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INFECTIOUS COMPLICATIONS AND IMMUNE/INFLAMMATORY RESPONSE IN CARDIOGENIC SHOCK PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT—**Introduction:** Patients with cardiogenic shock (CS) are at a high risk of developing infectious complications; however, their early detection is difficult, mainly due to a frequently occurring noninfectious inflammatory response, which accompanies an extensive myocardial infarction (MI) or a postcardiac arrest syndrome. The goal of our prospective study was to describe infectious complications in CS and the immune/inflammatory response based on a serial measurement of several blood-based inflammatory biomarkers. **Methods:** Eighty patients with CS were evaluated and their infections were monitored. Inflammatory markers (C-reactive protein, procalcitonin, pentraxin 3, presepsin) were measured seven times per week. The control groups consisted of 11 patients with ST segment elevation myocardial infarction without CS and without infection, and 22 patients in septic shock. **Results:** Infection was diagnosed in 46.3% of patients with CS; 16 patients developed an infection within 48 h. Respiratory infection was most common, occurring in 33 out of 37 patients. Infection was a significant or even the main reason of death only in 3.8% of all patients with CS, and we did not find statistically significant difference in 3-month mortality between group of patients with CS with and without infection. There was no statistically significant prolongation of the duration of mechanical ventilation associated with infection. Strong inflammatory response is often in patients with CS due to MI, but we found no significant difference in the course of the inflammatory response expressed by evaluated biomarkers in patients with CS with and without infection. We found a strong relationship between the elevated inflammatory markers (sampled at 12 h) and the 3-month mortality: the area under the curve of receiver operating characteristic ranged between 0.683 and 0.875. **Conclusion:** The prevalence of infection in patients with CS was 46.3%, and respiratory tract infections were the most common type. Infections did not prolong statistically significantly the duration of mechanical ventilation and did not increase the prevalence of hospital mortality in this high-risk CS population. CS due to acute myocardial infarction was accompanied by a strong and highly variable inflammatory response, but it did not reach the intensity of the inflammatory response observed in patients with septic shock. An extensive immune/inflammatory response in patients with CS is linked to a poor prognosis.

KEYWORDS—Cardiogenic shock, C-reactive protein, infection, inflammatory response, pentraxin 3, presepsin, procalcitonin

INTRODUCTION

The in-hospital mortality of patients with cardiogenic shock (CS) remains high (between 54% and 63%), though routine revascularization by primary percutaneous coronary intervention (PCI) led to a slight but significant decrease in mortality (1–3). In general, infectious complications raise the hospital mortality of

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critically ill patients (4). Patients with CS are at a particularly high risk of developing infection: according to recent publications dealing with CS, as much as 45% of patients with CS have undergone cardiopulmonary resuscitation (CPR) (5), and the risk of bronchoaspiration and the subsequent development of aspiration pneumonia is estimated at up to one-third of these patients (6); patients who have undergone CPR are treated with hypothermia, which increases the risk of respiratory infection and sepsis (6); 90% of patients with CS are treated with mechanical ventilation, which increases the risk of ventilator-associated respiratory infection (7); multiple invasive access sites increase the risk of infection in patients with CS (8); and severe congestive heart failure in patients with CS facilitates the development of respiratory infection (9). A recently published study of patients with acute heart failure suggested that an adequate and timely initiated antibiotic therapy of infection can improve the patients' prognosis (10). In clinical practice, inflammatory markers such as C-reactive protein (CRP), procalcitonin or newly identified presepsin (soluble CD14 subtype) (11), and pentraxin 3 (PTX3) (12) contribute to an early suspicion of infection. A single determination of inflammatory markers in patients with CS with acute myocardial infarction (MI) is of limited significance with respect to suspicion of infection because these patients develop an aseptic inflammatory response either as part of their immune response (in reaction to an extensive tissue damage in MI) (13), or as part of the postcardiac arrest syndrome after CPR (14).

The primary outcome of the present study was to describe infectious complications in patients with CS, and to describe the immune/inflammatory response and its influence on the short-term prognosis using four different inflammatory biomarkers depending on the development of infection. Patients hospitalized with septic shock (patients with an extreme inflammatory response and with a confirmed severe infection) and patients with ST segment elevation myocardial infarction (STEMI) without CS and without infection were evaluated as control groups for the description of the immune response using the time course of inflammatory biomarkers in comparison with patients with CS.

METHODS

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital Brno (Czech Republic). Written informed consent forms were obtained from the patients either before their participation in the study, or after regaining consciousness. For patients who failed to regain consciousness, anonymous data were processed with the consent of a relative.

The study cohort involved patients with CS and acute coronary syndrome hospitalized in the Coronary Care Unit at the Department of Cardiology of the University Hospital Brno, whereas patients with septic shock were hospitalized in the Intensive Care Unit of the University Hospital Brno.

Patients with CS were included in the study between January 2006 and June 2011. A total of 131 patients were screened; the exclusion criteria were as follows: ongoing resuscitation since the time of admission without return of spontaneous circulation (15 patients), nonconfirmation of acute MI as the cause of the state of shock (22 patients), nonacquisition of the study consent form (3 patients), malignancy (8 patients), and inflammatory disease or connective tissue disease (3 patients).

The diagnosis of acute MI (type 1 according to the Third Universal Definition of Myocardial Infarction (15)) was based on the rise or fall of markers of myocardial necrosis (high-sensitive cardiac troponin T), with at least one of the following: symptoms consistent with MI; ECG changes (new or presumably new significant ST-T wave abnormalities, new left bundle branch block, or a newly developed pathological Q wave); imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality; and identification of an intracoronary thrombus. The diagnosis of acute heart failure was assessed according to clinical signs upon hospital admission and/or during hospitalization (Killip class I–IV). CS was defined as hypotension with systolic blood pressure (SBP) at most 90 mmHg lasting at least 30 min despite adequate left ventricular filling (pulmonary capillary wedge pressure or left ventricle end-diastolic pressure >15 mmHg) or if the patient required vasopressor therapy (dopamine ≥ 7 μg/kg/min or norepinephrine ≥ 0.15 μg/kg/min) more than 30 min to keep SBP at least 90 mmHg due to heart failure confirmed by a low cardiac index less than 2 L/min/m^2 or by echocardiography (left ventricular dysfunction with ejection fraction $<40\%$, acute mitral regurgitation or acute septal defect); or if patients had signs of tissue hypoperfusion (oliguria <20 mL/h; mottled and cold skin; signs of encephalopathy; acidosis or blood lactate >2.2 mmol/L) (16, 17). Septic shock was defined as hypotension with SBP at most 90 mmHg despite adequate volume resuscitation (intravenous crystalloids ≥ 30 mL/kg) in patients with confirmed sepsis and after exclusion of other reasons for hypotension (18).

