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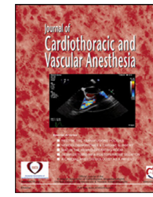

Original Article

Prolonged Systemic Inflammatory Response Syndrome After Cardiac Surgery

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Objectives: Cardiac surgery induces systemic inflammatory response syndrome (SIRS), leading to higher morbidity and mortality. There are no individualized predictors for worse outcomes or biomarkers for the multifactorial, excessive inflammatory response. The interest of this study was to evaluate whether a systematic use of the SIRS criteria could be used to predict postoperative outcomes beyond infection and sepsis, and if the development of an exaggerated inflammation response could be observed preoperatively.
Design: The study was observational, with prospectively enrolled patients.
Setting: This was a single institution study in a hospital setting combined with laboratory findings.
Participants: The study included a cohort of 261 volunteer patients.
Interventions: Patients underwent cardiac surgery with cardiopulmonary bypass, and were followed up to 90 days. Biomarker profiling was run preoperatively.
Measurements and Main Results: Altogether, 17 of 261 (6.4%) patients had prolonged SIRS, defined as fulfilling at least 2 criteria on 4 consecutive postoperative days. During hospitalization, postoperative atrial fibrillation (POAF) was found in 42.2% of patients, and stroke and transient ischemic attack in 3.8% of patients. Prolonged SIRS was a significant predictor of POAF (odds ratio [OR] 4.5, 95% CI 1.2-17.3), 90-day stroke (OR 4.5, 95% CI 1.1-18.0), and mortality (OR 10.7, 95% CI 1.7-68.8). Biomarker assays showed that preoperative nerve growth factor and interleukin 5 levels were associated with prolonged SIRS (OR 5.6, 95%, CI 1.4-23.2 and OR 0.7, 95%, CI 0.4-1.0, respectively).
Conclusions: Nerve growth factor and interleukin 5 can be used to predict prolonged systemic inflammatory response, which is associated with POAF, stroke, and mortality.

Key Words: cardiac surgery; cardiopulmonary bypass; cytokines; postoperative atrial fibrillation; postoperative care; SIRS

SYSTEMIC INFLAMMATORY response activates physiologic, immunologic, biochemical, and circulatory mechanisms that respond to inner and outer stress. The concept of systemic inflammatory response syndrome (SIRS) was created to explain an excessive inflammation process independent of cause, and consists of abnormal body temperature, tachycardia, tachypnea,

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hyperventilation, and abnormal white blood cell count (WBC), according to the 1991 consensus.[1] Postoperative SIRS is known to increase morbidity and mortality[2]; however, reliable detection of SIRS leading to adverse events is challenging because up to 90% of patients meet the clinical criteria at some time point during the first postoperative month—most without developing sepsis or postoperative infection.[3]

The inflammatory process activated during cardiac surgery is largely due to tissue trauma, hypoperfusion, ischemia-reperfusion injury, and the artificial circulatory system contact of cardiopulmonary bypass (CPB).[4] These lead to the production and release of circulating pro- and antiinflammatory cytokines and chemokines in a cascade of monocyte and macrophage activation,[5] but it has been difficult to find strong predictors, biomarkers, or single-target therapy for the development of SIRS after cardiac surgery.[6,7]

This study introduced the idea that continuous postoperative search for SIRS may help identify patients at high risk for postoperative adverse events. The benefit of using SIRS criteria in a clinical setting is that the evaluation is straightforward, cost-effective, and easily repeatable. By incorporating biomarker profiling, the study aimed to find patients prone to developing prolonged inflammation postoperatively.

Methods

Patient Selection

The present analysis included a prospective cohort of 300 consecutive adult patients, of whom 282 underwent cardiac surgery from February 2016 to September 2017 at the Heart Center of the Turku University Hospital, Turku, Finland. This institution is a university and tertiary referral hospital for a population of 876,000 inhabitants of Southwest Finland. These patients are participants of the CAREBANK study, an ongoing Finnish prospective cohort study of patients undergoing adult cardiac surgery at the Turku University Hospital (ClinicalTrials.gov identifier: NCT03444259), first posted on February 23, 2018. Follow-up data were collected prospectively both by individual contacts via phone calls using a structured questionnaire, and from hospital records at prespecified time points. This study focused on in-hospital and 90-day outcomes to best evaluate the immediate and short-term effects of postoperative systemic immune response. Mortality data were obtained from patient records, as well as from the nationwide registry (Statistics Finland). The CAREBANK has received approval from the Ethical Committee of the Hospital District of Southwest Finland, and adheres to the Declaration of Helsinki as revised in 2002. CAREBANK data were monitored by an independent third party. Written informed consent was obtained from the study subjects. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Cytokines

Consecutive blood samples were collected in the morning time after fasting or in an emergency setting. Preoperative serum was centrifuged from the whole blood and ethylenediaminetetraacetic acid plasma. The serum samples were labeled and stored at −70°C until analyses. The analyses for all 300 samples were done in separate sessions. Cytokine analyses were performed blinded to procedures and outcomes. Cytokine array analyses were done using the enzyme-linked immunosorbent assay according to manufacturer instructions (Elabscience, Houston, TX). The optical density values were analyzed using Tecan Infinite M200 and Magellan 7.2. software for Microsoft Windows (Tecan Group, Männedorf, Switzerland). Multiplex Immunoassays were done using the Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex (#12007283; BioRad) according to the manufacturer's instructions.

