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A Transapical or Transluminal Approach to Aortic Valve Implantation Does Not Attenuate the Inflammatory Response

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ABSTRACT

Background: Cardiopulmonary bypass (CPB) and cardiac surgery cause an inflammatory response, as measurable by an increase in the concentration of C-reactive protein (CRP), a nonspecific inflammation marker. Previous publications have demonstrated typical perioperative CRP concentration profiles in cases of uncomplicated aortic valve replacement (AVR) with CPB. A regression analysis for modifying factors showed that chronic disease (heart failure, diabetes, and pulmonary disease), along with obesity and sex, all tend to influence the CRP response. We analyzed the inflammatory response to aortic valve implantation (AVI) with interventional techniques, mainly transapical but also transfemoral and transaxillary approaches, in a retrospective case-control study design.

Methods: Sixty-eight patients who underwent AVI by the transapical (59 patients), transfemoral (7 patients), or transaxillary (2 patients) approach were matched by age, sex, body mass index (BMI), and chronic-disease state (absence or presence of diabetes, pulmonary disease, and renal impairment) with 68 patients who underwent conventional AVR with CPB. We compared the 2 groups with respect to perioperative CRP concentration, EuroSCORE, and outcome data (time to extubation and 30-day mortality). All data were collected prospectively and analyzed retrospectively.

Results: The 2 groups—the study population (interventional) and the control population (conventional)—were similar in age, sex distribution, BMI, and chronic-disease status. As expected, the study population had a significantly higher median EuroSCORE. The 2 groups had similar postoperative CRP profiles over time, but the interventional group had significantly higher peak concentrations on days 2, 3, and 4. The short-term outcomes, as assessed by ventilation time and 30-day mortality, were similar for the 2 groups.

Conclusions: Using an interventional transcatheter approach to AVI (thereby eliminating CPB from the procedure and reducing surgical trauma) does not attenuate the patient's innate inflammatory response.

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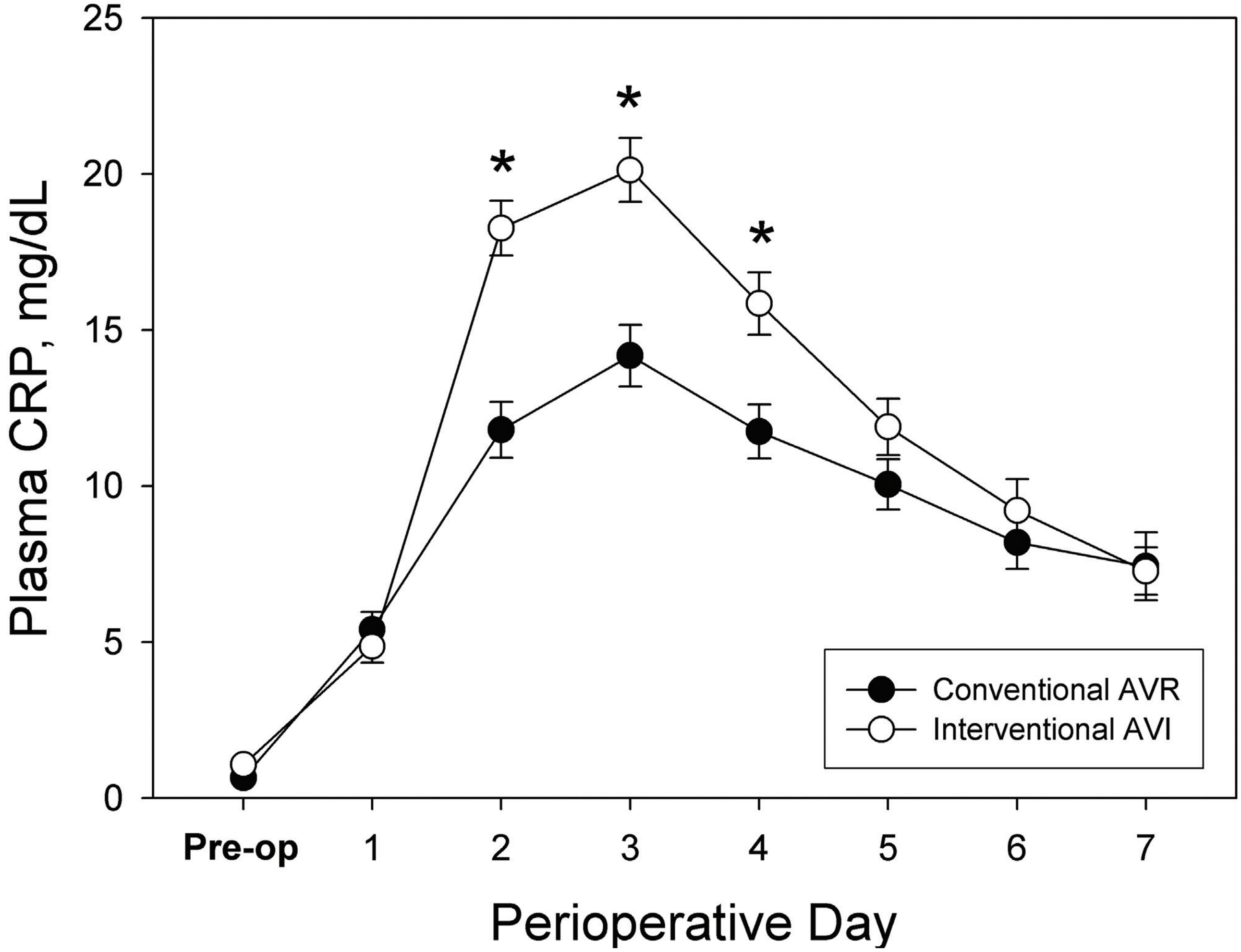
INTRODUCTION

