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MAJOR ARTICLE

Postoperative Inflammation and Fever After Elective Aortic Valve and Aortic Root Replacement: A Retrospective Cohort Study

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Background. Fever after cardiac surgery is common. More knowledge of postoperative fever could lead to better patient selection for diagnostic workup and empirical antibiotic treatment. We aimed to analyze the postoperative course of inflammation and fever after elective aortic valve and aortic root replacement.

Methods. In a retrospective single-center cohort study, we included 3 groups of patients after elective cardiac surgery: aortic root with aortic valve replacement (Bentall procedure, from 2014 to 2021), valve-sparing root replacement (VSRR, from 2014 to 2021), and isolated surgical aortic valve replacement (SAVR, from 2018 to 2021). Exclusion criteria were age <18 years, cardiac surgery other than described, use of deep-hypothermic circulatory arrest, reoperations, and preexisting infections. Primary outcome measure was the number of patients per group with postoperative fever (≥38°C). Secondary outcome measures were the percentage of patients per group with infections and outcome.

Results. Among 307 patients included (76 Bentall, 40 VSRR, 191 SAVR), 71% had postoperative fever. Fever occurred significantly more often in the Bentall (84%) and VSRR group (83%) compared with patients after SAVR (64%, $P = .001$). Seventeen patients had fever due to infection versus 202 with diagnoses of postoperative inflammation. In case of infection, fever was significantly higher (38.8°C vs 38.4°C, $P = .03$), and both the number of days with fever and hospital admission duration were significantly longer.

Conclusions. Postoperative fever is more often observed after Bentall procedure and VSRR compared to SAVR. In diagnoses of infection, there is a higher and prolonged fever.

Keywords. Bentall procedure; elective cardiac surgery; fever; SAVR; surgical aortic valve replacement; valve-sparing root replacement; VSRR.

Fever after cardiac surgery is a well-known phenomenon [1, 2]. Due to tissue trauma and extracorporeal circulation, proinflammatory cytokine release elicits fever [2–6]. Etiology is therefore noninfectious in most cases [7, 8], especially in case of fever within the first 48 hours after surgery [4]. Although infections seem rare [1, 2, 9], infection in patients with new prosthetic cardiac devices is a major complication and associated with high morbidity and mortality [4, 8, 10]. Empirical antibiotic treatment is therefore frequently started in patients developing fever after cardiac surgery, especially in case of prosthetic material, probably leading to overtreatment. Although cardiopulmonary bypass (CPB) seems to have a major role in the development of fever after cardiac surgery [6], the natural course of postoperative inflammation and fever after specific types of cardiac surgery involving both CPB and the placement of prosthetic material has not been systematically evaluated. Insight in the postoperative course of fever and inflammation after elective cardiac surgery with CPB leads to better patient selection for additional diagnostics and empirical antibiotic treatment. Therefore, we aimed to describe the postoperative course of inflammation and fever after elective cardiac surgery in patients who underwent aortic root with aortic valve replacement (Bentall procedure), aortic root without aortic valve replacement (valve-sparing root replacement [VSRR]), and isolated surgical aortic valve replacement (SAVR).

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METHODS

Patient Consent Statement

According to Dutch law and in consultation with the Ethics Committee of the Radboud University Medical Center

(Radboudumc), this study was exempt from approval by an ethics committee. No informed consent was required since there were no patient identifiers employed.

Patients and Methods

We performed a retrospective study of adult patients who underwent elective cardiac surgery at the Department of Cardiothoracic Surgery at Radboudumc between 2014 and 2021. The operative techniques were (both bio- and mechano-) Bentall procedure (group 1), VSRR (group 2), and isolated (both bio- and mechano-) SAVR (group 3). Because of the large number of patients available in group 3, data were reviewed from 2018 until 1 January 2022. Patients were excluded in case of age <18 years, cardiac surgery other than described (including reoperations, isolated supracommissural aortic replacement [SCAR], aortic arch surgery, and combined surgery), use of deep-hypothermic circulatory arrest, preexisting infections, and nonelective surgery. Surgical indication and subsequent technique had been made by the Heart Team of Radboudumc. All patients underwent surgical procedures via median sternotomy. The VSRR consisted both of reimplantation and remodeling techniques. Data were obtained from electronic medical records and transmitted to Castor Electronic Data Capture.

