The Systemic Inflammatory Response Syndrome Predicts Short-Term Outcome After Transapical Transcatheter Aortic Valve Implantation

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Objective: **Despite the minimally invasive nature of transcatheter aortic valve implantation (TAVI), the incidence of acute kidney injury (AKI) and mortality is of major concern. Several studies showed that outcome was influenced by the systemic inflammatory response syndrome (SIRS) in patients undergoing percutaneous TAVI. The purpose of this study was to investigate whether SIRS after transapical TAVI was associated with short-term outcome.**

Design: **Retrospective analysis of prospectively collected data.**

Setting: **Intensive care unit in a tertiary-care hospital.**

Participants: **In 121 patients undergoing transapical TAVI for severe aortic stenosis between March 2010 and October 2013, the incidence of SIRS during the first 48 hours was studied. The relation between the occurrence of SIRS and any adverse event during hospital stay was investigated. Any adverse event was defined as the composite of mortality, AKI, infection, stroke, myocardial infarction, and bleeding.**

Intervention: **none.**

Measurements and Main Results: **Sixty-five (53.7%) patients developed SIRS during 48 hours after transapical TAVI. The occurrence of SIRS was associated independently with an increased risk of any adverse event (adjusted odds ratio: 4.0, 95% confidence interval [CI]: 1.6-9.6; $p = 0.002$), which was mainly an increased risk of death (odds ratio: 5.5, 95% CI: 1.1-25.9; $p = 0.031$). Patients with SIRS had a longer median duration of intensive care unit stay compared with patients without SIRS (2 *v* 1 day; $p < 0.001$).**

Conclusions: **SIRS predicts short-term outcome in patients undergoing transapical TAVI.**

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KEY WORDS: ***systemic inflammatory response syndrome, mortality, acute kidney injury, aortic valve, treatment outcome, cardiac surgical procedure***

SINCE ITS INTRODUCTION IN 2007, approximately 9,000 patients in Europe undergo transcatheter aortic valve implantation (TAVI) every year for symptomatic severe aortic stenosis.[1] This treatment modality is reserved for high-risk patients not suitable for conventional cardiac surgery. An important difference between surgical and transcatheter aortic valve replacement is that, in the latter, cardiopulmonary bypass, known for inducing an inflammatory response and subsequent organ failure, is not used.[2] Despite the less invasive nature of TAVI, postprocedural mortality and morbidity rates are high.[3,4] A pilot study in 40 patients showed that patients undergoing transapical TAVI had a higher level of high-sensitivity C-reactive protein and a higher leucocyte count compared with patients undergoing transfemoral TAVI.[5] Few studies examined the relation between postprocedural systemic inflammatory response syndrome (SIRS) and outcome in patients undergoing percutaneous TAVI.[6,7] The impact of SIRS on short-term outcome after transapical TAVI has yet to be determined. The objective of the present study was to determine the incidence of SIRS after transapical TAVI and its effect on short-term outcome.

METHODS

The local Medical Ethics Committee (Research and Development Department, St. Antonius Hospital) approved the study and waived the need for informed consent.

From March 2010 until October 2013, a total of 127 consecutive patients with severe symptomatic aortic stenosis underwent elective transapical TAVI under general anesthesia. Operative risk was considered high for all patients and a transfemoral approach was not feasible due to inaccessible femoral arteries. Detailed information about the transapical TAVI procedure has been described before.[8,9] In short, a small anterolateral mini-thoracotomy was used in the fifth intercostal space, followed by puncture of the left ventricular apex after obtaining adequate ACT ($\geq$250 seconds) with heparin. Then, under fluoroscopic guidance, balloon valvuloplasty of the native aortic valve was performed using a short run of rapid ventricular pacing (180 beats per minute), followed by positioning of the prosthesis using a second rapid pacing run when indicated. Several types of valves were used: Edwards SAPIEN (Edwards Lifesciences, Irvine, California), JenaValve (JenaValve Technology GmbH, Munich), or Medtronic Engager (Medtronic, Minneapolis, Minnesota). Afterward, all patients were admitted to the intensive care unit (ICU). Patients were extubated in the ICU immediately after arrival or, if necessary, after rewarming until core temperature exceeded 36.5°C. If a temporary cardiac pacemaker was necessary, the pacing rate did not exceed 90 beats per minute. None of the patients received beta-blockers during the procedure or during the first 48 hours after TAVI. Patients in whom the inflammatory response after transapical TAVI was affected by confounding variables (reoperation within 48 hours and use of cardiopulmonary bypass during TAVI) or when the inflammatory response could not be studied (death within 48 hours of surgery) were excluded. All patients were followed up until hospital discharge. Periprocedural data were routinely gathered prospectively in a computerized medical system and subsequently analyzed. Because the operative procedure time could not be retrieved in all patients, fluoroscopy time was used as a surrogate for operative procedure time.