The final diagnosis of infection was established in accordance with CDC criteria for infections (19) based on the consensus of two independent physicians who had all patients' medical records, results of cultivation tests, and standard laboratory tests, including the blood count and the levels of CRP and procalcitonin (if these were performed as part of standard care, not results of series measurements performed as part of the study).

A prospective follow-up to screen for symptoms and signs of infections during hospitalization was based on the following protocol: collection of tracheal aspirates, swab samples from the nose and throat, and urine samples for microbiological testing were done routinely on the first day of mechanical ventilation in all patients and then regularly twice a week. If an infection was suspected, repeated collections and cultivations of samples were undertaken (tracheal aspirates, bronchoalveolar lavage fluid [BALF], urine, blood cultures—three samples taken within 1.5 h) to identify microorganisms and the source of infection. An infection of the respiratory tract (pneumonia or infection of the lower respiratory tract) was suspected in the presence of fever, expectoration or aspiration of purulent sputum, wheezing or rales upon physical examination, and new radiographic pulmonary infiltrates (chest x-ray was performed when lung infection was suspected). An infection of urinary tract was suspected in the presence of fever with dysuria together with bacteriuria and leukocyturia. Sepsis and bloodstream infection were suspected in the presence of shivers, fever, hemodynamic deterioration, and progression of hypotension with oliguria. If a primary infection of the bloodstream was suspected, the intravenous cannula/central venous catheter was removed and the tip was cultivated. Similarly, tips of urine catheters and urine samples were tested if a urinary infection was suspected. Samples for microbiological testing were collected before the initiation of antibiotic therapy (20).

Standardized prophylactic antibiotic regimens were not used. Antibiotic therapy was initiated according to decision of the treating physician if there was a high clinical suspicion of infection accompanied by an inflammatory response (temperature $>38^\circ$C).

In all patients, the onset of systemic inflammatory response syndrome (SIRS) was evaluated according to temperature more than 38°C and white blood cell count more than 12,000/μL. Other criteria (heart rate >90/min and respiratory rate >20/min) used in SIRS in patients with CS and on mechanical ventilation were not appropriate; this methodology was previously published by SHOCK Investigators (13).

Laboratory methods

Samples of venous blood for the determination of inflammatory biomarkers were drawn at seven time points: sample 1 (upon hospital admission), sample 2 (12 h after hospital admission), sample 3 (24 h after hospital admission), sample 4 (morning of the third day; $\approx$48 h after hospital admission), sample 5 (morning of the fourth day; $\approx$72 h after hospital admission), sample 6 (morning of the fifth day; $\approx$96 h after hospital admission), and sample 7 (morning of the seventh day).

Samples were centrifuged within less than 10 min in a refrigerated centrifuge. Plasma and serum were stored at -80°C. The refrigerated centrifuge and freezer were located in the Intensive/Coronary Care Unit. Standard biochemical and hematological blood tests were performed immediately upon hospital admission, and then each day in the morning, or depending on the patient's condition.

All laboratory methods were undertaken according to the manufacturer's instructions of the assay kits. Cardiac troponin T levels (Roche Diagnostics, Indianapolis, Ind) were assessed 24 h after the onset of chest pain. CRP levels were analyzed by a commercial immunoturbidimetric method using the CRPL3 kit (Roche, Basel, Switzerland) on a Cobas 8000 system. Procalcitonin levels were analyzed using the commercial kit Elecsys BRAHMS PCT (Roche) on a Cobas 8000 system. Plasma concentrations of PTX3 were measured using a

commercially available sandwich enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minn). Presepsin levels were measured using the commercial kit Pathfast (Mitsubishi Chemical Europe, Dusseldorf, Germany).

Statistical analyses

Standard descriptive statistics were used for the analyses. Continuous variables were described by the median value as well as by the 5th and 95th percentiles. Categorical variables were described by counts and percentages. The significance of differences between the two groups was assessed using the Mann-Whitney test for continuous variables and the chi-squared test for categorical variables. The statistical significance of differences between the three groups was assessed using the Kruskal-Wallis test for continuous variables.

Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to determine if the inflammatory biomarkers were good predictors of the 3-month mortality. The level of significance was set at $\alpha = 0.05$. The software SPSS 22.0.0.1 (IBM, Armonk, NY) was used for data analyses.

The peak value of a biomarker means the value at the time of peak according to time-dependent curve of biomarker for all patients.

RESULTS

Baseline characteristics

All patients were Caucasian. The baseline characteristics of 80 patients with CS according to the presence of infection are shown in Table 1. Infection was diagnosed in 37 patients (46.3%). Upon hospital admission, patients with CS with infection had a higher SBP upon admission (100 vs. 90 mmHg; $P = 0.003$) when compared with patients with CS without infection. In the CS group, 87.5% of patients had STEMI, and 12.5% of them had non-STEMI. Patients with CS had often comorbidities such as hypertension (55.0%), diabetes mellitus (43.8%), and/or chronic obstructive pulmonary disease (7.5%). Median value of the left ventricle ejection fraction was 36%, renal replacement therapy was used in 8.8% of patients, therapeutic hypothermia was used in 37.5% of patients, and intra-aortic balloon counterpulsation was used in 48.8% of patients.