Outcome Measures and Definitions

The primary outcome measure was the number of patients per group with postoperative fever, defined as a temperature of ≥38.0°C (measured with an validated ear thermometer), during the first 14 days after surgery. The highest daily temperature measured was registered. Secondary outcome measures were the percentage of patients per study group with suspected infection, the percentage of patients per study group with microbiologically proven infection, the percentage of patients per study group treated with antibiotic treatment postoperatively, outcome during hospitalization including (re)interventions (including resternotomy and other invasive procedures, eg, pericardiocentesis and pacemaker implantation), and follow-up after discharge including readmissions, (re)interventions, and all-cause mortality. Patient characteristics and specific parameters (including extracorporeal circulation [ECC] time, aortic cross-clamp (AoX) time during surgery, and the use of dexamethasone prophylaxis preoperatively), inflammatory parameters, microbiological diagnosis, antibiotic treatment, clinical diagnoses of infection, and outcome measures were recorded for all patients. Comorbidity at baseline was scored using the Charlson Comorbidity Index (CCI) [11, 12]. Body mass index (BMI, in kg/m^2) was recorded from the day of admission before surgery, or, in case this was unknown, the most recent known BMI before surgery was used. Inflammation parameters were determined up to 2 weeks after surgery or up to hospital discharge. In case fever was absent for ≥24 hours, reappearance of fever was classified as a new episode of fever. Fever was classified as postoperative inflammation (including Dressler syndrome), infection, medication-related, or of other cause. Fever was classified as infection when cultures (of any kind) were positive for bacteria, and/or based on the clinical judgment of responsible physicians. Infections were further categorized as mediastinitis, vascular graft infection, urinary tract infection (UTI, both complicated and uncomplicated), hospital-acquired pneumonia (HAP), superficial wound infection, infected hematoma, infected central or peripheral catheter, pericarditis, and other infections. Primary outcome measures were analyzed for the period of the initial admission. The number of days of hospitalization after surgery was only recorded for the period of initial admission in Radboudumc. All-cause mortality, infection-related readmissions, and infection-related (re)interventions were recorded for the entire study period, while readmissions and interventions otherwise were recorded up to 1 year after surgery. Only data available in Radboudumc were used.

Statistical Analysis

Statistical analysis was conducted using SPSS software (version 25.0). Comparisons between the 3 groups were conducted using 1-way analysis of variance. Continuous variables were expressed as median (interquartile range [IQR]) or mean (standard deviation [SD]), and categorical variables with percentages. For assessment of differences between patients with fever diagnosed with infection versus patients with fever diagnosed with postoperative inflammation, descriptive statistics were used including mean and SD for continuous variables, and tested with the independent t test. Categorical variables were described with percentages, and tested with the χ^2 test. P values <.05 were considered statistically significant.

RESULTS

Database retrieval yielded 393 patients for eligibility screening, of whom 307 were included in this study in the following groups: Bentall procedure (group 1, n = 76), VSRR (group 2, n = 40), and SAVR (group 3, n = 191) (Figure 1). Baseline characteristics are depicted in Table 1. The prevalence of a connective tissue disease was higher in the VSRR group compared with the other 2 groups ($P < .001$). Of these, all but 1 (diagnosed with Loeys-Dietz syndrome) had Marfan syndrome. Slight differences in the choice of antibiotic prophylaxis were found between the groups as antibiotic prophylaxis changed over time.