The systemic inflammatory response syndrome was defined according to existing guidelines as fulfilling at least 2 of the following criteria for 1 hour or more: Temperature <36.0°C or >38.0°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or PaCO2 <32 mmHg, and leucocyte count <4 or >12 (10^9/L).[10]

The outcome parameters were acute kidney injury (AKI), stroke, postprocedural infectious complication, bleeding complication,

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1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2014.10.005

myocardial infarction, and in-hospital mortality and were scored after the inclusion period of SIRS. A postprocedural infectious complication was defined as clinical evidence of infection (eg, new infiltrate on chest x-ray, fever, productive cough) that required antibiotic treatment. The other parameters were defined as stated by the updated Valve Academic Research Consortium consensus report.[11] The effect of SIRS on any adverse event was determined, a composite of all outcome parameters previously mentioned. Other study parameters were length of ICU stay, length of hospital stay, in-hospital mortality, and the highest sequential organ failure assessment (SOFA) score (total and for each organ system separately) during the first 72 hours of ICU admission. The total SOFA score consists of the score of 6 organ systems (respiratory, central nervous, cardiovascular, liver, renal, and coagulation) and assesses the degree of organ failure.[12] This score was calculated daily during ICU stay. T.R. collected all preprocedural data and outcome parameters. P. G. or S.R. determined in each patient if SIRS occurred.

Serum creatinine level, leucocyte count, and C-reactive protein were measured the day before the procedure and on postprocedural days 1, 2, and 3. Acute kidney injury was defined as an increase in serum creatinine to 150% or more (1.5-fold compared with baseline) or an increase of >26 µmol/L within 72 hours after TAVI.[11] Chronic renal failure was defined as an estimated glomerular filtration rate calculated by the simplified Modification of Diet in Renal Disease formula <60 mL/min/1.73 m^2.[13]

Continuous data are presented as the mean ± standard deviation or median and interquartile range (IQR) as appropriate. The Kolmogorov-Smirnov test was used to test for normal distribution. To compare variables between groups, the chi-square test was used for dichotomous variables and Student's *t* test or Mann-Whitney U test was used for continuous variables, where appropriate. Univariate analyses were performed to examine the crude associations of periprocedural characteristics and SIRS and outcome parameters. Multivariate analysis was performed to examine the adjusted association of SIRS and any adverse event. To do so, a multivariate logistic regression model was constructed considering all variables that were imbalanced between the arms ($p \leq 0.10$) as depicted in Table 1, 2 and 3. A variable was retained in the model as a confounder if it changed the odds ratio (OR) of SIRS and any adverse event by more than 10%. P values of <0.05 were considered significant in all analyses. Data were analyzed using IBM SPSS Statistics 22.0 software (IBM, Armonk, NY).

A power analysis was performed to determine optimal sample size. Based on prior literature reports, the incidence of SIRS and any adverse event was estimated as at least 30% and 7%, respectively.[7] Based on the assumption that patients with SIRS have a 3-fold risk of any adverse event compared with patients without SIRS, the number of study patients needed was 88 (power = 80%, $\alpha = 0.05$). The sample size was not adequate to detect risks less than 3-fold with adequate power. Individual outcome parameters were not powered to detect risk increases.

RESULTS

Of the 127 studied patients, 6 were excluded (4 patients underwent sternotomy or rethoracotomy within 48 hours after the procedure, 1 patient died within 24 hours of admission due to periprocedural dissection of the left main coronary artery, and 1 patient was on cardiopulmonary bypass during TAVI). The final study population consisted of 121 patients.