The systemic inflammatory response syndrome commonly occurs after cardiac surgery and is implicated in several undesirable physiological alterations in the immediate postoperative period, including impeding gas exchange and causing end-organ dysfunction (ie, renal impairment and microvascular injury). C-reactive protein (CRP) is a nonspecific inflammation marker that increases in response to a variety of insults, including cardiopulmonary bypass (CPB) and cardiac surgery [Gabay 1999]. The normal reference interval of CRP concentrations is 0–0.5 mg/dL. Previous studies have demonstrated typical perioperative CRP concentration profiles after cardiac surgery, including uncomplicated aortic valve replacement (AVR) using CPB [Ayala 2007]. These studies analyzed large numbers of patients and demonstrated a typical peak in CRP values on postoperative day 3. Furthermore, utilizing regression analysis, the same research group identified factors that could modify the inflammatory response. These factors included obesity, sex, and chronic disease (ie, diabetes, chronic pulmonary disease, and renal impairment).

Recent developments in interventional approaches to aortic valve implantation (AVI) have opened up new treatment options for patients who do not qualify for conventional AVR. These techniques, which use not only the transapical approach but also the transfemoral and transaxillary approaches, are rapidly expanding the indications to patients with higher perioperative risk, including some who may be offered this strategy as an alternative to traditional operations.

CPB causes a significant inflammatory response. Certainly, exposure to a foreign surface within the tubing and oxygenator plays an important role, but as the experience with off-pump coronary artery bypass (OPCAB) surgery has shown, the removal of CPB itself does not ablate the inflammatory response [Kilger 1998; Parolari 2007].

Our aim was to examine whether an interventional approach to AVI without CPB and median sternotomy modifies the perioperative inflammatory response.



Perioperative C-reactive protein (CRP) concentrations for the interventional aortic valve implantation (AVI) group and the conventional aortic valve replacement (AVR) groups. In both groups, a steep increase in the CRP concentration until the third postoperative day was followed by a steady decline until day 7. Data are presented as the mean ± SEM. *$P < .05$, versus conventional AVR. Preop indicates preoperative.

METHODS

The requirement for individual patient consent was waived for this retrospective study.

The patients for the interventional study group were selected according to the following inclusion criteria: elective interventional (transapical, transfemoral, or transaxillary) AVI without CPB; the availability of complete demographic data (age, sex); the availability of complete data on comorbidities (body mass index [BMI], diabetes, pulmonary disease, renal impairment); and the availability of sufficient CRP data (preoperative and sufficient postoperative data to delineate the peak and "tail-off").

From the initial population of 160 patients who underwent interventional AVIs at our institution between April 2008 and July 2009, we excluded 14 patients because CPB was used during the interventional procedure. Complete data on age, sex, and comorbidities were available for all of these patients. Sixty-seven patients had to be excluded because of missing CRP measurements on the relevant days.