Outcome Measures

Group 1: Bentall Procedure

Of the 76 patients who underwent a Bentall procedure, 64 (84.2%) developed fever. Characteristics of fever are depicted in Table 2. In 56 patients with fever (87.5%), fever was classified

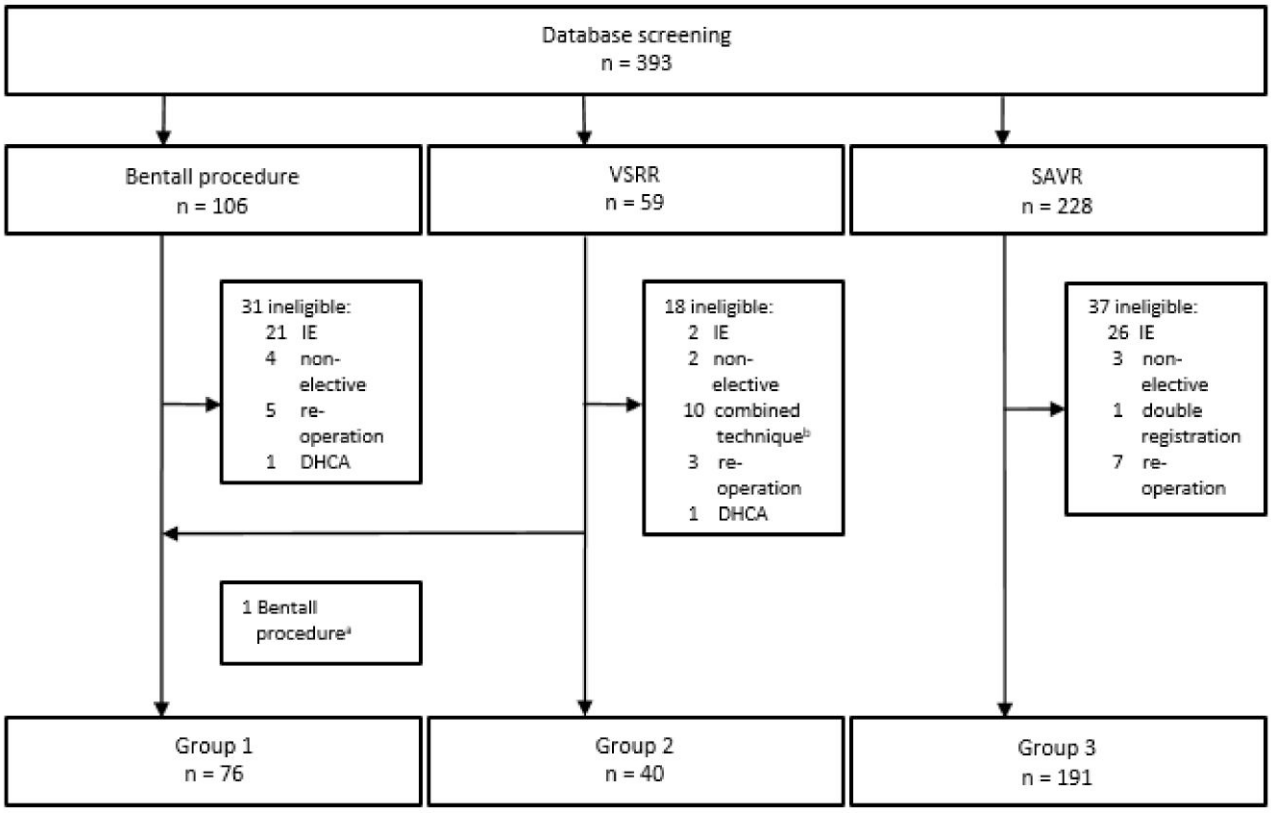

Figure 1. Flowchart of included patients. [a]Initially planned for a valve-sparing root replacement (VSRR) procedure, but procedure was changed to a mechano-Bentall procedure because of perioperative findings. [b]These patients underwent a partial VSRR procedure combined with a supracommissural aortic replacement. Abbreviations: DHCA, deep-hypothermic circulatory arrest; IE, infectious endocarditis; SAVR, surgical aortic valve replacement; VSRR, valve-sparing root replacement.