During the first 48 hours after TAVI, SIRS occurred in 65 (53.7%) patients. The use of preprocedural ß-blocker therapy, steroids, or statins did not influence the incidence of SIRS (Table 1). Potential risk factors for the development of SIRS such as red blood cell transfusion (23.1% *v* 19.6%; p = 0.647), number of rapid ventricular pacing runs (3 *v* 3; p = 0.670), valve-in-valve implantation (4.6% *v* 3.6%; p = 1.000), postdilatation of the valve prosthesis (26.2% *v* 30.9%; p = 0.565), and fluoroscopy time (30 *v* 24 minutes; p = 0.145) were comparable in patients with and without SIRS. The valve type used was not associated with the occurrence of SIRS. Forty-eight (39.7%) patients suffered from any adverse event. Baseline and periprocedural characteristics of patients with and without any adverse event are presented in Tables 2 and 3.

Table 1. Baseline Characteristics According to the Occurrence of SIRS

Variable	SIRS (n = 48)	No SIRS (n = 73)	p value
Male, n (%)	30 (46.2)	28 (50.0)	0.673
Age, years	80.1 ± 6.7	79.5 ± 6.5	0.651
BMI, kg/m^2(%)	26.2 ± 5.0	26.8 ± 4.5	0.454
Comorbidity			
Diabetes, n (%)	17 (26.2)	16 (28.6)	0.766
COPD, n (%)	28 (43.1)	19 (33.9)	0.303
Hypertension, n (%)	63 (96.9)	52 (92.9)	0.414
Coronary artery disease, n (%)	55 (84.6)	47 (83.9)	0.918
Congestive heart failure, n (%)			
NYHA ≤2	28 (43.1)	19 (33.9)	0.303
NYHA >2	37 (56.9)	37 (66.1)	
Atrial fibrillation, n (%)	22 (33.8)	17 (30.4)	0.682
Previous myocardial infarction, n (%)	18 (27.7)	18 (32.1)	0.593
Previous PCI, n (%)	24 (36.9)	22 (39.3)	0.790
Previous cardiac surgery, n (%)	21 (32.3)	28 (50.0)	0.048
Previous stroke, n (%)	14 (21.5)	13 (23.2)	0.825
Peripheral artery disease, n (%)	27 (41.5)	19 (33.9)	0.390
Chronic renal failure, n (%)	27 (41.5)	24 (42.9)	0.884
Pulmonary hypertension, n (%)	22 (33.8)	17 (30.4)	0.682
Additive EuroSCORE	10 (9-11)	10 (8-11)	0.842
Normal LVEF	24 (36.9)	22 (39.3)	0.790
Preoperative medication use			
ß-blocker	17 (26.2)	20 (35.7)	0.255
Statin, n (%)	47 (72.3)	35 (62.5)	0.250
Steroids, n (%)	4 (6.2)	6 (10.7)	0.511

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome.

The development of SIRS was associated with a greater degree of postprocedural organ failure as assessed by total SOFA score (4, IQR 3-6 *v* 3, IQR 2-4.75, Fig 1). Patients with SIRS had an almost 3-fold increased risk of any adverse event compared with patients without SIRS (OR: 2.8, 95% CI: 1.3-6.1; p = 0.007, Table 4). Patients with SIRS were more likely to experience postprocedural bleeding (OR 3.6, 95% CI: 1.0-13.6) or death (OR: 5.5, 95% CI: 1.1-25.9). The rate of postprocedural infections was 18.5% in patients with SIRS and 10.7% in patients without SIRS (p = 0.232). In multivariate regression analyses, the occurrence of SIRS was associated independently with an increased risk of any adverse event (adjusted odds ratio (AOR): 4.0, 95% CI: 1.6-9.6; p = 0.002, Table 5). Total median length of hospital stay was similar in both groups (7 days in patients with SIRS *v* 6 days in patients without SIRS, p = 0.518); SIRS did affect the median length of ICU stay (2 *v* 1 day; $p < 0.001$, Fig 2).