Median time between the hospital admission and the onset of infection was 48 h. Three-month mortality was 51.3% (41 out of 80 patients). Kaplan-Meier survival curves (Fig. 1A) showed that a significant number of patients without infection died within the first 24 h, i.e., before the potential onset of infection (15 out of 29 patients who died); Figure 1B shows the prognosis of patients who survived the first 24 h after admission, and in which infection might theoretically develop; no statistically significant differences in survival were found between CS groups with and without infection ($P = 0.557$). Median

TABLE 1. **Baseline demographic and laboratory characteristics of cardiogenic shock patients according to onset of infection**

Variable	CS without infection (n = 43)	CS with infection (n = 37)	*P*
Age	64 (47; 81)	66 (42; 83)	0.839
Women	19 (44.2%)	10 (27.0%)	0.162
BMI, kg/m^2	27.5 (22.0; 32.9)	27.3 (21.7; 37.3)	0.802
Systolic BP upon admission, mmHg	90 (50; 160)	100 (80; 175)	**0.003**
Diastolic BP upon admission, mmHg	60 (30; 85)	70 (50; 100)	**0.001**
HR upon admission, /min	87 (40; 113)	98 (44; 142)	0.107
Systolic BP, minimum, mmHg	65 (40; 90)	75 (50; 85)	0.061
Diastolic BP, minimum, mmHg	40 (20; 60)	40 (30; 55)	0.053
Hypertension	25 (58.1%)	19 (51.4%)	0.653
Diabetes mellitus	21 (48.8%)	14 (37.8%)	0.371
History of MI/PCI/CABG	12 (27.9%)	10 (27.0%)	1.000
COPD	4 (9.3%)	2 (5.4%)	0.681
ACEI/ARBs upon admission	19 (44.2%)	14 (37.8%)	0.655
Beta-blockers upon admission	15 (34.9%)	12 (32.4%)	1.000
CPR before admission	22 (51.2%)	13 (35.1%)	0.179
Time from diagnosis to admission, h	3 (1; 25)	5 (1; 26)	0.148
Time from diagnosis to infection, h	—	48 (10; 247)	—
LVEF, %	35 (16; 66)	34 (15; 61)	0.362
Creatinine, μmol/L	116 (66; 239)	109 (65; 204)	0.172
Natrium, mmol/L	139 (133; 145)	138 (128; 143)	0.246
Potassium, mmol/L	4.1 (2.5; 6.0)	4.0 (2.8; 6.9)	0.949
Troponin T/I peak (relative value)	220.0 (0.0; 1,142.9)	327.4 (3.0; 2,482.1)	0.067
Glycemia, mmol/L	13.0 (5.5; 34.3)	12.4 (5.3; 25.4)	0.189
Hemoglobin, g/L	137 (111; 157)	144 (102; 166)	0.110
Hemoglobin, minimum, g/L	110 (63; 157)	104 (65; 141)	0.256
Leukocytes	16.1 (8.7; 30.3)	15.3 (7.6; 27.9)	0.327
Leukocytes, maximum	20.2 (7.8; 33.8)	18.9 (10.1; 34.7)	0.923
Antibiotics	15 (34.9%)	36 (97.3%)	**0.001**
Mechanical ventilation	37 (86.0%)	34 (91.9%)	0.494
Intra-aortic balloon counterpulsation	21 (48.8%)	18 (48.6%)	1.000
Renal replacement therapy	3 (7.0%)	4 (10.8%)	0.698
Therapeutic hypothermia	19 (44.2%)	11 (29.7%)	0.184
Duration of stay, d	2 (0; 19)	13 (3; 27)	**0.001**

ACEI indicates angiotensin-converting enzyme inhibitor; ARBs, antagonist for the type-2 receptor of angiotensin II; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; LVEDP, left ventricular end-diastolic pressure; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Categorical variables represented as n (%) and continuous variables as median (5th; 95th percentile).
P values from the Kruskal-Wallis test or chi-squared maximum-likelihood test (categorical variables).
Bold values express statistically significant results.

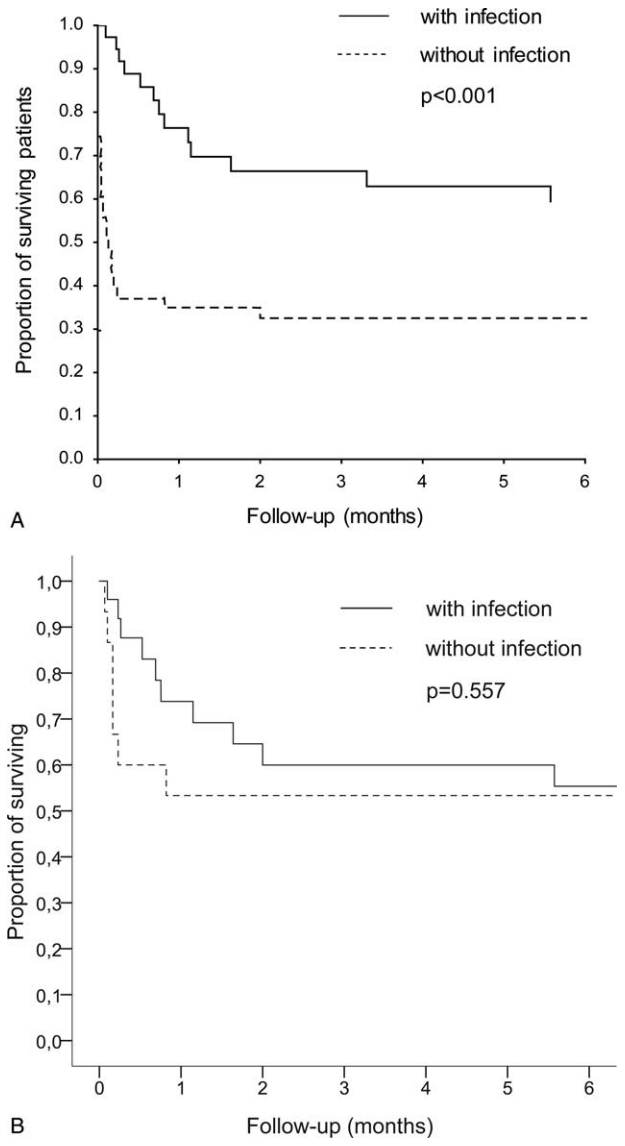

Fig. 1. **Survival of patients with CS according to the diagnosed infection: (A) from admission, and (B) from 24 h after admission.**

duration of hospitalization of patients without infection was shorter (2 days, range 0–19 days) in comparison with those with infection (13 days, range 3–27 days). The observation was done (at least in part) due to a high mortality during the first 24 h. When we compared only patients surviving after 3 months, those with infection tended to have a longer duration of mechanical ventilation (76 h, range 10–245 h) compared with those without infection (48 h, range 5–192 h); nevertheless, the difference was not statistically significant ($P = 0.441$). Thirty-seven patients with CS had an identified infection: 25 patients were diagnosed with a respiratory tract infection (RTI), 6 patients with an RTI and urinary tract infection (UTI), 4 patients with a UTI, and 2 patients with a bloodstream infection and RTI. In six patients, at least two microorganisms were detected.