Outcomes

The primary objective was to study the effect of ongoing systemic inflammatory response on immediate and 90-day outcomes after adult cardiac surgery on CPB. The hypothesis was that in-hospital-detected prolonged inflammatory state can predict worse outcomes. The secondary objective was to study the utility of preoperative biomarkers to help recognize high-risk patients. Patients were determined to be SIRS-positive if they fulfilled at least 2 of the following requirements: heart rate higher than 90 bpm, body temperature below 36°C or over 38°C, respiratory rate over 20/min or arterial carbon dioxide level in blood gas analysis below 4.3 kPa, leukocyte count less than 4×10^9/L or greater than 12×10^9/L in blood. SIRS criteria were handled as continuous variables from 0 to 4 based on the number of SIRS criteria met. The concept of prolonged SIRS was defined as having 2 or more clinical SIRS criteria met daily for 4 consecutive postoperative days. Postoperative atrial fibrillation (POAF) refers to new-onset atrial fibrillation (AF) that develops after surgery, and new-onset atrial fibrillation refers to the recording of an AF or atrial flutter after index hospitalization. Postoperative atrial fibrillation and new-onset atrial fibrillation were confirmed by a 12-lead electrocardiography recording or telemonitoring, indicating an AF episode of 5 minutes or longer postoperatively without a history of preoperative AF or atrial flutter. Transient ischemic attack (TIA) was defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. Ischemic stroke was defined as a permanent focal neurologic deficit confirmed by a neurologist and confirmed via computed tomography or magnetic resonance imaging. Only strokes considered definite by the treating neurologist or physician were included in the present study. Transfusion refers to the administration of packed red blood cells. Postoperative mediastinitis and pneumonia were defined as a symptom of infection, fever, malaise, elevation of C-reactive protein or leukocyte count, and/or imaging finding consistent with infection at the mediastinal or pulmonary area and without signs of alternative diagnoses with similar presentation. Patients with postoperative infections were not excluded from the analysis. Redo surgery for bleeding was defined as resternotomy because of bleeding.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM SPSS, Inc, Armonk, NY). Continuous variables are reported as median and interquartile range or mean and standard deviation as appropriate. Categorical variables are reported as counts and percentages. The Shapiro−Wilk test of normality was performed on all baseline characteristics. The chi-square test and Fischer's exact test were used to evaluate the difference in categorical variables and outcomes, whereas continuous variables were evaluated using an independent sample t-test or Mann−Whitney U test. Logistic regression was performed to identify independent risk factors for prolonged SIRS and postoperative outcomes. Multivariate logistic regression (type I and III) was performed by including variables of relevance with $p < 0.05$ in the univariate analyses. Statistical significance was set at $p < 0.05$ in multivariate analysis. For investigated parameters, predictive validity was determined with the area under the receiver operating characteristics curve. Due to the observational nature of the study, a formal sample size calculation was not carried out.

Results

Study Population

A total of 282 patients underwent cardiac surgery, of whom 266 had CPB. Five patients died during index hospitalization and were excluded. Of the remaining 261 patients, SIRS criteria values were available on all, excluding missing data of 5 patients on the fourth postoperative day (POD). There were 126 (48.3%), 172 (65.9%), 85 (32.3%), and 41 (15.7%) SIRS-positive patients on the first, second, third, and fourth POD, respectively (Fig 1). The most common SIRS criterion was increased respiratory frequency, followed by increased heart rate and an abnormal WBC on the first and second POD. The most common criterion was increased heart rate, followed by increased respiratory rate and abnormal WBC on the third and fourth POD. Altogether, 17 (6.4%) patients met the definition of prolonged SIRS. The baseline characteristics of the study groups did not differ except for the incidence of chronic lung disease (Table 1). Perioperative and intensive care unit (ICU) characteristics were similar between the study groups (Table 2). Chronic lung disease was the only independent risk factor for prolonged SIRS in a univariate analysis of baseline, perioperative, and ICU characteristics.

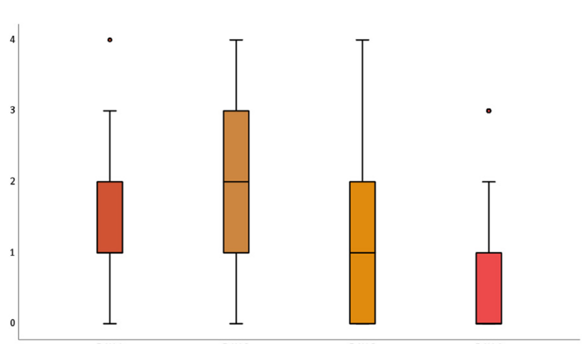

Fig 1. Systemic inflammatory response syndrome criteria (0-4) on postoperative days.