Within the interventional study group, 9 patients underwent a transluminal procedure, 2 patients underwent AVI via a transaxillary approach, and 7 patients underwent AVI via a transfemoral approach. A Sapien valve (Edwards Lifesciences, Irvine, CA, USA) was implanted in all patients who underwent their operation via a transapical approach. In the transluminal subgroup, 6 patients had Sapien valves implanted, and the remaining 3 patients received CoreValves (Medtronic, Luxembourg).

The inclusion criteria for the conventional AVR control group were as follows: elective isolated AVR under CPB; implantation of a biological valve; operation performed at Deutsches Herzzentrum Berlin between January 2006 and December 2008; availability of complete demographic data (age, sex); availability of complete data on comorbidities (BMI, diabetes, pulmonary disease, renal insufficiency); and availability of sufficient CRP values (preoperative and sufficient postoperative results to delineate the peak and "tail-off").

Table 1. Description and Comparison of the 2 Populations*

	Conventional AVR	Interventional AVI	P
Age, y	79.4 ± 6.3	79.8 ± 6.6	.71
BMI, kg/m²	27.2 ± 4.4	27.3 ± 5.1	.91
Male/female sex, n	24/44	24/44	.86
Diabetes mellitus, n (%)	13 (19)	13 (19)	.83
COPD, n (%)	20 (29)	26 (38)	.37
Renal failure, n (%)	11 (16)	9 (13)	.81

*Data are presented as the mean ± SD or as number (percent) as indicated. For the parameters included in the matching process, there was no significant difference between the interventional study population and the conventional control population. AVR indicates aortic valve replacement; AVI, aortic valve implantation; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

At our institution, 879 patients underwent isolated conventional biological AVR between January 2006 and December 2008. Complete demographic data and information about relevant comorbidities were available for all of these patients. CRP values were searched during the matching process. Acceptably congruent pairs were found for 68 patients included in the study population. Eleven interventional patients had to be excluded because no suitable match could be found from the control group.

For each individual patient from the study population, we sought a match that was as close as possible in age (±3 years) and BMI (±3 kg/m²), had the same sex, and had a similar noncardiac comorbidity profile. In only 8 cases did we pair matches with a single difference in their chronic-disease profile. Linear EuroSCOREs were recorded for both groups and compared with the Mann-Whitney rank sum test.

CRP concentrations were measured in our routine laboratory with a CRP Vario assay (Sentinel Diagnostics, Milan, Italy) and an Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). This assay was used consistently throughout the study.

For statistical comparisons of groups, including subgroup analysis, we used the Student t test for continuous data (CRP, age, BMI) and the chi-square test for dichotomous data (sex, chronic disease). The Bonferroni-Holm procedure was used to correct for multiple between-group comparisons of CRP concentrations. We used univariate linear regression to assess the dependence of peak postoperative CRP concentration on possible predisposing factors.

To correlate laboratory findings with clinical outcomes, we analyzed and compared 2 relevant end points: time to extubation and 30-day mortality. We used the Mann-Whitney rank sum test to compare ventilation times and used the chi-square test to compare 30-day mortality rates.

RESULTS

Comparison of the interventional group with the matched conventional group revealed no significant differences for any of the variables (mean age, mean BMI, chronic-disease profile; Table 1). The interventional group, however, did have significantly higher linear EuroSCOREs (median, 13; 25th and 75th percentiles, 11 and 14, respectively) than the matched conventional group (median, 9; 25th and 75th percentiles, 8 and 11) ($P < .0001$).

Table 2. Comparison of Outcome Data for the 2 Populations*

	Conventional AVR	Interventional AVI	P
Ventilation time, h†	24.9 (17.2;65.7)	21.3 (13.5;49.2)	.1219
30-Day mortality, n	6 of 64	3 of 68	.4771

*For time to extubation and 30-day mortality, there is no significant difference between the interventional study population and the conventional control population. AVR indicates aortic valve replacement; AVI, aortic valve implantation.

†Data are presented as the median (25th percentile;75th percentile).

We compared the subgroup of 9 patients who underwent interventional AVI via a transfemoral approach (7 patients) or a transaxillary approach (2 patients) with the larger group of patients who underwent their procedures via a transapical strategy (59 patients) and detected no significant difference with respect to postoperative CRP concentration profile. Therefore, these 9 patients remained included in the wider interventional study group.

Patients who underwent conventional AVR using CPB showed a typical postoperative CRP profile: an immediate steep increase to a peak on postoperative day 3, followed by a steady decline ("tail-off") until the end of data collection on day 7 (Figure).

