Hemodynamic Consequences of Two Different Surgical and Anesthetic Techniques for the Treatment of Aortic Valve Stenosis - A Randomized Comparison

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Introduction

During the last 6-7 years it has become possible to treat aortic stenosis by transcatheter aortic valve implantation (TAVI). This procedure can be done via the femoral artery or from the apex of the heart through the left ventricle, usually referred to as apical TAVI (In this study referred to as TAVI). This approach is primarily used in patients with stenotic iliac and femoral arteries. The TAVI can also be inserted from the subclavian artery or through the arch of the aorta. At our institution the two first mentioned approaches are the preferred methods.

The TAVI procedure or by anesthetising the SAVR patients using a different technique. The advantages may be even more pronounced now as TAVI today is a treatment that is well established. Aortic stenosis is the most common valvular heart disease and it is becoming even more prevalent with our ageing population [1]. For the last five decades the standard treatment for symptomatic aortic stenosis has been surgical valve replacement [2], which requires a sternotomy, cardiopulmonary bypass (CPB) and aortic cross-clamping.

The trans catheter aortic valve replacement has increased dramatically with promising short- and medium-term results [3-9]. According to The PARTNER Trial, TAVI reduces mortality in patients with severe aortic stenosis who are not candidates for standard surgical aortic valve replacement (SAVR) [10]. Further TAVI and SAVR seem to imply a similar 1-year risk of all-cause mortality in high risk patients [11]. Complications from the TAVI procedure are well documented and include death, vascular damage, stroke, permanent pacemaker insertion, aortic regurgitation and postoperative dialysis [10,12-14]. However, it has to be taken into consideration that the studies presented so far have included severely ill patients not applicable to conventional surgery. The TAVI has been associated with more adverse events than the trans femoral procedures, possibly because of patient selection bias and because of an increased surgical stress due to thoracotomy, incision of the pericardium and the risk of respiratory insufficiency in the postoperative period.

The TAVI and the SAVR procedure differ widely regarding both surgery and anesthesia. Patients undergoing TAVI pose unique and complex challenges for the anesthetist due to advanced age, multiple comorbidities and a severe aortic stenosis combined with rapid hemodynamic fluctuations during the procedure [15-17].

The anesthetic technique that we primarily use for the TAVI procedures is based on the fact that the patients are very old, severely ill and they are sometimes deemed inoperable to conventional surgery...
because of multiple co-morbidities. Thus the technique chosen is very different from the one used for SAVR.

The purpose of the present study was to describe the perioperative hemodynamic changes in two comparable groups of very fragile patients participating in a randomized trial to different methods of treatments for severe aortic stenosis and thus two very different anesthetic approaches.

Patients and Methods

The present study is a subset of the STACATO trial [18]. The study was planned as a prospective multicenter clinical trial in the Nordic region with an intention to include 200 patients. The first patient was included November 2008. Following inclusion of 70 patients, the study was terminated prematurely due to advice from the Data Safety Monitoring Board (DSM), based on a general impression of too many adverse events and procedure related complications following the TAVI treatment. This subset includes the 58 patients from our institution.

All patients were preoperatively evaluated at our weekly Heart Team valve meetings with participation of cardiologists, cardiac surgeons and anesthesiologists. The patients received detailed information on the study and the different treatment modalities by a study coordinator and a cardiac surgeon before randomization to either TAVI or SAVR.

The study complied with the Declaration of Helsinki and was approved by the ethics committee of the Region of Midt (Record nr. M-20080118). All patients provided written, informed consent before participation in the trial. Following oral and written information, the patients who accepted participation were examined with transeosophageal echocardiography (TOE), and aortography, to ensure technically feasibility for both SAVR and TAVI.

Criteria of inclusion and exclusion

Inclusion criteria were elective surgery, significant valvular AS (valve area <1 cm²), age ≥75 yrs. and eligibility to both SAVR and TAVI procedure. Exclusion criteria were coronary artery disease requiring treatment, previous myocardial infarction, and previous percutaneous catheter intervention (PCI) within 12 months and the need for other heart surgery (i.e., mitral or tricuspid valve surgery), unstable cardiac condition requiring preoperative assist device, inotropes or intravenous nitrates, on-going infection requiring antibiotics, stroke within one month, reduced pulmonary function (FEV1 <1 L or <40% of expected) and renal failure to be treated by hemodialysis.

Primary study endpoints

The primary endpoint in the STACATO trial was the composite of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis. Secondary endpoints included: all-cause death, cardiac death, stroke, myocardial infarction, New York Heart Association (NYHA) function class, SF-36 composite physical and mental functional scores, echocardiographic parameters (aortic valve area, peak aortic valve gradient, aortic valve leakage, left ventricular ejection fraction), duration of hospital stay, operation for bleeding, and permanent pacemaker treatment [18].