Table 2. Baseline Characteristics According to the Occurrence of Any Adverse Event

Variable	Adverse Event (n = 48)	No Event (n = 73)	p value
Male gender, n (%)	26 (54.2)	32 (43.8)	0.266
Age, years	79.4 ± 6.4	80.1 ± 6.7	0.592
BMI, kg/m^2(%)	25.9 ±4.4	27.2 ± 5.1	0.154
Comorbidity			
Diabetes, n (%)	23 (47.9)	10 (13.7)	<0.001
COPD, n (%)	18 (37.5)	29 (39.7)	0.806
Hypertension, n (%)	48 (100)	67 (91.8)	0.080
Coronary artery disease, n (%)	40 (83.3)	62 (84.9)	0.813
Congestive heart failure, n (%)			
NYHA ≤2	14 (29.2)	33 (45.2)	0.077
NYHA >2	34 (70.8)	40 (54.8)	
Atrial fibrillation, n (%)	17 (35.4)	22 (30.1)	0.543
Previous myocardial infarction, n (%)	19 (39.6)	17 (23.3)	0.055
Previous PCI, n (%)	17 (35.4)	29 (39.7)	0.633
Previous cardiac surgery, n (%)	20 (41.7)	29 (39.7)	0.832
Previous stroke, n (%)	11 (22.9)	16 (21.9)	0.897
Peripheral artery disease, n (%)	19 (39.6)	27 (37.0)	0.773
Chronic renal failure, n (%)	26 (54.2)	25 (34.2)	0.030
Pulmonary hypertension, n (%)	19 (39.6)	20 (27.4)	0.161
Additive EuroSCORE	10 (9-11)	10 (8-11)	0.496
Normal LVEF	25 (52.1)	50 (68.5)	0.069
Preoperative medication use			
ß-blocker, n (%)	18 (37.5)	19 (26)	0.180
Statin, n (%)	33 (68.8)	49 (67.1)	0.851
Steroids, n (%)	5 (10.4)	5 (6.8)	0.515

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention.

DISCUSSION

Results demonstrated that SIRS after transapical TAVI is common and that SIRS is associated independently with worse short-term outcome, including an increased risk of in-hospital mortality. Sinning et al performed a prospective study investigating the relation between SIRS and outcome in 152 patients undergoing percutaneous TAVI.[7] In that study, postprocedural SIRS occurred in 40.1% of all patients and this was independently associated with an increased 1-year mortality risk (HR: 4.0; 95% CI: 1.8-9.2; p = 0.001). In another paper, the same author studied the influence of periprocedural renal function on outcome after percutaneous TAVI.[6] Systemic inflammatory response syndrome after TAVI was present in 60% of all patients and closely related to AKI (60% in patients with SIRS *v* 21% in patients without SIRS, p = 0.002). Furthermore, patients with SIRS were at increased risk for 1-year mortality (OR: 2.5; 95% CI: 1.0-6.2; p = 0.04). Although preprocedural impaired renal function and AKI were associated with mortality in the present study cohort, different numbers of AKI in patients with or without SIRS were not observed (24.6% and

Table 3. Periprocedural Characteristics

Variable	Adverse Event (n = 48)	No Event (n = 73)	p value
Procedural characteristics			
Rapid pacing runs, n	3 (3-3)	3 (3-3)	0.281
Valve-in-valve, n (%)	4 (8.3)	1 (1.4)	0.080
Postdilatation, n (%)	13 (27.7)	21 (28.8)	0.895
Fluoroscopy time, min	30 ± 23	24 ± 10	0.145
Red blood cell transfusion, n (%)	11 (22.9)	15 (20.5)	0.756
Valve type			
Edwards SAPIEN	40 (83.3)	54 (74.0)	0.470
JenaValve	6 (12.5)	15 (20.5)	
Medtronic Engager	2 (4.2)	4 (5.5)	
Prosthetic valve performance			
Aortic insufficiency, n (%)	26 (54.2)	40 (54.8)	0.946
- Grade 1	13 (27.1)	25 (34.2)	0.773
- Grade 2	11 (22.9)	12 (16.4)	
- Grade 3	2 (4.2)	3 (4.1)	
Postoperative medication use			
Statin, n (%)	20 (41.7)	19 (26.0)	0.072
Steroids, n (%)	4 (8.3)	7 (9.6)	1.000