Primary Outcome

Table 3 details the immediate and 90-day adverse events between study groups. Altogether, 42.2% of patients were diagnosed with POAF, with a significantly higher incidence in the prolonged SIRS group. In a univariate analysis, prolonged SIRS was an independent risk factor for POAF (odds ratio [OR] 4.5, 95% CI 1.2-17.3). In a multivariate analysis of the independent significant baseline, perioperative and ICU characteristics, prolonged SIRS (OR 6.7, 95% CI 1.4-32.9) was a strong risk factor for POAF, when increasing age, active smoking, delayed ventilation, length of the ICU stay, and transfusion during hospitalization also were included in the model. Prolonged SIRS did not reach statistical significance to predict POAF at 90 days.

Immediate postoperative stroke and TIA incidence (3.8%) were significantly higher in the prolonged SIRS group (Table 3), and in a univariate analysis transfusion (OR 12.2, 95% CI 1.5-98.0), prolonged SIRS (OR 7.3, 95% CI 1.7-31.1) and peripheral artery disease (OR 6.9, 95% CI 1.3-37.0) were strong independent risk factors for stroke and TIA. Prolonged SIRS was still an independent risk factor for stroke and TIA occurrence at 90 days in a univariate analysis (OR 4.5, 95% CI 1.1-18.0).

Prolonged SIRS was an independent risk factor for mortality at 90 days in a univariate analysis (OR 10.7, 95% CI 1.7-68.8). After excluding patients with chronic pulmonary disease (n = 45), prolonged SIRS (n = 12) remained an independent predictor of stroke and TIA as well as mortality at 90 days (OR 6.3, 95% CI 1.5-26.7 and OR 14.5, 95% CI 2.2-97.0, respectively) in a univariate analysis.

Biomarker Profiling and Prolonged SIRS

An array of 48 cytokines was run from preoperative plasma to identify immunologic characteristics in patients who developed prolonged SIRS (Supplementary Table S1).

Nerve growth factor (NGF) and interleukin 3 (IL-3) levels were significantly higher, whereas interleukin 5 (IL-5), interleukin 17 (IL-17), eotaxin, basic fibroblast growth factor (FGF-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage inflammatory-protein (MIP-1α) levels were significantly lower in prolonged SIRS group compared with patients not progressing with prolonged SIRS (Fig 2).

Preoperative NGF (area under the curve [AUC] 0.7, 95% CI 0.6-0.8, p = 0.007) and IL-3 (AUC 0.7, 95% CI 0.5-0.8, p = 0.043) positively predicted prolonged SIRS, whereas IL-5 (AUC 0.3, 95% CI 0.2-0.4, p = 0.0014), IL-17 (AUC 0.3, 95% CI 0.2-0.5, p = 0.0496), eotaxin (AUC 0.3, 95% CI 0.1-0.4, p = 0.005), FGF-2 (AUC 0.3, 95% CI 0.2-0.4, p = 0.011), GM-CSF (AUC 0.3, 95% CI 0.2-0.5, p = 0.033), and MIP-1α (AUC 0.3, 95% CI 0.2-0.5, p = 0.044) had a negative