Surgical procedures

The TAVI procedures were performed at a cardiac catheterization laboratory by two cardiac surgeons, an interventional cardiologist and a cardiologist handling trans esophageal echo measurements to choose the right valve size. A 23 or 26 mm Edwards SAPIEN ™ Trans catheter Heart Valve (THV) prosthesis (Edwards Life sciences) was introduced in its delivering system via the apex of the heart, through a left mini-thoracotomy. The incision was guided by echocardiographic visualisation of the left ventricular apex. After ensuring correct position by TOE and fluoroscopy, the THV was implanted during rapid ventricular pacing (160-200b beats per minute) by expansion of a balloon catheter within the valve. A catheter for postoperative local analgesia was placed in the wound incision with the tip pointing towards the intercostal nerve. A bolus of 10-15 ml of Bupivacain 5 mg/ml was given in the catheter before wound closure. Finally a chest tube for drainage was inserted before closure of the thoracotomy.

Surgical aortic valve replacement was performed through a sternotomy during CPB. The native valve was resected and a Magenta Ease™ aortic heart valve (Edwards Lifesciences) was implanted.

Invasive hemodynamic monitoring

The TAVI group was taken to the cardiac catheterization laboratory for the procedure. Upon arrival a continuous 5-lead electrocardiogram (ECG) and peripheral saturation (SAT) monitoring was established. Invasive lines for hemodynamic monitoring were inserted using local anesthesia, for the measurement of systolic- (SBP), diastolic- (DBP) and mean arterial blood pressure (MAP), central venous pressure (CVP) and pulmonary artery pressure (PAP). Continuous cardiac index (CI) and mixed venous saturation (SvO₂) were measured with a thermistor-tipped, flow-directed pulmonary artery catheter (PAC) (744 HF75, Edwards Life sciences, Germany) and a Vigilance monitor (VGS 2, Edwards Critical-care, Irvine, USA). The SAVR group was taken to the operation theatre and they were anesthetized prior to placement of similar monitoring equipment as in the TAVI group.

The observation period was divided in three periods. Pre valve: SAVR: 50 minutes before the initiation of CPB. TAVI: from the start of surgery until 10 minutes before introducing the valve; Post valve: SAVR: from termination of CPB and TAVI: from 10 minutes after expanding the valve (TAVI group) until the patient was ready for transfer to the recovery unit; Recovery: from arrival in the recovery unit until 09:00 the next morning.

Anesthesia

Patients in the SAVR group followed our standard anesthesia for cardiac surgery which consists of a Propofol infusion of 100-200 mg/h followed by Sufentanil 1-2 µg/kg given in 1-2 minutes. The Propofol was continued at 100-300 mg/h during surgery and a total dose of Sufentanil 3.0-5.0 µg/kg was administered. The patients were transferred to the recovery unit and the Propofol infusion was continued until the patient was eligible for extubation after 2-5 hours.

The patients in the TAVI group were anesthetized using midazolam 2.5 mg, sufentanil (0.3-0.4 µg/kg), S-ketamin 0.5 mg/kg and rocuronium 0.6 mg/kg to facilitate tracheal intubation. The anesthesia was maintained with sevoflurane 1-2% throughout the procedure. Patients were extubated at the end of the procedure and transferred to the recovery unit for observation.
Statistical analyses

The analysis of all hemodynamic data was done off-line after completion of the study. Normality of data was checked by D'Agostino-Pearson test for normal distribution. Study results are presented as mean ± SD or median (interquartile range) according to type of distribution. For inter-group comparisons, continuous data were analyzed with an independent samples t-test or Mann-Whitney test and categorical data with a χ²-test. Hemodynamic changes and blood test sampled over time were analyzed with 2-way ANOVA or ANOVA for repeated measurements where appropriate. Analyses were performed with MedCalc® software version 12.3 (Mariakerke, Belgium). A probability value of <0.05 was used to define statistical significance.

Results

The number of patients included was 58. Three patients were excluded after randomization; one patient declined participation, the second unexpectedly met the exclusion criteria of impaired pulmonary function and the third due to anticipated anatomical problems. Further, one TAVI patient was re-operated with SAVR because of a rupture of the aorta shortly after the first procedure, leaving 30 patients in the SAVR group and 24 patients in the TAVI group. There was no difference in selected preoperative demographic parameters.