as postoperative inflammation, while fever in the other patients was classified as infection (12.5%). In a patient with multiorgan failure with fulminant colitis, the only positive blood culture was found (for both *Staphylococcus epidermidis* and *Bacteroides thetaiotaomicron*) from the 20 obtained blood cultures in case of fever. Diagnosis of UTI was based on clinical symptoms combined with a positive urinary culture with *Escherichia coli* in 1 patient, and *Proteus mirabilis* in another. In 2 patients with fever, pericardial fluid was obtained and was positive for *S epidermidis* in 1 patient, who was eventually diagnosed with a vascular graft infection. In 6 patients sputum cultures were obtained, of which only 1 patient had a positive culture. The cultured *Haemophilus influenzae* was considered not clinically relevant. The other infections were not microbiologically proven, but diagnosed on clinical and radiological grounds. Antibiotic treatment in patients with and without diagnosis of infection is shown in Table 2. Of the patients with fever, 9 patients were treated empirically, versus targeted in the other 3. Compared to the other groups (Table 3), the length of hospital stay was longer ($P = .001$), and more (re)interventions occurred during initial hospitalization ($P = .005$), including pericardiocentesis (n = 9), resternotomy due to blood loss (n = 6), and pacemaker implantation (n = 3). During follow-up, 18 patients were readmitted, mostly because of other complications than infection-related (Table 3). Twelve patients underwent a reoperation, of which 4 were infection-related: vascular graft infection (n = 3) and local wound infection (n = 1).

Group 2: VSRR

Of the 40 patients who underwent a VSRR, 33 (82.5%) developed fever (Table 2). Only 1 patient (3.0%) with fever was diagnosed with an infection, versus 32 patients (97.0%) in which fever was classified as postoperative inflammation. One of the 15 blood cultures taken from patients with fever appeared to be positive, but the growth of *Staphylococcus capitis* was regarded as contamination. A total of 5 patients with fever were treated with antibiotics, of whom 4 eventually were diagnosed with postoperative inflammation. Patients were admitted for a median of 7 days (IQR, 7.0–10.5), and (re)interventions occurred in 4 patients (10%), including pericardiocentesis (n = 2), and pacemaker implantation (n = 2). During follow-up, 9 patients were readmitted, 4 because of infectious-related complications (Table 3), including mediastinitis (n = 1), viral infection

Table 1. Baseline Characteristics

Characteristic	Bentall (n = 76)	VSRR (n = 40)	SAVR (n = 191)	*P* Value[a]
Demographics				
Age, y	59.5 (49.0–68.8)	45.5 (33.0–52.0)	68.0 (62.0–73.0)	<.001
Male sex	51 (67.1)	29 (72.5)	131 (68.6)	.84
BMI, kg/m^2	26.2 (24.5–29.7)	24.9 (22.6–28.3)	27.7 (24.8–30.4)	.02
CCI score [11]	2 (2)	1 (1)	3 (2)	<.001
Myocardial infarction	2 (2.6)	2 (5.0)	15 (7.9)	.27
(i)CVA/TIA	7 (9.2)	0	18 (9.4)	.13
Connective tissue disease	10 (13.2)	23 (57.5)	0	<.001
Liver disease	0	0	3 (1.6)	.40
Diabetes	4 (5.3)	1 (2.5)	37 (19.4)	.001
Malignancy	0	0	4 (2.1)	.29
Prophylactic treatment perioperatively[b]				
Cefuroxime	14 (18.4)	14 (35.0)	0	<.001
Cefazolin	61 (80.3)	27 (67.5)	190 (99.5)	<.001
Cefotaxime	0 (0)	0 (0)	1 (0.5)	NA
Dexamethasone	59 (77.6)	33 (82.5)	149 (78.0)	.80
ECC, min	137 (120.0–162.0)	169.5 (155.5–204.8)	101 (7.09–118.0)	<.001
AoX, min	104 (90.3–118.0)	135 (123.5–154.8)	71 (55.0–83.0)	<.001

Results are expressed as median (interquartile range) for continuous variables and No. (%) for categorical variables.

Abbreviations: AoX, aortic cross-clamp; BMI, body mass index; CCI, Charlson Comorbidity Index; ECC, extracorporeal circulation; (i)CVA, (ischemic) cerebrovascular accident; MI, myocardial infarction; NA, not applicable; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack; VSRR, valve-sparing root replacement.

[a]Comparisons were conducted using 1-way analysis of variance. *P* values <.05 were considered statistically significant.

[b]Two patients received no prophylactic antibiotic treatment: 1 in the Bentall group and 1 in the SAVR group. One patient in the VSRR group received both cefuroxime and cefazolin. One patient in the SAVR group received both cefuroxime and cefotaxime.