Table 1
Baseline Characteristics of the Study Cohorts

	Prolonged SIRS n = 17	No Prolonged SIRS n = 244	p Value	OR (95% CI)	p Value
Age	70 (67-76)	67 (60-73)	0.15	1.06 (0.97-1.06)	0.54
BMI	26 (24-32)	28 (25-31)	0.79	1.0 (0.90-1.11)	0.99
Preoperative eGFR	67 (20)	74 (62-86)	0.19	0.98 (0.96-1.01)	0.18
Female	6 (35.3%)	47 (19.3%)	0.12	2.29 (0.81-6.5)	0.12
Treatment for dyslipidemia	11 (64.7%)	165 (67.6%)	0.80	0.88 (0.31-2.46)	0.80
Treatment for diabetes II	3 (17.6%)	63 (25.8%)	0.57	0.62 (0.17-2.21)	0.46
Treatment for diabetes I	1 (5.9%)	11 (4.5%)	0.56	1.32 (0.16-10.91)	0.79
Treatment for hypertension	14 (82.4%)	194 (79.5%)	1	1.2 (0.33-4.35)	0.78
Heart failure	5 (29.4%)	30 (12.3%)	0.060	2.97 (0.98-9.03)	0.06
Preoperative atrial fibrillation	5 (29.4%)	53 (21.7%)	0.55	1.5 (0.51-4.45)	0.46
Coronary artery disease	8 (47.1%)	154 (63.1%)	0.19	0.52 (0.19-1.4)	0.19
Previous myocardial infarction	7 (41.2%)	57 (23.4%)	0.14	2.30 (0.84-6.31)	0.11
Recent myocardial infarction	3 (17.6%)	34 (13.9%)	0.72	1.32 (0.36-4.85)	0.67
Active endocarditis	0 (0%)	3 (1.2%)	1	NA	1.0
Prior PCI	0 (0%)	35 (14.3%)	0.14	NA	1.0
Prior stroke	2 (11.8%)	27 (11.1%)	1	1.07 (0.23-4.94)	0.93
Carotid artery disease	0 (0.0%)	7 (2.9%)	1	NA	1.0
Peripheral artery disease	1 (5.9%)	10 (4.1%)	0.53	1.46 (0.18-12.15)	0.73
Pulmonary artery hypertension	9 (52.9%)	76 (31.1%)	0.064	2.49 (0.92-6.69)	0.07
Chronic lung disease	5 (29.4%)	22 (9.0%)	0.021	4.21 (1.36-13.04)	0.01
Active smoking	1 (6.3%)	43 (17.8%)	0.32	0.31 (0.04-2.4)	0.26
Ex-smoker	8 (50.0%)	102 (42.0%)	0.53	1.38 (0.5-3.81)	0.53
Obstructive sleep apnea	2 (11.8%)	22 (9.0%)	0.66	1.35 (0.29-6.27)	0.71
CPAP	2 (11.8%)	11 (4.5%)	0.20	2.82 (0.57-13.91)	0.20
Any malignancy	5 (29.4%)	33 (13.5%)	0.082	2.66 (0.88-8.05)	0.08
Autoimmune disease*	2 (11.8%)	40 (16.4%)	1	0.68 (0.15-3.09)	0.62
Chronic dialysis	0 (0%)	4 (1.7%)	1	NA	1.0

NOTE. Prolonged SIRS is defined as a systemic inflammatory response lasting for 4 days postoperatively. Cross-table and univariate logistic regression risk factors are for prolonged SIRS.

Continuous variables are reported as median and IQR or mean and SD. Categorical variables are reported as counts and percentages. Binary logistic regression: odds ratio with 95% CI.

Abbreviations: BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; eGFR, estimated glomerular filtration rate; OR, odds ratio; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome.

* Autoimmune disease: composite variable for hypothyroidism, inflammatory bowel disease, rheumatoid arthritis, psoriatic arthropathy, and systemic lupus erythematosus.

prediction value to prolonged SIRS (Fig 3). In the generalized linear model with age and sex as adjusted variables, preoperative NGF was associated with higher and IL-5 with lower prolonged SIRS risk (OR 5.6, 95% CI 1.4-23.2, p = 0.018 and OR 0.7, 95% CI 0.4-1.0, p = 0.037, respectively).

Discussion

This study aimed to systematically observe clinical markers and biomarker activity for inadequate adaptation to postoperative systemic inflammatory response in patients undergoing cardiac surgery on CPB. There were several findings: (1) Postoperative SIRS criteria were fulfilled in most patients at some time point; therefore, tracking clinical markers many days instead of a single time point or tracking prolonged SIRS helped to identify the high-risk patients; (2) prolonged SIRS was an independent risk factor for POAF, and for stroke and mortality within 90 days; and (3) NGF and IL-5 biomarkers preoperatively predicted prolonged SIRS.

Cardiac surgery is the culmination of major surgery and, thus, physiologic stress. On top of the tissue trauma, endotoxemia, and ischemia-reperfusion injury, the artificial CPB circuit provokes systemic inflammation through complement and cytokine activation,[8] which in turn induces higher tissue permeability and amplified inflammation.[9] Pulsatile and linear CPB induce a higher peak in cytokine activity postoperatively compared with off-pump procedures.[10]

More than 90% of critically ill patients are SIRS-positive at some time point in the ICU setting,[11] and every fourth surgical patient manifests at least 2 SIRS criteria due to causes other than infection in a standard care ward.[12] This study suggested that observing clinical markers of inflammatory state on more than 1 POD enhances the accuracy in differentiating between beneficial and pathologic host response.

Interestingly, a higher SIRS score on the first 4 PODs has been reported to correlate with longer ICU stay, a higher risk of multiple organ dysfunction, and mortality postoperatively,[2] although cardiothoracic surgery was excluded. The few studies on patients undergoing cardiac surgery found that patients with 3 or more SIRS criteria on the first POD had a higher in-hospital mortality,[13] and SIRS on the first POD predicted poor in-hospital composite outcome, including death.[14] This study

