A similar finding was found in a study comparing beating heart and on-pump coronary surgery (5). However, when comparing baseline and peak values there was a significant increase in the complement markers also in the TAVI group, peaking two hour after surgery indicating an activation of the complement cascade, although in a much lower scale than in the SAVR patients.

The same significant difference between the groups was observed in the generation of the chemokines MIP-1β and MCP-1, which are synthesised mainly by mononuclear cells. The two groups differed significantly when comparing AUC, but a significant increase from baseline to peak value indicated a certain activation in the TAVI patients as well, although to a much lower grade.

In studies comparing the inflammatory response during coronary surgery with or without heart lung machine, Castellheim and coworkers demonstrated significantly lower generation of eotaxin, MIP-1β, and IL-12 in patients operated on with beating heart compared to those operated with a heart lung machine, indicating that the extracorporeal circulation is an important activator for these markers. We observed no statistically different generation of eotaxin and IL-6 in the present study, although there was a significant increase in both groups. This is consistent with previous studies comparing off-pump an on-pump coronary surgery (15). The mechanism for the generation of these cytokines differed strictly from that of the complement activation products and therefore could not be explained as secondary to complement activation.

IL-6 showed a different pattern than the other markers. In both groups a rapid increase was observed during surgery, reaching a peak 2 hours after surgery, and after a temporary drop, the levels continued increasing throughout the study period. Wan and co-workers described a peak in IL-6 20 hours after surgery in patients having beating heart surgery and no difference in response compared to on-pump surgery (16), very similar to what we found when comparing IL-6 generation after TAVI and SAVR. These findings may indicate that IL-6 is less triggered by the artificial surfaces of the extracorporeal circuit and less dependent on complement activation than the other markers. Studies of cytokines in the coronary sinus following aortic cross-clamping have demonstrated that the myocardium is a major source for IL-6 generation (17). It has further been demonstrated that ischemia and reperfusion cause induction of IL-6 mRNA production by cardiac myocytes (18). The present study indicates that the TAVI procedures even when performed transfemorally may induce generation of IL-6.

All patients in the SAVR were operated with a Bioline heparin coated extracorporeal system. Previous studies have shown reduced levels of neutrophil elastase, C3a, IL-6, and IL-8 at 2 h after cardiopulmonary bypass (CPB) with this coating as compared to an uncoated Quadrox system (19). In the present study we therefore compared open surgery with an optimized biocompatible extracorporeal system with the TAVI procedure. Obviously there are several factors causing inflammatory reaction in the SAVR patient. Although the biocompatible surface attenuates the inflammatory reaction, it does not completely abolish it. Furthermore, open surgery involves more tissue damage than the relatively minor surgical accesses used for the different TAVI procedures.

There was a significant increase in troponin T in both groups, without differences between the groups, indicating that also the TAVI procedure caused some degree of myocardial injury. Although the troponin T levels increased in all patients, no persistent ECG changes were observed, suggesting that the intraoperative injury leading to troponin T generation did not cause permanent injuries.

In the TAVI group, three different surgical approaches were used in this study. In nine patients TAVI was introduced by the retrograde approach through the femoral artery. This approach, however, was contraindicated in 11 patients due to severe arteriosclerosis in the femoral arteries and aorta. In these patients transaortal or transapical approaches were used on different indications. In both these groups a small thoracotomy was performed. We therefore also compared the generation of the different inflammatory markers between the TAVI patients operated with a small thoracotomy and those with a transfemoral approach, and found no difference in biomarkers between the different methods of application of the valve (data not shown). Although this study was not designed to compare the inflammatory response between the different TAVI methods the lack of significant differences in cytokine and complement activation between the different approaches indicates that any such difference was negligible. This also corresponds with previous results where we studied complement activation in patients undergoing lung surgery and found no activation of inflammatory markers associated with thoracotomy (4).

This study thus confirms that although there is a measurable inflammatory response in patients being treated by TAVI either transfemorally, transaortic or transapically, the response is significantly lower than in patients having aortic valve replacement on extracorporeal circulation and suggesting that the TAVI operated patients might have lesser disturbed homeostasis and better preserved organ function due to a lower systemic inflammatory response. It is important however, to emphasize that during this study, all the TAVI implantations occurred without adverse advents during surgery. Cases of ventricular fibrillation or major bleedings may in itself cause an inflammatory response. SIRS has been reported in as many as 39-54% of TAVI patients during their stay in hospital, and has shown to affect the prognosis (20, 21). Although there is as a well-documented association between the inflammatory response and SIRS the symptoms are unspecific, and there may be different inflammatory pathways leading to the syndrome.

**Conclusion**

This study demonstrates that the activation and release of important inflammatory markers that are associated with the development SIRS, is significantly less during valve replacement with TAVI as compared to surgical aortic valve replacement. This was particularly significant for markers that are known to be associated with extracorporeal circulation, including complement- and neutrophil activation markers. Inflammatory markers that are associated with tissue injury like troponin T and IL-6 seems to be generated as much during TAVI than SAVR, indicating that the burden on the myocardial tissue may not be much different between the two methods.