Table 2. Main Outcomes

Characteristic	Bentall (n = 76)	VSRR (n = 40)	SAVR (n = 191)	*P* Value[a]
Fever	64 (84.2)	33 (82.5)	122 (63.9)	.001
Maximum temperature, °C	38.3 (38.1–38.6)	38.5 (38.2–39.0)	38.4 (38.1–38.6)	.14
Days after surgery	2 (1–3)	2 (1–3)	1 (1–2)	.064
Total No. of days with fever	2 (1–3)	2 (1–4)	2 (1–3)	.077
Episodes of fever				
1	36 (56.3)	21 (63.6)	86 (70.5)	.001
2	22 (34.4)	9 (27.3)	28 (23.0)	.006
3	6 (9.4)	3 (9.1)	8 (6.6)	.42
Laboratory results in case of fever				
CRP, mg/L[b]	147 (71–190)	143 (89.5–261.5)	85 (60–115)	<.001
Leukocytes, × 10^9 cells/L	14.2 (11.7–16.3)	13.1 (12.1–16.7)	13.0 (11.0–16.2)	.68
Clinical diagnosis in case of fever				
Postoperative inflammation	56 (87.5)	32 (97.0)	114 (93.4)	.20
Infection	8 (12.5)	1 (3.0)	8 (6.6)	.20
UTI	2 (25)	0	4 (50)	.61
HAP	2 (25)	1 (100)	3 (37.5)	.82
Infected hematoma	1 (12.5)	0	0	.22
Wound infection	0	0	1 (12.5)	.74
Mediastinitis	1 (12.5)	0	0	.22
Prosthetic infection	1 (12.5)	0	0	.22
Other (multiorgan failure with fulminant colitis)	1 (12.5)	0	0	.22
Antibiotic treatment in case of fever	12 (18.8)	5 (15.2)	15 (12.3)	.50
Postoperative inflammation	4 (5.3)	4 (10)	7 (3.7)	.23
Infection	8 (10.5)	1 (2.5)	8 (4.2)	.23

Results are expressed as median (interquartile range) for continuous variables and No. (%) for categorical variables.

Abbreviations: CRP, C-reactive protein; ECC, extracorporeal circulation; HAP, hospital-acquired pneumonia; SAVR, surgical aortic valve replacement; UTI, urinary tract infection; VSRR, valve-sparing root replacement.

[a]Comparisons were conducted using 1-way analysis of variance. *P* values <.05 were considered statistically significant.

[b]Measured in 47 patients in the Bentall group, in 29 patients in the VSRR group, and in 87 patients in the SAVR group.

(n = 1), and fever without known cause (n = 2). Also, 12 patients underwent a reoperation, of which 2 were infection-related: mediastinitis (n = 1) and endocarditis (n = 1).

Group 3: SAVR

Of the patients receiving a SAVR, 63.9% developed postoperative fever, which was less compared to the other groups (*P* = .001; Table 2). In case of fever, patients in the SAVR group had the lowest C-reactive protein (CRP) level compared to the other groups (*P* < .001). In 8 patients (6.6%) with fever, the fever was classified as being caused by an infection. Diagnosis of UTI was based on clinical symptoms in combination with a positive urinary culture with *E coli* in 2 patients, *P mirabilis* in 1 patient, and both *P mirabilis* and *Morganella morganii* in the other. All patients with fever diagnosed with HAP were not microbiologically proven, but diagnosed on clinical and radiological grounds. Also, the wound infection was not microbiologically confirmed, but diagnosed on clinical grounds. Of the 15 patients with fever who were treated with antibiotics, 7 eventually were diagnosed with postoperative inflammation (Table 2). Patients were admitted for a median of 7 days (IQR, 5.0–8.0), and 20 patients were reoperated during initial hospitalization, including resternotomy due to blood loss (n = 11), pacemaker implantation (n = 4), sternal refixation (n = 2), paravalvular leakage (n = 1), pericardiocentesis (n = 1), and bronchoscopy because of atelectasis (n = 1). Additionally, 1 patient underwent electrical cardioversion because of atrial fibrillation. During follow-up, 22 patients were readmitted, but only 4 because of infection-related complications (Table 3), including endocarditis (n = 1), local wound infection (n = 1), viral infection (n = 1), and a suspicion for mediastinitis (n = 1). Also, 20 patients underwent a reoperation, of which 2 were infection-related: sternal refixation (n = 1) and endocarditis (n = 1).