The hemodynamic data are shown in Figure 1. Substantial differences were found in most parameters in the three periods; pre-bypass, post-bypass and recovery, except in heart rate (HR) (P=0.880), mean pulmonary artery pressure (MPA) (P=0.424), CVP (P=0.177) and SvO₂ (P=0.166) in the pre-bypass period. Patients in the SAVR group had lower values of CI and stroke volume index (SVI) than the TAVI patients in all periods (p<0.001). After CPB and during recovery HR was higher in the SAVR group (P<0.001), who also had a higher frequency of active pacemakers. Mean arterial pressure was higher in the TAVI group before (P<0.001) and after valve placement (P<0.001), but lower during recovery (P<0.001). SvO₂ was higher in the SAVR group both post-bypass (P<0.001) and during recovery (P<0.001). CVP and systemic vascular resistance index (SVRI) was higher in the TAVI group both pre- (CVP, P=0.002; SVRI, P=0.024) and post CPB (CVP, P=0.001; SVRI, P=0.001), while both factors were higher in the SAVR group during recovery (P<0.001).

Data from arterial blood samples are shown in Figure 2. Repeated measurement analysis did not show any overall difference between SAVR and TAVI patients with regard to pH (P=0.347), pCO₂ (P=0.833), hematocrit (Hct) (P=0.732), s-lactate (P=0.568), pO₂ (P=0.486) and sO₂ (P=0.875). However, some differences were seen, especially at the end of surgery, where significantly higher pO₂ (49.6 (36.3-61.4) vs. 10.3 (8.5-14.7); P<0.0001), higher sO₂ (1.00 (0.99-1.0) vs. 0.95 (0.93-0.99); P=0.0001) and higher s-lactate, though not clinically significant (1.2 (1.0-1.4) vs. 0.8 (0.5-0.9); P=0.003) together with lower Hct (0.28 (0.26-0.29) vs. 0.31 (0.28-0.35); P=0.045) and pCO₂ (4.78 (4.44-5.04) vs. 5.87 (4.61-6.33); P=0.024) were found in the SAVR group. At the end of surgery no difference was found in pH, but at 6 and 12 hours after surgery the pH was closer to normal in the TAVI patients.

Regarding the changes in s-creatinine and in creatinine clearance (Figure 3), we divided the observation time into two periods (day 0-2 and day 3-8) due to the hemodilution in relation to cardiopulmonary bypass. In both groups we found increased s-creatinine (P<0.001) in the first period, while the creatinine clearance decreased (P<0.001). In the following days the change in s-creatinine (P=0.959) and creatinine clearance (P=0.653) stabilized within groups over time without any differences. A more pronounced increase in s-creatinine was seen in the TAVI group (P=0.034).

The use of cardiovascular medical and mechanical support is shown. No differences were found in the perioperative use of inotropes, vasoconstrictors or vasodilators. The operative procedure was significantly shorter in the TAVI group, while no differences were found in time spent in the recovery unit (ICU) or length of stay in hospital. The TAVI patients were extubated immediately after termination of the procedure while the SAVR patients were extubated according to our standard criteria in the ICU with a median time of 347 minutes.
Figure 2: Arterial blood gas samples for SAVR and TAVI. No overall differences between groups (repeated measurements) in pCO$_2$ (P=0.833) oxygen content (pO$_2$) (P=0.486), oxygen saturation (sO$_2$) (P=0.875) pH (P=0.347), hematocrit (Hct) (P=0.568). At the end of surgery differences between groups was seen in all parameter except pH (P=0.465), which however was significantly lower after extubation in SAVR patients (6 hours P=0.0027 and 12 hours P<0.0001). At the end of surgery pO$_2$ (P<0.0001), sO2 (P=0.0001) and s-lactate was significant higher in the SAVR group, while hematocrit (P=0.045) and pCO$_2$ (P=0.0002) was significant higher in TAVI patients. (All individual time points Mann-Whitney test).

The patients in the SAVR group had a significantly higher positive perioperative fluid balance (1,933 ml vs. 388 ml), (P<0.0001). In the postoperative period the SAVR group had a lower fluid balance, however not quite statistically significant (315 ml vs. 863 ml, P=0.051). The total mean fluid balance for the first perioperative day ended up as 976 ml higher in the SAVR group (P=0.001).

The patients in the SAVR group received significantly more sufentanil preoperatively than the TAVI patients. No difference was found in the postoperative requirement of alfentanil and morphine.

Discussion

The main result of the present study was that the perioperative management of the TAVI group resulted in more stable hemodynamics both per- and postoperatively than in SAVR group. The patients were all comparable with regard to their preoperative status. They were all eligible to conventional surgical treatment of aortic stenosis, but they were randomized to have their aortic stenosis treated by either TAVI or SAVR. Thus we find it interesting from an anesthesiological point of view that the patients are subject to a very different hemodynamic impact in response to the chosen anesthetic method and thus to the entire sum of the impact from anesthesia and surgery will have an importance on the end result. This is to our knowledge the first report on hemodynamic changes in fully comparable groups who undergo two very different surgical procedures.