Out of 37 patients with infection, 16 patients had a diagnosis of infection within 48 h after hospital admission (RTI: 12 cases; UTI: 2 cases; RTI and UTI: 2 cases), 21 patients had a diagnosis of infection after 48 h (RTI: 13 cases; UTI: 2 cases; RTI and UTI: 4 cases; bloodstream infection and RTI: 2 cases). Microorganisms associated with infections in patients with CS according to source are shown in Table 2. Eight patients had ventilator-associated pneumonia (VAP) according to radiographic pulmonary infiltrates accompanied with new massive purulent secretions, fever and leukocyte count more than 12×10^9/L, but did not have positive results of microbiologic testing (cultivation was either not done, or the result was negative due to a previously initiated antibiotic therapy).

According to revision of two independent physicians, infection was a significant or even the main reason of death in three patients (3.8% of all patients with CS). Clinical signs of SIRS were found in 53.8% of all patients, and in 50% of patients without confirmed infection. When we evaluated only patients surviving at least 24 h (i.e., those in which SIRS could have theoretically developed as a consequence of reaction to acute MI with CS), SIRS was reported in 68.8% of all patients with CS.

Time course of biomarkers in CS with respect to infection

Time courses of four inflammatory biomarkers (CRP, procalcitonin, presepsin, and PTX3) in CS according to infection

Table 2. **Microorganisms associated with infections in patients with cardiogenic shock according to the primary source of infection**

Respiratory tract	n	Urinary tract	n	Bloodstream	n
Staphylococcus aureus	7	*Escherichia coli*	6	Coagulase-negative staphylococci	1
Klebsiella pneumoniae	4	*Pseudomonas aeruginosa*	2	*Pseudomonas aeruginosa*	1
Pseudomonas aeruginosa	3	*Candida albicans*	1		
Streptococcus pneumoniae	3	*Proteus mirabilis*	1		
Candida albicans	3	*Klebsiella pneumoniae*	1		
Alpha-hemolytic streptococci	2				
Coagulase-negative staphylococci	2				
Escherichia coli	1				
Haemophilus influenzae	1				
Group C beta-hemolytic streptococci	1				
Unidentified	8				

Eight other patients had ventilator-associated pneumonia according to radiographic infiltrates accompanied with new massive purulent secretions, fever and leukocyte count more than 12×10^9/L, but did not have positive results of microbiologic testing (cultivation was not done or the result was negative due to a previously initiated antibiotic therapy).
Infection was identified in 37 patients with CS: 25 patients with a respiratory tract infection (RTI), 6 patients with an RTI and urinary tract infection (UTI), 4 patients with a UTI, and 2 patients with a bloodstream infection and RTI. In six patients, at least two microorganisms were detected.

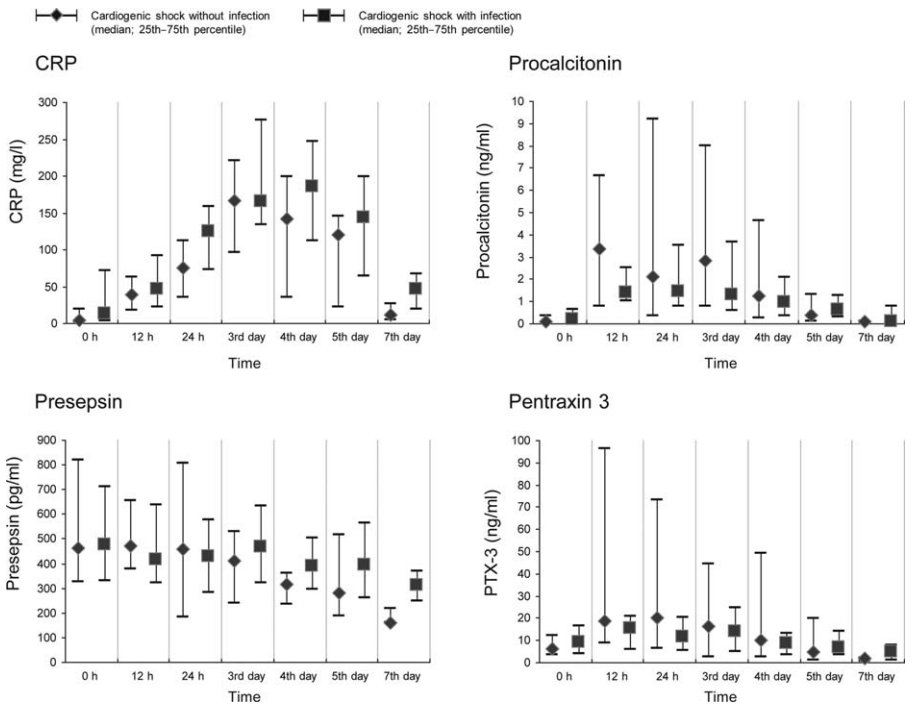

FIG. 2. **Time course of expression of C-reactive protein, procalcitonin, presepsin, and pentraxin 3 in patients with CS according to the presence of infection.**

are shown in Figure 2 and in Supplemental Table 1, http://links.lww.com/SHK/A484.

Peak values of CRP in patients with CS were reached between the mornings of the third and fourth day (≈48–72 h after the onset of MI). In patients with infection, there was a nonsignificant trend toward a faster elevation of CRP at 24 h after admission (65 vs. 120 mg/L; $P = 0.074$), higher and longer sustained values on the fifth day (73 vs. 127; $P = 0.108$) and on the seventh day (12 vs. 48; $P = 0.088$), and later peaks depending on the onset of infection. Patients with infection did not have significantly higher peak values (166 vs. 182 mg/L; $P = 0.124$).

Peak values of procalcitonin were detected earlier (between 12 and 48 h after hospital admission), and there was no significant difference between patients with CS without and with infection (2.1 vs 1.4 ng/mL; $P = 0.325$).

Presepsin reached peak values in both groups of patients with CS irrespective of infection 12 h after admission (429 vs. 527 pg/mL; $P = 0.168$), and decreased after the third day. A nonsignificant trend toward a gradual decrease of presepsin levels was apparent in the group of patients without infection, in contrast to the group of patients with infection.

Peak values of PTX3 in patients with CS were detected 12 to 48 h after hospital admission irrespective of infection (18.9 vs. 14.1 ng/mL; $P = 0.354$).