Table 3. Outcome of Initial Admission and Follow-up

Outcome	Bentall (n = 76)	VSRR (n = 40)	SAVR (n = 191)	*P* Value[a]
Outcome of initial admission				
Mortality during hospitalization	1 (1.3)	0	2 (1)	.78
Length of stay, d	8 (6.0–10.8)	7 (7.0–10.5)	7 (5.0–8.0)	.001
(Re)intervention during hospitalization	18 (23.7)	4 (10.0)	21 (11.0)[b]	.005
Follow-up				
All-cause mortality	4 (5.2)	2 (5.0)	9 (4.7)	.98
Readmission	18 (23.7)[c]	9 (22.5)[d]	22 (11.5)[e]	.024
Related to infection	7 (38.9)	4 (44.4)	4 (18.2)	.24
Other causes	11 (61.1)	5 (55.6)	18 (82.8)	.24
(Re)intervention in follow-up	12[f] (15.8)	12 (30.0)	20 (10.5)[g]	.005
Related to infection	4 (33.3)	2 (16.7)	2 (10.0)	.26
Other causes	8 (67.7)	10 (83.3)	18 (90.0)	.26
Follow-up duration, wk	229 (161.0–303.8)	269.5 (143.0–352.3)	129 (86.0–166.0)	<.001

Results are expressed as median (interquartile range) for continuous variables and No. (%) for categorical variables.

Abbreviations: SAVR, surgical aortic valve replacement; VSRR, valve-sparing root replacement.

[a]Comparisons were conducted using 1-way analysis of variance. *P* values <.05 were considered statistically significant.

[b]Including 1 patient who was cardioverted because of atrial fibrillation.

[c]One patient was readmitted twice, 1 patient 3 times, and 1 patient 4 times.

[d]One patient was readmitted twice, and 1 patient 3 times.

[e]One patient was readmitted twice, and 2 patients 3 times.

[f]Two patients were reoperated twice.

[g]One patient was reoperated twice.

Subgroup Analysis

Comparing the 219 patients with fever versus the 88 patients (Table 4) without fever with regard to AoX and ECC time, patients who developed fever had statistically significant longer AoX time (mean, 92.2 [SD, 34.6] and 81.0 [SD, 31.7] minutes, respectively; $P = .009$), and ECC time (mean, 125.0 [SD, 44.5] and 113.4 [SD, 39.2] minutes, respectively; $P = .03$). In those patients who received dexamethasone prophylaxis, significantly fewer patients developed fever ($P = .02$). Among the 219 patients with fever (71%), a total of 17 patients were diagnosed with an infection (7.8%). Between those patients with infection versus postoperative inflammation, no differences were observed with regard to age, BMI, total CCI score, and whether or not dexamethasone prophylaxis was administered preoperatively. In case of infection, fever ($P = .03$; Supplementary Figure 1), CRP level ($P = .02$), and leukocytes ($P = .03$) were all higher, and both the total number of days with fever ($P < .04$) and duration of hospital admission ($P < .02$) were longer compared to patients with postoperative inflammation. In addition, more patients needed (re)interventions during the initial admission ($P = .02$) and a higher 30-day mortality was observed ($P < .001$) in patients with diagnoses of infection. No difference in the average duration of the onset of fever from surgery was found, and no difference was observed in ECC time and AoX time (Table 4). Subgroup analysis of patients with fever onset ≤2 days postsurgery still revealed 11 patients with fever due to infection (group 1, n = 5), VSRR (group 2, n = 1), and SAVR (group 3, n = 5). Although the number of patients with fever eventually classified as infectious is smaller, the overall proportion was comparable to the analysis including all days of onset **of fever**.