Table 2
Surgical Characteristics of the Study Cohorts

	Prolonged SIRS n = 17	No Prolonged SIRS n = 244	p Value	OR (95% CI)	p Value
Elective surgery	13 (76.5%)	206 (84.4%)	0.49	0.6 (0.19-1.94)	0.39
Urgent surgery	4 (23.5%)	34 (13.9%)	0.29	1.9 (0.59-6.17)	0.29
Emergency/salvage surgery	0 (0.0%)	4 (1.6%)	1	NA	1.0
Type of procedure					
AVR biologic prosthesis/mechanical prosthesis	8 (47.1%)	79 (32.4%)	0.29	1.86 (0.69-5.0)	0.22
CABG	8 (47.1%)	148 (60.7%)	0.27	0.58 (0.22-1.55)	0.27
Isolated CABG	7 (41.2%)	112 (45.9%)	0.71	0.83 (0.3-2.24)	0.71
MVP	1 (5.9%)	20 (8.2%)	1	0.7 (0.09-5.56)	0.74
MVR	0 (0.0%)	10 (4.1%)	1	NA	1.0
Surgery on the ascending aorta	1 (5.9%)	24 (9.8%)	1	0.57 (0.07-4.51)	0.6
David procedure	0 (0%)	4 (1.6%)	1	NA	1.0
Bentall-DeBono procedure	2 (11.8%)	13 (5.3%)	0.25	2.37 (0.49-11.48)	0.28
Maze procedure	0 (0%)	8 (3.3%)	1	NA	1.0
Pericardiectomy	0 (0%)	3 (1.2%)	1	NA	1.0
LAA closure	0 (0%)	36 (14.8%)	0.14	NA	1.0
Other procedures	0 (0%)	4 (1.6%)	1	NA	1.0
Indications for CABG					
Stable angina	2 (11.8%)	84 (34.4%)	0.055	0.25 (0.06-1.14)	0.07
Unstable angina, NSTEMI or STEMI	6 (35.3%)	64 (26.2%)	0.41	1.53 (0.55-4.32)	0.42
Surgery length (min)	226 (49)	228 (199-265)	0.63	1.0 (0.99-1.01)	0.58
Aortic cross-clamping time (min)	86 (22)	89 (73-108)	0.50	0.99 (0.97-1.01)	0.43
Cardiopulmonary bypass time (min)	116 (28)	115 (100-140)	0.72	1.0 (0.98-1.01)	0.54
Antegrade cardioplegia	17 (100%)	237 (98.3%)	1	NA	1.0
Retrograde cardioplegia	6 (37.5%)	76 (31.7%)	0.63	1.3 (0.45-3.69)	0.63
Delayed ventilation*	0 (0%)	23 (9.5%)	0.38	NA	1.0
Duration of mechanical ventilation (h)	8.5 (5.5-14.3)	6.0 (4.5-11.5)	0.34	0.99 (0.96-1.02)	0.53
Norepinephrine† (mg)	5.5 (2.3-12.7)	3.3 (1.4-10.5)	0.30	1.0 (0.97-1.01)	0.64
Epinephrine† (mg)	0.7 (0.4-NA)	0.2 (0.1-1.1)	0.37	1.27 (0.17-9.59)	0.82
Milrinone† (mg)	4.0 (4.0-12.2)	3.0 (2.7-6.0)	0.12	1.0 (0.95-1.04)	0.69
Levosimendan† (mg)	11.3 (10.7-17.0)	12.0 (11.1-21.8)	0.28	0.9 (0.75-1.09)	0.28
Cardiac output min (L/min)	2.8 (2.1-3.8)	3.2 (2.6-3.9)	0.23	0.67 (0.37-1.2)	0.18
Cardiac output max (L/min)	5.2 (4.6-6.2)	5.6 (4.5-6.5)	0.60	0.9 (0.63-1.29)	0.57
Euroscore II	2% (1%-3%)	1% (1%-2%)	0.08	1.17 (0.93-1.46)	0.173
Hb (g/L)					
I POD	104.3 (10.6)	105.0 (98.0-116.0)	0.67	0.99 (0.95-1.03)	0.51
II POD	96.8 (8.8)	98.0 (88.5-107.0)	0.63	0.99 (0.95-1.03)	0.47
III POD	94.0 (9.7)	95.0 (87.0-105.0)	0.70	0.98 (0.94-1.03)	0.43
IV POD	94.6 (8.5)	94.0 (89.0-104.0)	0.70	0.98 (0.94-1.03)	0.38
Blood products administered during hospitalization					
Packed red blood cells	10 (58.8%)	100 (42.0%)	0.18	1.97 (0.73-5.36)	0.18
Fresh frozen plasma	5 (55.6%)	53 (32.1%)	0.16	2.64 (0.68-10.24)	0.16
Platelets	4 (50.0%)	65 (36.7%)	0.47	1.72 (0.42-7.12)	0.45
ICU variables					
Length of ICU stay (h)	23 (22-25)	24 (22-26)	0.91	0.99 (0.97-1.01)	0.47
Total intravenous fluids (mL)	3,237 (2,891-4,168)	3,011 (2,470-3,924)	0.15	1.0 (1.0-1.001)	0.21
Chest drain output (mL 12 h)	417 (295-510)	400 (290-620)	0.88	1.0 (0.998-1.001)	0.45
Diuresis (mL 12 h)	1,899 (649)	1,910 (1,599-2,376)	0.57	1.0 (0.999-1.001)	0.59

NOTE. Prolonged SIRS is defined as a systemic inflammatory response lasting for 4 days postoperatively. Crosstable and univariate logistic regression risk factors for prolonged SIRS. Continuous variables are reported as median and IQR or mean and SD. Categorical variables are reported as counts and percentages. Binary logistic regression: Odds ratio with 95% CI.