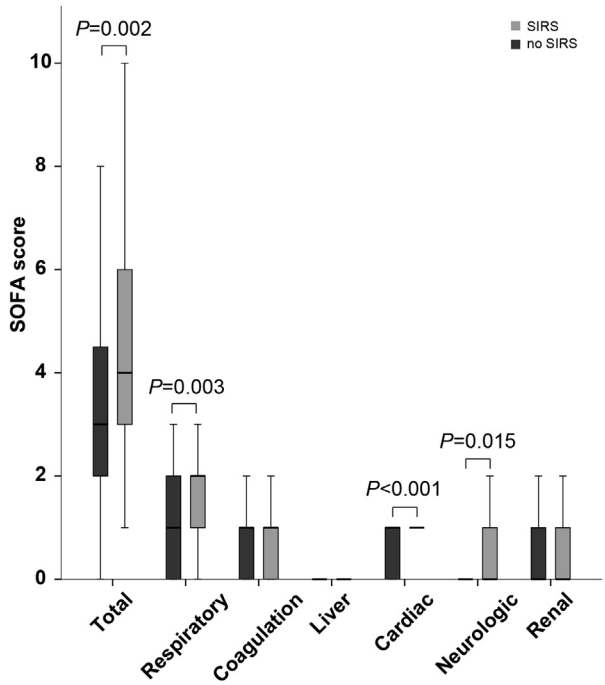

Fig 1. Highest SOFA scores during the first 72 hours of ICU admission after transapical TAVI dependent on the occurrence of SIRS. Abbreviations: SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

Table 4. Clinical Outcomes for the Occurrence of SIRS

	SIRS (n = 65)	No SIRS (n = 56)	p value
Mortality, n (%)	11 (16.9)	2 (3.6)	0.018
AKI, n (%)	16 (24.6)	10 (17.9)	0.367
Stroke, n (%)	1 (1.5)	0 (0.0)	1.000
Infection, n (%)	12 (18.5)	6 (10.7)	0.232
Bleeding, n (%)	11 (16.9)	3 (5.4)	0.047
Myocardial infarction, n (%)	4 (6.2)	0 (0.0)	0.123
Any adverse event, n (%)	33 (50.8)	15 (26.8)	0.007

NOTE. All p values are nominal. Individual outcomes, except for any adverse event, were not powered to show differences.

Abbreviations: AKI, acute kidney injury; SIRS, systemic inflammatory response syndrome.

Table 5. Multivariate Logistic Regression Analysis for Predictors of Any Adverse Event

	Univariate Analysis				Multivariate Analysis		
	OR	(95% CI)	p Value		OR	(95% CI)	p value
SIRS	2.8	(1.3-6.1)	0.008	SIRS	4.0	(1.6-9.6)	0.002
DM	5.8	(2.4-13.9)	<0.001	DM	6.9	(2.6-18.1)	<0.001
Previous MI	2.2	(0.9-4.7)	0.057	Previous MI	2.2	(0.9-5.5)	0.089
Decreased LVEF	2.0	(0.9-4.2)	0.220				
eGFR <60	2.6	(1.4-5.0)	0.003				
Valve-in-valve	6.6	(0.7-60.5)	0.098				

Abbreviations: CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

17.9%, p = 0.367, respectively). The present results confirmed that SIRS is associated independently with outcome after TAVI and that this association is also present in patients undergoing a transapical approach. In contrast to the previously mentioned studies reporting an independent association of SIRS and 1-year mortality, it was observed that SIRS was associated with short-term outcome. This difference might be related to the fact that, in general, patients undergoing transapical TAVI are less healthy and potentially more susceptible to post-operative insults (eg, SIRS) than patients undergoing transfemoral TAVI.

It is not clear whether SIRS actually is related to specific procedure-related factors, except for surgery itself. In the present study, no risk factors for the occurrence of SIRS were identified. The question is whether SIRS occurs by chance or whether all possible risk factors simply were not identified. Sinning et al showed that an increased number of rapid ventricular pacing runs, a surrogate for low cardiac output, predicted the development of SIRS after percutaneous TAVI (OR: 1.8; 95% CI: 1.1-2.8; p = 0.025).[7] These periods of low cardiac output are likely to induce ischemic injury to organs and initiate a systemic inflammatory response.[14,15] Balloon valvuloplasty of the native aortic valve, dilatation of the prosthesis, and arrhythmias also may contribute to a low-cardiac-output state. In addition, the impact of low cardiac output may be aggravated by pre-existing vascular insufficiency, which often is present in patients undergoing TAVI (38% of patients in the present study suffered from peripheral artery disease). Consequently, SIRS-related mortality might be a result of multiple organ injury due to procedure-related tissue hypoperfusion. The numbers of rapid ventricular pacing runs in patients with and without SIRS were similar in the present study, but it is possible that patients with SIRS suffered from worse hypotension induced by rapid ventricular pacing runs than patients without SIRS. Unfortunately, data regarding perioperative blood pressure could not be obtained for all patients.