DISCUSSION

This study shows that fever after elective cardiac surgery with prosthetic device implantation is common and most often explained by postoperative inflammation. Fever is more often observed after Bentall procedure and VSRR compared to SAVR. Patients with fever due to infection have a higher temperature, higher inflammatory parameters, prolonged fever duration, and longer hospital admission compared to those with postoperative inflammation.

Due to wide variations in, for example, patient selection and study methods [13], it is difficult to directly compare our results with previous studies concerning the development of postoperative fever. Overall, our results seem comparable with previous studies with smaller sample sizes [1, 2, 9]. Fever was most frequently observed in the Bentall and VSRR groups. This could be explained by the significant longer ECC and AoX times, parameters related to each other and resulting in increased tissue damage, compared to the SAVR group [14]. Although speculative, the prosthetic material itself might induce a proinflammatory cytokine release, which might lead to a more pronounced reaction in the Bentall and VSRR groups compared to the SAVR group based on the amount of prosthetic material. The overall incidence of infection as explanation for fever was

Table 4. Patients With and Without Fever[a]

Characteristic	Patients With Fever (n = 219)		Patients Without Fever (n = 88)
	Diagnosis of Infection (n = 17)	Diagnosis of Postoperative Inflammation (n = 202)	
Type of surgery			
Bentall	8 (47.1)	56 (27.7)	12 (13.6)
VSRR	1 (5.9)	32 (15.8)	7 (8.0)
SAVR	8 (47.1)	114 (56.4)	69 (78.4)
Patient characteristics			
Age, y	62.0 (14.3)	60.5 (13.6)	61.0 (13.8)
BMI, kg/m^2	27.0 (3.5)	27.4 (4.9)	27.7 (4.7)
CCI score [11]	2.7 (1.5)	2.4 (1.5)	2.3 (1.3)
Diabetes	3 (18)	31 (15)	8 (9)
Dexamethasone prophylaxis	12 (71)	153 (76)	76 (86) ($P = .02$)[b]
Laboratory results			
CRP, mg/L[c]	154 (78.7) ($P = .02$)[d]	112 (65.8)	93 (57.0) ($P = .03$)[b]
Leukocytes, × 10^9 cells/L)	16.0 (5.3) ($P = .03$)[d]	13.8 (3.8)	14.2 (4.2)
Characteristics			
Maximum temperature (°C) in case of fever	38.8 (0.63) ($P = .03$)[d]	38.4 (0.39)	NA
Appearance of fever after surgery, d	1.7 (1.7)	1.8 (1.3)	NA
Total No. of days with fever	5.8 (6.2) ($P = .04$)[d]	2.4 (1.9)	NA
Hospital admission, d	18.6 (17.4) ($P = .02$)[d]	7.8 (3.6)	6.7 (3.1) ($P < .001$)
(Re)intervention during hospitalization[e]	6 (35) ($P = .02$)[d]	28 (14)	9 (10)
30-d mortality	2 (12) ($P < .001$)[d]	1 (0.5)	0 (0)
ECC, min	117.1 (53.2)	125.7 (43.8)	113.4 (39.2) ($P = .03$)[b]
AoX, min	88.5 (46.3)	92.5 (33.6)	81.0 (31.7) ($P = .009$)[b]

Results are expressed as mean (standard deviation [SD]) for continuous variables and No. (%) for categorical variables.

Abbreviations: AoX, aortic cross-clamp; BMI, body mass index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; ECC, extracorporeal circulation; NA, not applicable; SAVR, surgical aortic valve replacement; VSRR, valve-sparing root replacement.

[a]Descriptive statistics were used including mean (SD) for continuous variables, and tested with the independent *t* test. Categorical variables were described with percentages, and tested with the χ^2 test. Only statistically significant results are reported.

[b]Significantly different compared to the total group of patients with fever.

[c]Measured in 16 patients diagnosed with infection, in 147 patients diagnosed with postoperative inflammation, and in 52 patients without fever.

[d]Significantly different compared to patients with fever and diagnosis of postoperative inflammation.

