

Systemic Inflammatory Response Syndrome After Acute Myocardial Infarction Complicated by Cardiogenic Shock

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Background: The role of inflammation in patients with coronary artery disease is emerging. We sought to assess the profile and outcomes of patients with a clinical syndrome of severe systemic inflammation that led to a diagnosis of suspected sepsis in the setting of acute myocardial infarction complicated by cardiogenic shock (CS).

Methods: Patients enrolled in the randomized SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial (n=302) were divided into those with clinical signs of severe systemic inflammation (eg, fever [94%] or leukocytosis [72%]) that led to a diagnosis of suspected sepsis (n=54 [18%]) and those without suspected sepsis (controls; n=243 [80%]). The patients with suspected sepsis were then further subdivided into those who were considered to be potentially infectious (positive culture result ["culture-positive"]; n=40) and those who were not (negative culture result ["culture-negative"]; n=14).

Results: Severe systemic inflammation was diagnosed 4 and 2 days after the onset of CS in culture-positive and culture-negative patients, respectively. Patients who developed systemic inflammation tended to be younger

($P=.05$) and to have lower systemic vascular resistance (SVR) near the onset of CS ($P=.006$). Many culture-positive patients (40%) had undergone coronary artery bypass graft surgery. However, the lower the initial SVR, the higher the risk of developing culture-positive systemic inflammation ($P=.01$), even after controlling for age and coronary artery bypass graft surgery. A time-dependent model, adjusted for age, showed that culture-positive patients were at significantly higher risk for death than were controls (hazard ratio, 2.22; 95% confidence interval, 1.32-3.76; $P=.008$).

Conclusions: Almost one fifth of patients with acute myocardial infarction complicated by CS showed clinical signs of severe systemic inflammation, and those who were culture-positive for sepsis had twice the risk of death. The observation of lower SVR at the onset of shock in patients who subsequently had culture-positive systemic inflammation suggests that inappropriate vasodilation may play an important role in the pathogenesis and persistence of shock and in the risk of infection.

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CARDIOGENIC SHOCK (CS) IS the leading cause of hospital death in patients with acute myocardial infarction (AMI), and the incidence has remained constant at 60% to 70% for 3 decades.¹ Cardiogenic shock in the setting of an AMI has traditionally been viewed as simply a mechanical problem: an acute reduction in myocardial contractility leads to reduced stroke volume and cardiac output, which leads to hypotension and systemic hypoperfusion.² Recent data suggest that this paradigm should be expanded.³ Studies have revealed a pivotal role for a systemic inflammatory response syndrome (SIRS) that includes the release of inflammatory mediators, the expression of inducible nitric oxide (NO), and an inappropriate peripheral circula-

tory response.⁴⁻⁷ Systemic inflammation is associated with a high risk of future primary and secondary coronary events, including stable and unstable coronary heart disease syndromes.⁸⁻¹¹ It is also evident in many other conditions associated with shock.

The SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial was a randomized trial of early revascularization for AMI complicated by CS. Its design,¹² primary results,¹³ and 1-year follow-up¹⁴ have previously been described. The SHOCK trial provides a unique opportunity to explore the systemic inflammatory state in patients with CS-complicating ST-elevation AMI. In the analysis reported herein, we assessed the prevalence, characteristics, and outcomes of patients who

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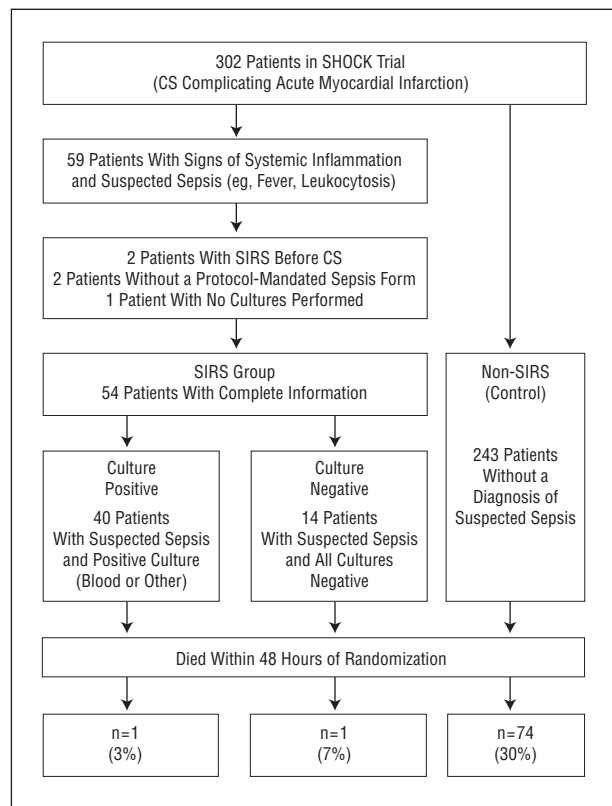