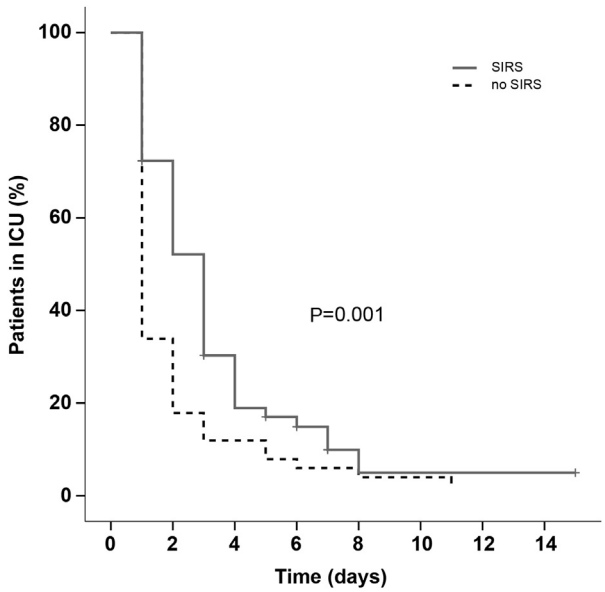

Fig 2. Median length of ICU stay after transapical TAVI dependent on the occurrence of SIRS. Abbreviations: SIRS, systemic inflammatory response syndrome; ICU, intensive care unit.

Numerous studies showed that excessive inflammation after cardiac and noncardiac surgery was associated with an increased risk of mortality and morbidity.[16–21] Why inflammation may lead to worse outcome after surgery is not straightforward. The exact mechanism is beyond the scope of this article, but involves tissue damage triggering the innate immune system.[22] In short, the innate immune system initiates the production of pro-inflammatory mediators and biomarkers. Inflammatory mediators (chemokines, cytokines, plasma cascades, and nitrogen and reactive oxygen species) reduce the production of nitric oxide, which may lead to mitochondrial dysfunction, the development of multiorgan failure (MOF), and ultimately death.[10] In this light, it is interesting that prophylactic corticosteroids led to a reduced incidence of respiratory failure and pneumonia and a reduced length of ICU and hospital stay in a recent randomized controlled trial in patients undergoing cardiac surgery.[23]

The systemic inflammatory response syndrome may emerge after a wide variety of noninfectious insults. Pancreatitis, trauma, tissue injury, surgery, ischemia, hemorrhagic shock, and burns may lead to SIRS. The definition of SIRS relies on vital signs and laboratory values that may be, but are not exclusively related to, a generalized inflammatory response. For example, heart rate and respiratory rate also are influenced by noninflammatory factors like pain or stress. The authors acknowledge that the individual SIRS criteria are non-specific. The addition of inflammatory biomarkers such as interleukin-6 (IL-6) or tumor necrosis factor- α (TNF-α) would have advanced the argument that postprocedural systemic inflammation was indeed present. Nonetheless, prior studies showed that patients with SIRS have higher levels of IL-6, IL-8, procalcitonin, and TNF-α compared

with patients without SIRS, confirming that SIRS is an expression of systemic inflammation.[7,24–27]

A second limitation is that patient data were routinely prospectively gathered in a computerized database. Although this database contains specific periprocedural data, there were some limitations (eg, detailed information about the length and duration of periprocedural hypotension could not be obtained for all patients, which is a possible confounder for the development of SIRS and mortality). Third, a composite endpoint was used, and all established limitations apply. However, postoperative inflammation has influence on many different outcome parameters that have no individual relationship; therefore, it would be incorrect not to study outcome in general.[23] Also, individual outcomes are rare and statistical power may not be sufficient for each individual outcome parameter. And fourth, the incidence of SIRS after transapical TAVI was studied, but the pathophysiologic mechanism was not clarified.

CONCLUSIONS

SIRS after transapical TAVI is common and associated with short-term outcome. Future work studying outcome in TAVI patients should focus on the cause of SIRS.

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