[e]All (re)interventions during initial hospitalization were included in this analysis.

low. This is supported by other studies regarding elective cardiac surgery, and Bentall and VSRR procedures in particular, in which infections as early postoperative complications are rare [1, 2, 7, 9, 10, 15]. Obviously, it is unclear whether specific infections are related to certain operative techniques due to the limited amount of infections observed.

Previous research showed no association between fever or leukocytosis and infection in the early postoperative period following cardiac surgery [9]. However, after the sixth postoperative day, a leukocytosis was observed significantly more often in patients with an infection. Specificity of fever or leukocytosis was, however, only 15%. Andrade et al [1] found no differences in febrile response between infected and noninfected patients, and the routine laboratory evaluation allowed no differentiation. This contrasts our findings, with CRP, leukocytes, and maximum temperature being all significantly higher in case of infection. Additionally, no difference in time of occurrence of fever after surgery was found, and the total number of days with fever was higher in case of infection, the last being supported by findings of others [6]. In the context of additional biomarkers, procalcitonin (PCT), a biomarker for bacterial infection, appeared to be a useful marker for differentiating bacterial infections from other causes of postoperative fever in cardiac surgery patients [4], and seems to predict postoperative complications in cardiac surgery [16]. Although interesting, during the study period PCT was unavailable in our hospital and therefore not registered.

The preoperative administration of dexamethasone seems to reduce the chance of developing postoperative fever, without influencing the risk of infection. The discussion whether or not to administer preoperative dexamethasone to diminish the postoperative inflammatory reaction is matter of debate, but lies outside the scope of this study.

In general, fever within the first 48 hours after surgery is attributed to the normal inflammatory response [4, 6]. Some even extend this period up to 5 days postoperatively [17]. In our study, of all patients with fever who received antibiotic treatment, 46.9% were diagnosed with postoperative inflammation

and therefore overtreated. Especially in the context of antimicrobial stewardship, a better patient selection for starting antibiotic treatment is needed. Based on our findings, we advocate a full physical examination in all patients with postoperative fever after elective cardiac surgery, including a low threshold for (repetitive) blood cultures. In case of absence of specific leads for an infectious diagnosis, it seems justified to withhold antibiotic treatment. This examination should be repeated if the fever persists for 3–5 days. In case of deterioration, unsuspected rise in fever, or an unsuspected increased CRP or leukocyte level, this should warrant careful evaluation for an infection, including imaging and empirical antibiotic treatment awaiting diagnostic workup.

Besides the retrospective character, this study has some limitations. First, data were included only from Radboudumc and therefore excluding the period of stay in case of discharge to other hospitals, readmissions, or (re)interventions elsewhere. Although most patients were readmitted to Radboudumc in case of complications, this might have influenced the results with regard to the duration of hospital stay and follow-up. Second, the sample size of this study was relatively small, increasing the likelihood of accidental findings. Finally, due to the difference in study period between the SAVR group and the other groups, it is difficult to directly compare the follow-up and long-term outcome, although this would probably not have influenced the final results as overall both in-hospital and all-cause mortality during follow-up were comparable with known literature [7, 15].

CONCLUSIONS

In elective cardiac surgery, fever is more often observed after Bentall procedure and VSRR compared to SAVR, and most often explained by postoperative inflammation. The threshold for empirical antibiotic treatment should therefore remain high, especially in case of absence of specific leads for infection. Compared to postoperative inflammation, infection is accompanied by a higher temperature, and higher levels of CRP and leukocytes. Also, infections were associated with prolonged fever, prolonged hospital admission, more (re)interventions, and a higher 30-day mortality.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S. P. K., G. S. C. G., and I. J. E. K. initiated the study. S. P. K., I. M. M. Z., G. S. C. G., and I. J. E. K. designed the study. S. P. K., G. S. C. G., and I. J. E. K. coordinated and supervised the study, with S. P. K. and I. J. E. K. being responsible for the daily supervision. I. M. M. Z., S. P. K., J. J., and I. J. E. K. were responsible for the study conduct, data collection, and data analysis. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This report was written by S. P. K. and I. J. E. K. All authors critically revised and approved the manuscript.

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Data availability. The data underlying this article will be shared on reasonable request to the corresponding author.

Potential conflicts of interest. All authors: No reported conflicts.

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