Patients who underwent interventional AVI showed a similar CRP concentration profile over time; however, the peak values on day 2, 3, and 4 were significantly higher. Regression analysis revealed no dependence of the CRP response on sex, BMI, or chronic disease, but we noted a slight dependence on age only in the conventional AVR group ($r = 0.27$; $P = .025$).

Analysis of the outcome data showed no significant difference in either ventilation time or 30-day mortality (Table 2).

DISCUSSION

This study is limited by its retrospective nature. The comparison of the groups with respect to postoperative CRP concentration was adequately powered; however, the analysis of the dependence of the CRP response on the individual factors of age, sex, BMI, and comorbidity profile was limited by the small sample size, owing to the novelty of the technique in question.

Studies that have investigated the inflammatory response, in particular the postoperative CRP concentration in patients undergoing OPCAB surgery, have also demonstrated a lack of attenuation in the postoperative CRP increase [Parolari 2007].

The first generation of OPCAB procedures managed to forsake CPB, but they still relied on a median sternotomy approach, therefore entailing significant surgical trauma. In later modifications, minimally invasive strategies (termed

MIDCAB) were developed, mainly via limited lateral thoracotomy approaches. One study that examined the postoperative CRP response in this patient group also demonstrated no impact on peak CRP concentrations [Kilger 1998].

It is important to note that CRP is a factor only of the innate humoral part of the immune system. Several studies that investigated other markers of inflammation, especially interleukins, demonstrated that modifications in the surgical approach altered the expression of these markers [Struber 1999; Wan 1999; Rasmussen 2007]. A comparison of different surgical strategies in coronary artery surgery found interleukin 8 (IL-8) expression to be attenuated when CPB was not used; however, the expression of anti-inflammatory cytokines such as IL-10 was also lower [Rasmussen 2007]. This decrease in both inflammatory and anti-inflammatory cytokines might partially explain why CRP, a more general marker of inflammation, is not attenuated. These other inflammatory and prothrombotic markers are not part of routine blood testing, and because of the retrospective study design, such data were not available for the conventional controls.

Studies have documented a strong correlation between increases in inflammatory markers such as CRP and the occurrence of cardiovascular events [Torres 2003]. This correlation is thought to be due to the prothrombotic effects of inflammation [Parolari 2007].

To our knowledge, preoperative risk scores have not been shown to relate to the inflammatory response other than the chronic-disease profiles and demographic data that we matched for. The matching process took into consideration the presence or absence of confounding disease states (diabetes, pulmonary, and renal disease), as well as age, sex, and BMI. These disease states have previously been shown to influence the inflammatory response. We did not differentiate the severity of disease, however, nor did we include the severity of cardiac disease. These states are integrated into the EuroSCORE, which reflects perioperative risk. Patients were selected for an interventional procedure because of an unacceptably high perioperative risk for a conventional procedure; therefore, it would be difficult to find a matched population in terms of predicted risk. In studies looking purely at outcome measures, a matching process would be of limited validity. Thus, the difference in EuroSCOREs reflects the patient-selection process.

At this point we should clarify that the values presented are for the linear EuroSCORE. For example, over the interventional population as a whole, our median linear EuroSCORE of 13 correlates with a median logistic EuroSCORE of 39.

The greater severity of confounding and cardiac disease as reflected by a higher EuroSCORE might be related to the higher CRP peak values. Thus, the patients' preoperative disease state, rather than the extent of surgical trauma or the use of CPB, would appear to determine the postoperative inflammatory response, as indicated by elevated CRP levels.

Transcatheter AVI is a novel technique for which valid outcome data are only beginning to emerge. Although our study was not powered to analyze patient outcome, it is noteworthy that despite the higher perioperative risk, as reflected by the higher EuroSCORE, for the study group, short-term outcome measures, as assessed by our end points of ventilation time and 30-day mortality, were comparable. This finding should stimulate further studies to compare longer-term outcomes after transapical AVI with those for conventional operations that use all proven modifications. As more AVI outcome data become available, it will be very interesting to compare these results with those for conventional operative strategies and then to look at areas in which the physiological responses to these 2 approaches differ.

In that context, it would furthermore be interesting to relate the postoperative inflammatory response to longer-term survival rates and to measures of patient satisfaction. Our findings will inform future prospective studies that collect data on all relevant markers of inflammation and will be of particular interest when further outcome comparisons can be made in the future.

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