The results show that a large dispersion of values of inflammatory biomarkers in patients with CS does not make it possible to demonstrate significant differences in their values depending on the development of infection. Inflammatory response in patients with CS can be significantly influenced by an out-of-hospital cardiac arrest and a subsequent development of the postcardiac arrest syndrome; we evaluated the inflammatory response by measuring CRP levels in patients with CS depending on the performed CPR before hospital admission and the presence on infection. Again, due to a large variability in the immune/inflammatory response, we did not detect a significant difference in the time course of CRP in the period of seven days (Fig. 3).

We therefore evaluated separately two patients with CS, with and without infection. Figure 4 clearly demonstrates how important it is to measure inflammatory markers repeatedly, and to know the time of a supposed peak to reveal a potential infection. Two types of kinetics are demonstrated: CRP and procalcitonin had low values upon hospital admission, with a subsequent early increase; in the infected patient, there was a clear increase after the time of the supposed peak at 48 h. A slight and continuous decrease in presepsin levels after 12 h was observed in the patient without infection, whereas the maximum value for presepsin was observed at 48 h in the infected patient. A significant difference in regards to infection was not observed in time courses of PTX3 levels.

Prognostic value of inflammatory biomarkers in CS

Previous results demonstrated a frequent elevation of inflammatory markers in patients with CS irrespective of infections. Using the c-statistic, we tested the prognostic value of inflammatory biomarkers to predict the 3-month mortality; we evaluated biomarkers that were measured during the first 24 h (samples 1–3). We found a strong relationship between the elevated inflammatory markers and the prognosis: we identified the best prognostic value for levels evaluated 12 h after hospital admission: the AUC of ROC for CRP, procalcitonin, presepsin, and PTX3 ranged between 0.683 and 0.875 (Table 3).

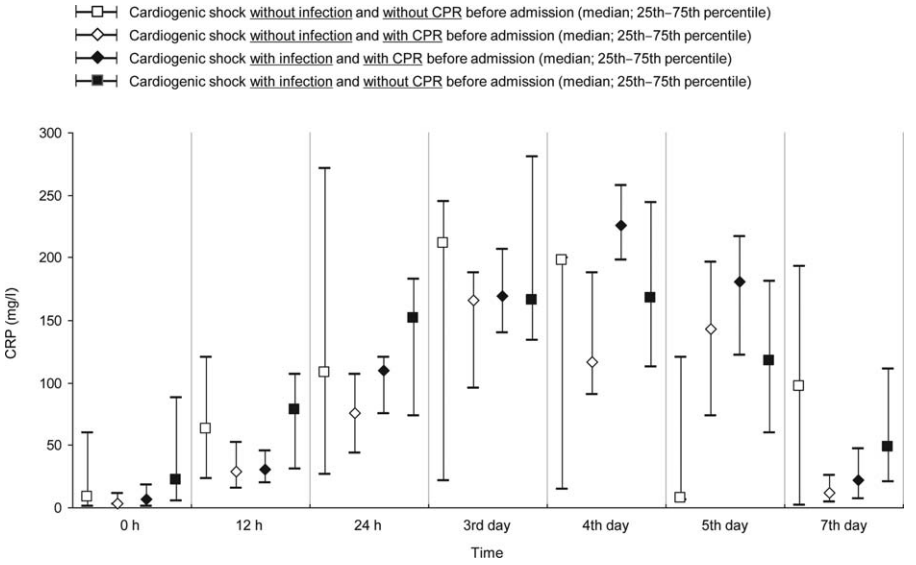

Fig. 3. **Time course of expression of C-reactive protein in groups of all patients with CS according to presence of infection and out-of-hospital cardiac arrest with cardiopulmonary resuscitation (CPR) before hospital admission.**

Comparison of immune/inflammatory response expressed by inflammatory biomarkers in patients with CS and patients with septic shock and patients with STEMI (without shock and infection)

The baseline characteristics of all patients with CS (irrespective to infection) in comparison with patients with septic shockand patients with STEMI are shown in Supplemental Table 2, http://links.lww.com/SHK/A484.

The time course of biomarkers in patients with septic shock demonstrates an extreme inflammatory response, which significantly exceeds the inflammatory response of patients with CS regardless of infection; on the contrary, the inflammatory response of STEMI patients without CS and without infection is significantly less intense, demonstrating a ''normal-average'' inflammatory response within MI treated by primary PCI without CS (Fig. 5).

DISCUSSION

The present study highlights two extremely important points in the care of patients with CS: infection is a frequent complication, which partially increases the hospital mortality of

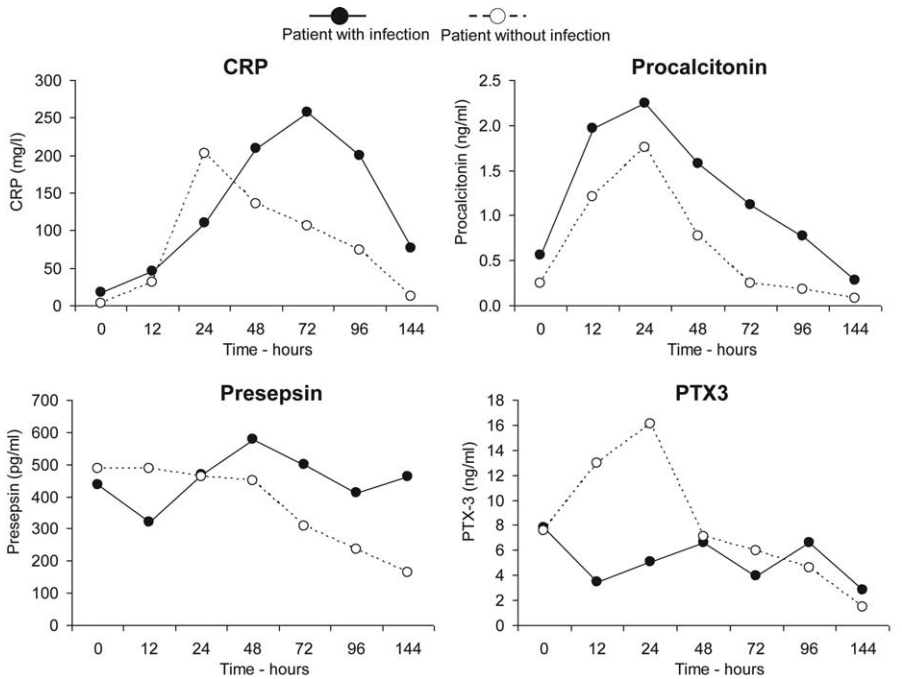

Fig. 4. **Time-related profiles of inflammatory parameters (C-reactive protein, procalcitonin, pentraxin 3, and presepsin) of two patients with CS with and without infection.**