**Figure 1.** *Concentrations of C3bc (AU/ml) and Terminal Complement Complex (TCC) (AU/ml)* (median values). T0: Baseline after insertion of arterial cannula during induction of anaesthesia after induction of general anesthesia and before systemic heparinization, T1: immediately after institution of cardiopulmonary bypass (CPB) or 30 minutes after start of surgery on the TAVI group. T2: 30 minutes after institution of CPB or 60 minutes after start of surgery in the TAVI group. T3: before closure of the wound. T4: 2 hrs postoperatively. T5: 6 hrs postoperatively. T6: 24 hrs postoperatively. Error bars indicate range between 25-quartile and 75-quartile. Where there is no error bar the height of the error bar would be shorter than the symbol and is therefore not shown. The area under the curve (AUC) was significantly different between the two groups (p<0.01) for both C3bc and TCC.



**Figure 2.** *Concentrations of myloperoxidase (MPO) (ng/ml) and eotaxin (pg/ml)*(median values). Time points and error bars are as indicated in the legend to Fig 1. The AUC was significantly different between the two groups (p<0.01) for both MPO and eotaxin.



**Figure 3.** *Concentrations of MIP-1β (pg/ml) and MCP-1 (pg/ml)* (median values). Time points and error bars are as indicated in the legend to Fig 1. The AUC differed significantly between the two groups (p<0.01) for both MIP-1β and MCP-1.



**Figure 4.** *Concentrations of IL-6* *(pg/ml) and troponin T (ng/ml)* (median values). Time points are and error bars as indicated in the legend to Fig 1. The AUC did not differ significantly between the two groups for IL-6 or troponin T.

**REFERENCES**

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.

2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European heart journal. 2003;24(13):1231-43.

3. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or =80 years. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2006;30(5):722-7.

4. Fosse E, Mollnes TE, Ingvaldsen B. Complement activation during major operations with or without cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1987;93(6):860-6.

5. Hoel TN, Videm V, Mollnes TE, Saatvedt K, Brosstad F, Fiane AE, et al. Off-pump cardiac surgery abolishes complement activation. Perfusion. 2007;22(4):251-6.

6. Pintar T, Collard CD. The systemic inflammatory response to cardiopulmonary bypass. Anesthesiol Clin North America. 2003;21(3):453-64.

7. Biglioli P, Cannata A, Alamanni F, Naliato M, Porqueddu M, Zanobini M, et al. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2003;24(2):260-9.

8. Vahanian A, Alfieri OR, Al-Attar N, Antunes MJ, Bax J, Cormier B, et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2008;34(1):1-8.

9. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, et al. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. European heart journal. 2012;33(12):1459-68.

10. Dahle G, Rein KA. Direct aorta ascending approach in transcatheter aortic valve implantation. Innovations (Phila). 2014;9(1):1-9.

11. Bergseth G, Ludviksen JK, Kirschfink M, Giclas PC, Nilsson B, Mollnes TE. An international serum standard for application in assays to detect human complement activation products. Mol Immunol. 2013;56(3):232-9.

12. Sablotzki A, Dehne MG, Mann V, Gorlach G, Muhling J, Zickmann B, et al. Plasma levels of selectins and interleukins in cardiovascular surgery using cardiopulmonary bypass. Thorac Cardiovasc Surg. 1999;47(1):26-31.

13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

14. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990;300(6719):230-5.

15. Castellheim A, Hoel TN, Videm V, Fosse E, Pharo A, Svennevig JL, et al. Biomarker profile in off-pump and on-pump coronary artery bypass grafting surgery in low-risk patients. Ann Thorac Surg. 2008;85(6):1994-2002.

16. Wan IY, Arifi AA, Wan S, Yip JH, Sihoe AD, Thung KH, et al. Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg. 2004;127(6):1624-31.

17. Wan S, DeSmet JM, Barvais L, Goldstein M, Vincent JL, LeClerc JL. Myocardium is a major source of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1996;112(3):806-11.

18. Kukielka GL, Smith CW, Manning AM, Youker KA, Michael LH, Entman ML. Induction of interleukin-6 synthesis in the myocardium. Potential role in postreperfusion inflammatory injury. Circulation. 1995;92(7):1866-75.

19. Tayama E, Hayashida N, Akasu K, Kosuga T, Fukunaga S, Akashi H, et al. Biocompatibility of heparin-coated extracorporeal bypass circuits: new heparin bonded bioline system. Artif Organs. 2000;24(8):618-23.

20. Schwietz T, Behjati S, Gafoor S, Seeger F, Doss M, Sievert H, et al. Occurrence and prognostic impact of systemic inflammatory response syndrome in transfemoral and transapical aortic valve implantation with balloon- and self-expandable valves. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;10(12):1468-73.

21. Rettig TC, Rigter S, Nijenhuis VJ, van Kuijk JP, ten Berg JM, Heijmen RH, et al. The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation. J Cardiothorac Vasc Anesth. 2015;29(2):283-7.