Abbreviations: AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LAA, left atrial appendix; MVP, mitral valve repair; MVR, mitral valve replacement; NA, not available; NSTEMI, non-ST-elevation myocardial infarction; POD, postoperative day; STEMI, ST-elevation myocardial infarction.

* Delayed ventilation >24 hours.

† Total dose.

showed an association with not only in-hospital, but also 90-day morbidity and mortality, when observing prolonged inflammation, although the results may be viewed with caution due to the small event rate in both groups. The idea of cumulative SIRS calculations was supported in a subgroup analysis of the raw data, in which individual SIRS-positive days did not similarly predict adverse events (data not shown).

Table 3
Postoperative Outcome

	Prolonged SIRS n = 17	No Prolonged SIRS n = 244	p Value	OR (95% CI)	p Value
Index hospitalization					
Death*	NA	2 (0.8%)	NA	NA	NA
POAF†	9 (75.0%)	76 (39.8%)	0.016	4.54 (1.19-17.31)	0.027
Cardioversion	2 (11.8%)	13 (5.3%)	0.25	2.37 (0.49-11.48)	0.28
Stroke and TIA	3 (17.6%)	7 (2.9%)	0.021	7.26 (1.69-31.12)	0.008
Stroke	3 (17.6%)	6 (2.5%)	0.015	8.5 (1.92-37.6)	0.005
TIA	0 (0%)	1 (0.4%)	1	NA	1.0
Postoperative pneumonia	2 (11.8%)	10 (4.1%)	0.18	3.12 (0.68-15.54)	0.17
Deep sternal wound infection/mediastinitis	0 (0%)	6 (2.5%)	1	NA	1.0
Reoperation for bleeding	2 (11.8%)	20 (8.2%)	0.64	1.49 (0.32-7.0)	0.61
De novo dialysis	0 (0%)	1 (0.4%)	1	NA	1.0
All adverse events	14 (82.4%)	125 (51.2%)	0.013	4.44 (1.25-15.85)	0.022
Length of hospital stay (d)	10 (8-16)	8 (7-11)	0.008	–	–
Heart rhythm at the time of discharge:					
Sinus rhythm	10 (58.8%)	188 (77.7%)	0.13	0.41 (0.15-1.13)	0.09
Atrial fibrillation or flutter	7 (41.2%)	49 (20.2%)	0.063	2.76 (0.999-7.61)	0.050
Other‡	0 (0%)	5 (2.1%)	1	NA	1.0
Events within 90 d					
NOAF after index hospitalization	4 (25.0%)	52 (21.6%)	0.76	1.21 (0.38-3.91)	0.75
Permanent anticoagulation	9 (56.3%)	55 (22.8%)	0.006	4.35 (1.55-12.21)	0.005
Myocardial infarction	0 (0%)	1 (0.4%)	1	NA	1.0
Stroke and TIA	3 (17.6%)	11 (4.5%)	0.055	4.5 (1.13-17.99)	0.033
Death	2 (11.8%)	3 (1.2%)	0.036	10.67 (1.65-68.77)	0.013
Composite outcome§	3 (17.6%)	14 (5.8%)	0.089	3.51 (0.9-13.64)	0.07

NOTE. Prolonged SIRS is defined as a systemic inflammatory response lasting for 4 days postoperatively. Crosstable and univariate logistic regression. In logistic regression, outcomes are predicted, and prolonged SIRS is observed. Continuous variables are reported as median and IQR or mean and SD. Categorical variables are reported as counts and percentages. Binary logistic regression: Odds ratio with 95% CI.

Abbreviations: NOAF, new-onset atrial fibrillation; POAF, postoperative atrial fibrillation; SIRS, systemic inflammatory response syndrome; TIA, transient ischemic attack.

* Patients deceased during index hospitalization were excluded.

† Patients with preoperative atrial fibrillation or atrial flutter were excluded from the variable.

‡ Pacemaker or junctional rhythm.

§ 90-day stroke, TIA, myocardial infarction, and death.

Atrial fibrillation is common after cardiac surgery, and carries an increased long-term risk of stroke and mortality after both isolated coronary artery bypass grafting (CABG) and CABG with concomitant procedures.[15,16] Postoperative atrial fibrillation increased 1-year mortality risk after both on-pump and off-pump cardiac surgery without a difference in occurrence postoperatively.[17] Inflammation activation, specifically complement and cytokine activation, enhances AF susceptibility,[18] and this study observed an unadaptive inflammation response to increase the risk 4-fold.