TABLE 3. **Prognostic value of inflammatory biomarkers for the prediction of 3-month mortality in cardiogenic shock patients irrespective of infection**

	Survival		Death						
	n	Median (5th–95th percentile)	n	Median (5th–95th percentile)	AUC	P	Cutoff	Sensitivity	Specificity
CRP/2	26	30.5 (8.5; 202.1)	16	63 (15.5; 238.6)	0.683	0.049	≥45.6	0.750	0.250
Proc./2	26	1.3 (0.2; 9.8)	16	3.4 (0.4; 557.5)	0.761	0.005	≥2.0	0.813	0.188
Pres./2	24	410 (239; 789)	11	655 (234; 2,587)	0.716	0.043	≥1,035	0.455	0.545
PTX3/2	24	10.5 (1.2; 58.0)	10	50.7 (11.4; 1,200)	0.875	0.001	≥26.5	0.800	0.200

AUC indicates area under the curve; CRP, C-reactive protein; Pres., presepsin; Proc., procalcitonin; PTX3, pentraxin 3.
Only biomarkers at 12 h (sample 2) are shown.

patients, and extends the time of mechanical ventilation; the immune/inflammatory response of patients with CS with acute myocardial infarction (AMI) is strong (expressed biochemically by levels of inflammatory biomarkers, and clinically by the development of SIRS) and very variable. This high variability makes it impossible to determine the cutoff value of inflammatory biomarkers for the suspicion of development of infection. Regardless of infection, an extensive immune/inflammatory response is linked to a poor prognosis.

Frequent infections in CS and especially RTIs (67.5% of all infections) were found. As mentioned in the ''Introduction,'' there is a number of reasons for the high incidence of infections, particularly the pulmonary ones: pulmonary congestion (9), mechanical ventilation (7), cardiac arrest with prehospital CPR (6), treatment by therapeutic hypothermia (21), and multiple invasive access sites.

According to randomized studies on the prevention of VAP, mortality attributable to VAP is ≈9% (22). In our study, infections led to an increase in mortality by only 3.8%: this might be due to a high mortality of the CS itself. In the literature, there is lack of information about infective complications in patients with CS. In the SHOCK trial, sepsis with positive culture results was reported in 13.3% of patients, with the predominant pathogen being *Staphylococcus aureus*, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*; independent predictors of sepsis were duration of use of intraaortic balloon pump and multiple central catheters (8). Nosocomial infections developed in 64% of a total of 220 patients with CS supported by venoarterial extracorporeal membrane oxygenation (ECMO). VAP (55%), bloodstream infection (18%), cannula infections (10%), and mediastinitis were identified (23). A high prevalence of infection (65%) has

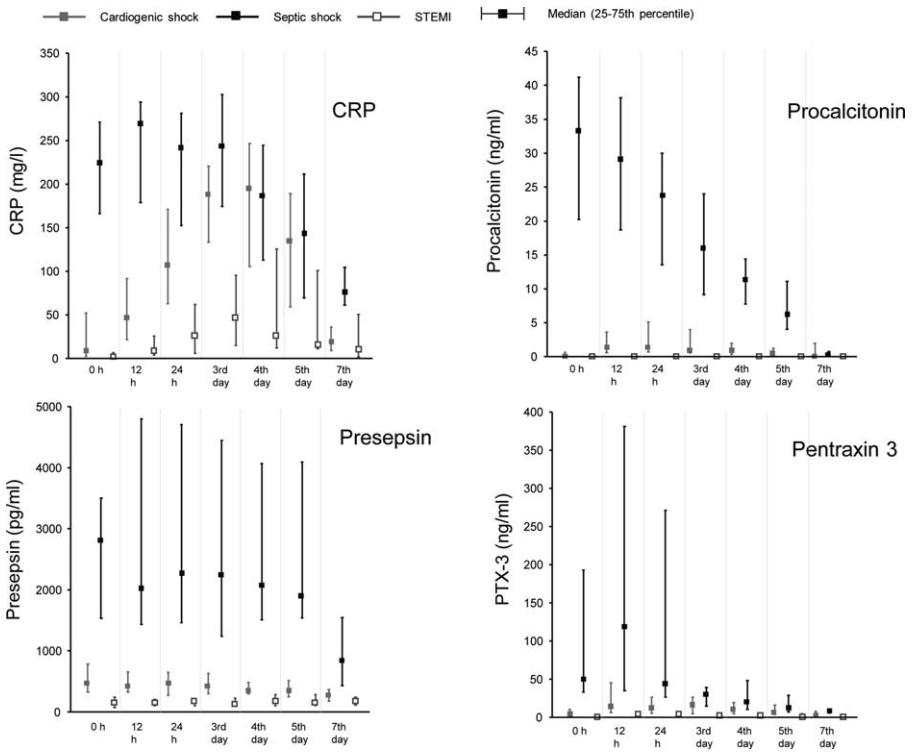

FIG. 5. **Time course of expression of C-reactive protein, procalcitonin, presepsin, and pentraxin 3 in patients with CS in comparison with control groups of patients with septic shock and patients with STEMI (without shock and without infection).**

also been reported in patients after cardiac arrest treated by hypothermia (6).

We did not find any clinical effect of fixed cultivation of bronchial aspirates and BALF samples on the first day of mechanical ventilation. However, respiratory infections were the most common infections in patients with CS, and half of them were presented within 48 h upon hospital admission; therefore, for patients undergoing mechanical ventilation, we suggest that bronchial samples are cultivated on the morning of the third day, and then regularly twice a week; in addition, if there is suspicion of an RTI, rules for the prevention of VAP should be followed immediately.

Immune/inflammatory response and the time course of presepsin and other inflammatory biomarkers in patients with CS

The immune/inflammatory response is very strong in patients with CS with AMI when compared with a control group of patients with STEMI without shock; nevertheless, it does not reach the extreme values of response seen in patients with septic shock. SIRS was clinically found in 68.8% of patients who survived the first 24 h, regardless of the development of infection.