Severe AS carries a 2 year mortality rate of 50-60% [10,11] and previous reports suggest that up to one third of patients with AS are denied surgery due to high predicted risk [19-24]. However in Denmark the number is probably lower due to the free and equal access to medical care and treatment [25]. Although considered a relatively safe procedure with mortality rates ranging from 2.5%-15% depending on the risk profile of the population [26-29], the treatment is poorly tolerated among a substantial part of the elderly population. It is poorly tolerated because of significant comorbidities such as poor left ventricular functioning, previous sternotomy (coronary artery bypass grafting) renal dysfunction, respiratory dysfunction and general vascular calcifications. There is also a considerable risk of postoperative neurological dysfunction, blood transfusion and wound infection following procedures which requires CPB.
In all time periods we find a lower mean arterial pressure and a significantly lower cardiac index and stroke volume index in the SAVR group compared to the TAVI group. This finding can be attributed to a combination of the anesthesiological management of the patient and the surgical stimulus, and it can potentially lead to a reduced perfusion of organs in the SAVR group. In contrast the SVO2 was lower in the TAVI group. These findings are probably a result of less stunning of the myocardium in the TAVI group, because they have not been on CPB and a lower extraction of oxygen in the SAVR group due to the influence of sufentanil in the recovery period and perhaps a better perfusion of organs on cardiopulmonary bypass and thus a reduced oxygen debt. The higher CVP and lower CI in the SAVR group could indicate primarily cardiogenic controlled blood pressures while the lower CVP and CI in the TAVI group is more indicative of a vasogenic controlled blood pressure. The SAVR patients also have a higher heart rate in the post valve- as well as in the recovery period. The relative tachycardia may be caused by the more frequent use of a pacemaker, pain or surgical stress or due to a relative intravascular hypovolaemia though the SAVR group received much more fluids than the TAVI-group patients.

These findings are worth taking into consideration when deciding whether a patient is better off having an aortic valve replacement by the conventional surgical approach or by the TAVI approach. Or perhaps a completely different anesthetic technique could be advantageously used for the SAVR procedure? Overall there were no differences in arterial blood samples despite the fact that TAVI patients were extubated in the cardiac catheterization laboratory while the SAVR patients were extubated after more than 5 hours. At the end of surgery the relatively great differences in pO2 and pCO2 between the groups can be explained by the fact that the SAVR patients were being ventilated while the TAVI patients were extubated right after termination of the procedure. The higher hematocrit in the TAVI patients is due to a significantly higher preoperative blood loss in the SAVR patients of 400 ml (282-541) vs. 71 ml (0-250). Moreover, dilution from the CPB plays a role in the SAVR group.

The increase in s-creatinine during the first postoperative days and later stabilizing values are in agreement with previously published data [30]. We find it interesting that the TAVI patients show the same pattern, regarding creatinine, as the patients on CPB who are accordingly hemodiluted and thus gain a higher perioperative volume load. However the fact that s-creatinine increase in the TAVI group and reach a higher level than in the SAVR group after day 2, may be attributed to the use of intravenous contrast during the TAVI procedure. This practice has changed due to more experience with the procedure. Today the thoracotomy is smaller, less intravenous contrast is given and the periods of rapid pacing are significantly shorter.

We found no difference in time spent in the ICU or in hospital. The reason for this was due to our protocol, where all patients were monitored until 09:00 the next morning. We did not collect data on the eligibility for discharge from the ICU. In the ward all patients followed the usual postoperative scheme.

The anesthetic needs for performing a TAVI procedure are very different compared to open surgery primarily due to a substantially lower level of expected surgical stress and pain.

**Limitations to the study**

There are some limitations to the study: We are aware, that we are comparing hemodynamic changes in patients that underwent very different surgical procedures, with the SAVR group obviously receiving a much larger surgical stress, and thus the anesthesia used for TAVI would simply be too little for the SAVR procedure. Still, despite the difficulty in comparison, it is interesting that the surgical procedure, and to a lesser extent the anesthetic management results in such different hemodynamics in a randomized clinical cohort.

**Conclusion**

It is advisable to take our results into consideration, when assessing whether a patient with a severe aortic stenosis would benefit the most from having an aortic valve replacement by conventional surgery with the corresponding deeper anesthesia, or as a TAVI procedure with a shorter acting anesthesia used. The difference in hemodynamic stress added to the patient merely by anesthetizing the patient is considerably different in the two approaches described above. The patient does not need to be as heavily anesthetized to go through the TAVI procedure, and thus the hemodynamic changes that may potentially lead to hypo perfusion of organs, can possibly be avoided by choosing the TAVI approach.

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