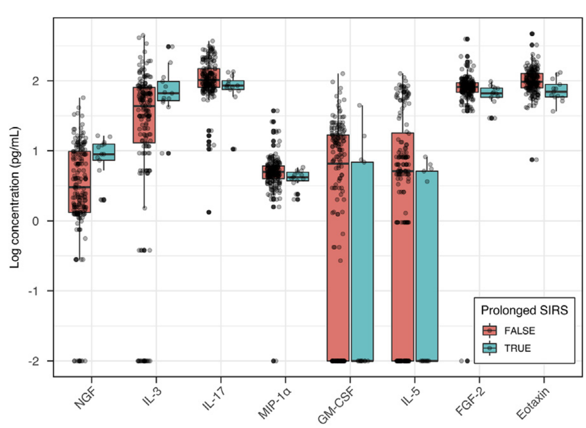

Fig 2. Significant differences in preoperative cytokine concentrations from the 48-cytokine discovery panel in patients with and without subsequent prolonged systemic inflammatory response syndrome. FGF-2, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3; MIP-1α, macrophage inflammatory-protein; NGF, nerve growth factor.

Prolonged SIRS and transfusion were the 2 major predictors of stroke within 90 days. CPB-related stroke has been largely studied, and off-pump CABG has been associated with a significant reduction in stroke incidence in observational studies; however, interestingly, randomized controlled trials did not support this.[19] Moreover, a large systematic review showed no increases in mortality, myocardial infarction, or stroke rate with CPB compared to off-pump.[20] Transfusion or postoperative hemoglobin levels did not differ between SIRS-positive and SIRS-negative, nor did they predict prolonged SIRS. Prolonged SIRS might be considered a new risk factor for postoperative stroke independent of CPB and red blood cell transfusion.

The aim of biomarker profiling was to discover patients at risk for an inadequate adaptation to a systemic inflammatory stimulus. Preoperative NGF and IL-5 showed promising predictions of prolonged SIRS, but these results need to be

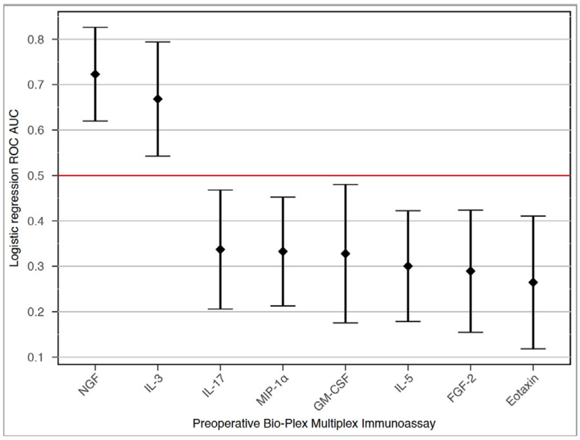

Fig 3. Receiver operating characteristics values and confidence intervals of the significant preoperative cytokine levels predicting prolonged systemic inflammatory response syndrome. FGF-2, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3; MIP-1α, macrophage inflammatory-protein; NGF, nerve growth factor; ROC AUC, receiver operating characteristic area under the curve.

validated in an independent cohort. NGF is a multifunctional, autocrine neurotrophin that is vital to the angiogenesis of endothelium, smooth muscle cells, and cardiomyocytes,[21] and promotes cardiovascular cell survival as proangiogenic after ischemia and infarction.[22] NGF synthesized by various granulocytes and lymphocytes increases IL-6 production seen in autoinflammatory diseases.[23] The higher preoperative NGF concentrations with prolonged SIRS patients in the present study were not autoimmune disease−related, as there was no difference in disease profiles at baseline. IL-5 has cardiomyocyte-protective qualities after myocardial infarction[24]; interestingly, patients with preoperatively lower IL-5 levels more often developed prolonged SIRS in the present study. Notably, IL-6, IL-8, or tumor necrosis factor levels (inflammatory cytokines that respond to CBP and amplify the injury cascade[25]) did not predict prolonged SIRS.

The strength of the study was the prospective setting with a relatively high number of variables and biomarkers per patient and a successful 90-day follow-up, compared with previous studies with smaller cohorts.[10,26] Patient groups were similar at baseline, perioperatively, and in the ICU setting, excluding the incidence of chronic lung disease. Chronic inflammation promotes autophagy in chronic lung disease, especially with smokers,[27] but there were no differences in smoking habits. Although chronic lung disease was a predictive variable for prolonged SIRS, excluding these patients at baseline still showed a significantly higher rate of stroke and mortality in the prolonged SIRS group within 90 days.

There were a few limitations in the study. The incidence of postoperative stroke and TIA was low (3.8% in total); however, this rate was in line with the modern postcardiac surgery ischemic stroke rate of about 2.0%.[28,29] This study did not differentiate between thromboembolic and hemorrhagic stroke events. Previous stroke predisposes to a higher risk of postoperative stroke,[30] and the current study did not exclude patients with previous stroke. Preoperative blood samples were taken on the morning of the surgery after fasting or in an emergency setting. Fast-acting cytokine levels might have been affected by the difference in collection times. The study setting was observational, which is why a strong correlation between prolonged SIRS and adverse events and biomarkers and prolonged SIRS prediction needs to be validated in a larger cohort.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2023.12.017.