For the first time, we showed a detailed time course of presepsin in a cohort of patients with AMI complicated by CS. In comparison with CRP and procalcitonin, presepsin had a slightly different course, with an earlier onset of the peak. For all markers, we demonstrated a significantly higher inflammatory response in patients with CS in comparison with the control STEMI group, but a significantly lower inflammatory response in comparison with patients with septic shock. This high variability of the inflammatory response in patients with CS makes it impossible to determine cutoff values for the detection of infection. Probably the main reason for this observation is that the inflammatory response due to these infections as expressed by the evaluated biomarkers is similar or lower in comparison with the inflammatory response due to myocardial necrosis in CS or postcardiac arrest syndrome. In this project, we analyzed other inflammatory markers as well (interleukin-6, soluble L-selectin, soluble P-selectin, soluble V-CAM-1, soluble ICAM-1, and complement activation product C5a); none of these markers have brought information making it possible to distinguish between infection and inflammatory aseptic reaction as part of CS during an acute MI, and these data are therefore not presented. The knowledge of time course of inflammatory biomarkers in patients with CS might be useful in the everyday clinical practice: an unexpected increase or maintenance of high values of inflammatory biomarkers after their supposed peak can support a diagnosis of infection and can help to decide about an early initiation of antibiotic therapy before a definitive result of microbiological cultivation. As shown in Figure 3, a combination of two biomarkers with different time courses (CRP with a peak at 48 h and presepsin with an early-onset peak after 12–24 h) and serial measurements might be helpful.

From the point of view of short-term prognosis, high levels of inflammatory markers during the first 24 h identify very well the group of highest-risk patients in CS who might benefit most from further intensive treatments such as mechanical circulatory support or ECMO. Inflammatory response in critically ill patients is generally a predictor of poor prognosis (24).

Nevertheless, inflammatory biomarkers have also their pathophysiological function in acute MI complicated with CS. An inflammatory response only partly corresponds with the size of the MI. CRP activates the complement system by the classic pathway, helping to lyse and to remove damaged myocardial cells (25). An inappropriately high inflammatory response with excessive production of CRP is accompanied by an increased infiltration of damaged tissue (as well as the surrounding myocardium) by macrophages, increased activity of metalloproteinases (MMP9) and activation of the complement system, and increased expression of chemotactic molecules such as monocyte chemoattractant protein (MCP)-1, all of which lead to an extension of myocardial damage and left ventricular remodeling (26, 27). An excessive production of CRP can stimulate cardiomyocytes as well as peripheral blood cells to increase the output of inducible nitric oxide synthase with an overproduction of nitric oxide (NO) (28) and, whereas physiological levels of NO have a cardioprotective effect, high NO concentrations have negative inotropic and cytotoxic effects on cardiomyocytes and participate in vasodilatation that may further lead to the development and progression of CS (29). Procalcitonin is a peptide precursor of the hormone calcitonin, but its physiological role during the inflammatory response is not clear. Its role in the metabolism of calcium, cytokine networks, modulation of NO synthesis, and pain-relieving effects has been considered (30). PTX3 seems to have (in comparison with CRP) a cardioprotective effect. PTX3 binds to component C1q and prevents unwanted and excessive activation of complement (31). Binding to P-selectin reduces further neutrophil infiltration into the site of myocardial injury (32), and binding to activated platelets reduces proinflammatory and prothrombotic effects in MI patients (33). In our work, high values of PTX3 associated with a poor prognosis are probably the result of an excessive inflammatory response, than PTX3 alone would actively contribute to a negative outcome. Presepsin is a soluble CD14 subtype, and its biological role has not been elucidated; it is a regulatory factor capable of modulating cellular and humoral immune responses by interacting directly with T and B cells (34). Unfortunately, recent studies leading to the suppression of inflammatory reactions in an unselected group of patients with acute MI have not proved any positive therapeutic effect yet (35).

Limitations—First, the study cohort was relatively small. Second, the study was carried out at a single center. Third, infectious complications are more difficult to recognize in patients with CS due to an aseptic inflammatory response: we cannot rule out that despite every effort, we did not manage to diagnose this infection in several patients, particularly in those who died early. On the contrary, if there is a suspicion of infection that might be linked to death, microbiological cultivation was performed in these deceased patients, from samples available from the dissection. Fourth, a large proportion of patients with CS underwent CPR and treatment with therapeutic hypothermia before hospital admission, which makes the interpretation of results even more difficult: the inflammatory response is not only

part of the immune response to an extensive myocardial necrosis, but also part of the postcardiac arrest syndrome with additional pathophysiological changes caused by therapeutic hypothermia. A high proportion of patients with CS who survive out-of-hospital cardiac arrest and resuscitation are currently an indispensable part of all large cohorts of patients with CS, and cannot be separated from the study (5, 36), but according to our subanalysis of time course of biomarkers in patients with CS depending on the presence of infection and CPR, no significant difference was shown between these groups. And fifthly, a high proportion of early deaths in patients with CS makes it significantly more difficult to evaluate the influence of infectious complications on the duration of hospitalization and on the duration of mechanical ventilation.

CONCLUSION

The prevalence of infection in patients with acute MI complicated by CS was 46.3%, and RTIs were the most common type. Infections did not prolong statistically significantly the duration of mechanical ventilation and did not increase the prevalence of hospital mortality in this high-risk CS population. CS due to AMI was accompanied by a strong and highly variable inflammatory response, but it did not reach the intensity of the inflammatory response observed in patients with septic shock. An extensive immune/inflammatory response in patients with CS is linked to a poor prognosis. Our results might lay the groundwork for a prospective study which would evaluate the use of repeated determination of levels of inflammatory biomarkers or their combinations, potentially contributing to an early decision about the initiation of antibiotic therapy in patients with CS with a suspicion of infection.