References

1 Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644–55.
2 Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: Effect of intensive care unit resuscitation. Arch Surg 1999;134:81–7.
3 Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: Incidence, morbidities and outcomes in surgical ICU patients. Intensive Care Med 1995;21:302–9.
4 Zakkar M, Ascione R, James AF, et al. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. Pharmacol Ther 2015;154:13–20.
5 Alazawi W, Pirmadjid N, Lahiri R, et al. Inflammatory and immune responses to surgery and their clinical impact. Ann Surg 2016;264:73–80.
6 Dieleman JM, Peelen LM, Coulson TG, et al. Age and other perioperative risk factors for postoperative systemic inflammatory response syndrome after cardiac surgery. Br J Anaesth 2017;119:637–44.
7 Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840–51.
8 Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–44.
9 Williams AT, Muller CR, Govender K, et al. Control of systemic inflammation through early nitric oxide supplementation with nitric oxide releasing nanoparticles. Free Radic Biol Med 2020;161:15–22.
10 Onorati F, Rubino AS, Nucera S, et al. Off-pump coronary artery bypass surgery versus standard linear or pulsatile cardiopulmonary bypass: Endothelial activation and inflammatory response. Eur J Cardiothorac Surg 2010;37:897–904.
11 Sprung CL, Sakr Y, Vincent JL, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely ill Patients (SOAP) study. Intensive Care Med 2006;32:421–7.
12 Ratzinger F, Schuardt M, Eichbichler K, et al. Utility of sepsis biomarkers and the infection probability score to discriminate sepsis and systemic inflammatory response syndrome in standard care patients. PLoS One 2013;8:e82946.
13 MacCallum NS, Finney SJ, Gordon SE, et al. Modified criteria for the systemic inflammatory response syndrome improves their utility following cardiac surgery. Chest 2014;145:1197–203.
14 Squiccimarro E, Labriola C, Malvindi PG, et al. Prevalence and clinical impact of systemic inflammatory reaction after cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:1682–90.
15 Kerwin M, Saado J, Pan J, et al. New-onset atrial fibrillation and outcomes following isolated coronary artery bypass surgery: A systematic review and meta-analysis. Clin Cardiol 2020;43:928–34.
16 Megens MR, Churilov L, Thijs V. New-onset atrial fibrillation after coronary artery bypass graft and long-term risk of stroke: A meta-analysis. J Am Heart Assoc 2017;6:e007558.
17 Almassi GH, Pecsi SA, Collins JF, et al. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: A report from the Randomized On Versus Off Bypass trial. J Thorac Cardiovasc Surg 2012;143:93–102.
18 Maesen B, Nijs J, Maessen J, et al. Post-operative atrial fibrillation: A maze of mechanisms. Europace 2012;14:159–74.
19 Alston RP. Brain damage and cardiopulmonary bypass: Is there really any association? Perfusion 2011;1:20–6.
20 Møller CH, Penninga L, Wetterslev J, et al. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: Systematic review with meta-analyses and trial sequential analyses. Eur Heart J 2008;29:2601–16.
21 Caporali A, Emanueli C. Cardiovascular actions of neurotrophins. Physiol Rev 2009;89:279–308.
22 Pius-Sadowska E, Machaliński B. Pleiotropic activity of nerve growth factor in regulating cardiac functions and counteracting pathogenesis. ESC Heart Fail 2021;8:974–87.
23 Stanisz AM, Stanisz JA. Nerve growth factor and neuroimmune interactions in inflammatory diseases. Ann N Y Acad Sci 2000;917:268–72.
24 Xu JY, Xiong YY, Tang RJ, et al. Interleukin-5-induced eosinophil population improves cardiac function after myocardial infarction. Cardiovasc Res 2022;118:2165–78.
25 Hill GE, Whitten CW, Landers DF. The influence of cardiopulmonary bypass on cytokines and cell-cell communication. J Cardiothorac Vasc Anesth 1997;11:367–75.
26 Parolari A, Camera M, Alamanni F, et al. Systemic inflammation after on-pump and off-pump coronary bypass surgery: A one-month follow-up. Ann Thorac Surg 2007;84:823–8.
27 Racanelli AC, Kikkers SA, Choi AMK, et al. Autophagy and inflammation in chronic respiratory disease. Autophagy 2018;14:221–32.
28 Sultan I, Bianco V, Kilic A, et al. Predictors and outcomes of ischemic stroke after cardiac surgery. Ann Thorac Surg 2020;110:448–56.
29 Gaudino M, Rahouma M, Di Mauro M, et al. Early versus delayed stroke after cardiac surgery: A systematic review and meta-analysis. J Am Heart Assoc 2019;8:e012447.
30 Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: An updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2011;41:607–24.