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REFERENCES

1. Awad HH, Anderson FA, Gore JM, Goodman SG, Goldberg RJ: Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. *Am Heart J* 163:963–971, 2012.
2. Spinar J, Parenica J, Vitovec J, Widimsky P, Linhart A, Fedorco M, Malek F, Cihalik C, Spinarová L, Miklik R, et al.: Baseline characteristics and hospital mortality in the Acute Heart Failure Database (AHEAD) Main registry. *Crit Care* 15:R291, 2011.
3. Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS, NRMI Investigators. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 294:448–454, 2005.
4. Osmon S, Warren D, Seiler SM, Shannon W, Fraser VJ, Kollef MH: The influence of infection on hospital mortality for patients requiring >48 h of intensive care. *Chest* 124:1021–1029, 2003.
5. ThieleF H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, et al.: Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 367:1287–1296, 2012.
6. Perbet S, Mongardon N, Dumas F, Bruel C, Lemiale V, Mourvillier B, Carli P, Varenne O, Mira JP, Wolff M, et al.: Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med* 184:1048–1054, 2011.
7. Kouraki K, Schneider S, Uebis R, Tebbe U, Klein HH, Janssens U, Zahn R, Senges J, Zeymer U: Characteristics and clinical outcome of 458 patients with acute myocardial infarction requiring mechanical ventilation. Results of the BEAT registry of the ALKK-study group. *Clin Res Cardiol* 100:235–239, 2011.
8. Kohsaka S, Menon V, Iwata K, Lowe A, Sleeper LA, Hochman JS, SHOCK Investigators. Microbiological profile of septic complication in patients with cardiogenic shock following acute myocardial infarction (from the SHOCK study). *Am J Cardiol* 99:802–804, 2007.
9. Alon D, Stein GY, Korenfeld R, Fuchs S: Predictors and outcomes of infection-related hospital admissions of heart failure patients. *PloS One* 8:e72476, 2013.
10. Maisel A, Neath SX, Landsberg J, Mueller C, Nowak RM, Peacock WF, Ponikowski P, Möckel M, Hogan C, Wu AHB, et al.: Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *Eur J Heart Fail* 14:278–286, 2012.
11. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, Borggrefe M, Hoffmann U: Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. *Crit Care* 18:507, 2014.
12. Muller B, Peri G, Doni A, Torri V, Landmann R, Bottazzi B, Mantovani A: Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. *Crit Care Med* 29:1404–1407, 2001.
13. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS, SHOCK Investigators. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 165:1643–1650, 2005.
14. Peberdy MA, Andersen LW, Abbate A, Thacker LR, Gaieski D, Abella B, Rittenberger JC, Clore J, Ornato J, Cocchi MN, et al.: Inflammatory markers following resuscitation from out-of-hospital cardiac arrest—a prospective multicenter observational study. *Resuscitation* 103:117–124, 2016.
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, et al.: ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J* 33:2551–2567, 2012.
16. TRIUMPH Investigators, Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, Van de Werf F, Hochman JS: Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 297:1657–1666, 2007.
17. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma B, Bueno H, Caso P, Dudek P, Gielen S, Huber K, et al.: ESC Committee for Practice Guidelines, ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 32:2999–3054, 2011.
18. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: SCCM/ESICM/ACCP/ATS/SIS, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31:1250–1256, 2003.
19. Horan TC, Andrus M, Dudeck MA: CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 36:309–332, 2008.
20. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 16:128–140, 1998.
21. Geurts M, Macleod MR, Kollmar R, Kremer PHC, van der Worp HB: Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis. *Crit Care Med* 42:231–242, 2014.
22. MelsenF WG, Rovers MM, Koeman M, Bonten MJM: Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med* 39:2736–2742, 2011.
23. Schmidt M, Bréchot N, Hariri S, Guiguet M, Luyt CE, Makri R, Leprince P, Trouillet L, Pavie A, Chastre J, et al.: Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. *Clin Infect Dis* 55:1633–1641, 2012.
24. Fraunberger P, Wang Y, Holler E, Parhofer KG, Nagel D, Walli AK, Seidel D: Prognostic value of interleukin 6, procalcitonin, and C-reactive protein levels in intensive care unit patients during first increase of fever. *Shock* 26:10–12, 2006.
25. Lagrand WK, Niessen HW, Wolbink GJ, Jaspars LH, Visser CA, Verheugt FW, Meijer CJ, Hack CE: C-reactive protein colocalizes with complement in human hearts during acute myocardial infarction. *Circulation* 95:97–103, 1997.
26. Griselli M, Herbert J, Hutchinson WL, Taylor KM, Sohail M, Krausz T, Pepys MB: C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. *J Exp Med* 190:1733–1740, 1999.
27. Takahashi T, Anzai T, Kaneko H, Mano Y, Anzai A, Nagai T, Kohno T, Maekawa Y, Yoshikawa T, Fukuda K, et al.: Increased C-reactive protein expression

exacerbates left ventricular dysfunction and remodeling after myocardial infarction. *Am J Physiol Heart Circ Physiol* 299:H1795–H1804, 2010.

28. Ikeda U, Maeda Y, Yamamoto K, Shimada K: C-Reactive protein augments inducible nitric oxide synthase expression in cytokine-stimulated cardiac myocytes. *Cardiovasc Res* 56:86–92, 2002.
29. Hochman JS: Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 107:2998–3002, 2003.
30. Maruna P, Nedelníkova K, Gürlich R: Physiology and genetics of procalcitonin. *Physiol Res* 49(suppl 1):S57–S61, 2000.
31. Nauta AJ, Bottazzi B, Mantovani A, Salvatori G, Kishore U, Schwaeble WJ, Gingras AR, Tzima S, Vivanco F, Egido J, et al.: Biochemical and functional characterization of the interaction between pentraxin 3 and C1q. *Eur J Immunol* 33:465–473, 2003.
32. Deban L, Russo RC, Sironi M, Moalli F, Scanziani M, Zambelli V, Cuccovillo I, Bastone A, Gobbi M, Valentino S, et al.: Regulation of leukocyte recruitment by the long pentraxin PTX3. *Nat Immunol* 11:328–334, 2010.
33. Maugeri N, Rovere-Querini P, Slavich M, Coppi G, Doni A, Bottazzi B, Garlanda C, Cianflone D, Maseri A, Mantovani A, et al.: Early and transient release of leukocyte pentraxin 3 during acute myocardial infarction. *J Immunol* 187:970–979, 2011.
34. Rey Nores JE, Bensussan A, Vita N, Stelter F, Arias MA, Jones M, Lefort S, Borysiewicz LK, Ferrara P, Labéta MO: Soluble CD14 acts as a negative regulator of human T cell activation and function. *Eur J Immunol* 29:265–276, 1999.
35. O'Donoghue ML, Glaser R, Cavender MA, Aylward PE, Bonaca MP, Budaj A, Davies RY, Dellborg M, Fox KAA, Gutierrez JAT, et al.: Effect of losmapimod on cardiovascular outcomes in patients hospitalized with acute myocardial infarction: a randomized clinical trial. *JAMA* 315:1591–1599, 2016.
36. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, et al.: Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 17:501–509, 2015.