Figure 1. Flowchart of the categorization of SHOCK (Should we emergently revascularize Occluded Coronaries for cardiogenic shock) trial patients (n=302). CS indicates cardiogenic shock; SIRS, systemic inflammatory response syndrome.

showed signs of severe systemic inflammation after CS-complicating ST-elevation AMI.

METHODS

SHOCK TRIAL

Patients eligible for the SHOCK trial had ST-segment elevation, new left bundle branch block, or posterior infarction with anterior ST-segment depression complicated by shock due to predominant left ventricular dysfunction. Cardiogenic shock was confirmed by both clinical and hemodynamic criteria. The clinical criteria were hypotension (systolic blood pressure <90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure >90 mm Hg) and end-organ hypoperfusion (cool, diaphoretic extremities or a urine output of <30 mL/h and a heart rate of >60/min). The hemodynamic criteria were a cardiac index of no more than 2.2 L/min per square meter and a pulmonary capillary wedge pressure of at least 15 mm Hg. The onset of shock had to occur within 36 hours of infarction.¹² From April 1993 through November 1998, 302 patients with suspected AMI complicated by CS were enrolled prospectively at 36 centers. The trial assessed the effects on 30-day mortality of an early revascularization strategy compared with a strategy of initial medical stabilization.

PATIENTS

A study-mandated form was completed if sepsis was suspected on the basis of signs of severe systemic inflammation

during hospitalization. Clinical suspicion was guided by the presence of fever, leukocytosis, or localized soft tissue erythema and tenderness. Fifty-nine patients had sepsis suspected because of 1 or more of these signs of severe systemic inflammation, and either fever or leukocytosis was present in all. Five patients were excluded from this analysis either because data or culture results were unavailable or because sepsis occurred before the onset of CS. The remaining 54 patients (SIRS group) were divided into those with culture results obtained from any site that were positive for bacterial growth ("culture-positive"; n=40) and those without any evidence of infectious etiology ("culture-negative"; n=14) (**Figure 1**). A third group included patients in the trial without clinically suspected sepsis (control; n=243).

CONFIRMATION OF SEPSIS

Blood culture results were obtained in all cases of suspected sepsis. The isolation of an organism from 1 or more bottles was accepted as significant for all organisms except coagulase-negative staphylococci, for which isolation from 2 or more bottles was required. The physicians directly in charge of the patient evaluated each positive blood culture result to determine whether it represented true infection or merely contamination. This decision was based on multiple factors, including the patient's history, physical examination findings, body temperature, clinical course, and blood culture results.

HEMODYNAMIC VARIABLES

Hemodynamic characteristics were reported from the time of initial evaluation for CS, not from the time of suspected sepsis diagnosis, which often occurred days later. The following hemodynamic values were recorded: systemic systolic blood pressure, systemic diastolic blood pressure, mean right atrial pressure or central venous pressure, mean pulmonary capillary wedge pressure, and cardiac index. Systemic vascular resistance (SVR) was available for 210 patients (31 culture-positive, 11 culture-negative, and 168 control patients, respectively) and was calculated for patients with complete hemodynamic data using the following formula:

$$80 \times \left(\left[\frac{1}{3} \times \text{Systolic Blood Pressure} - \frac{2}{3} \times \text{Diastolic Blood Pressure} \right] - \text{Right Atrial Pressure} \right) / \text{Cardiac Output}$$

One hundred eighty-three SVR values were recorded near the onset of shock. Twenty-seven patients had only SVR values available that were recorded at the time of randomization. The median difference in time from near shock onset to randomization for the 27 cases was 0.45 hour. For 81 patients with SVR values at both time points, SVR was similar (median difference, 33 dyne/s per centimeter⁵; interquartile range, -69 to 242 dyne/s per centimeter⁵). Most data were recorded while support measures were in use; vasopressor drugs, for example, were used in 93% of patients.

STATISTICAL ANALYSIS

Categorical variables are presented as percentages. Continuous variables are presented as the mean ± SD for normally distributed variables or the median and quartiles for skewed data. Comparisons were made among the 3 groups (culture-positive vs culture-negative vs control). The distributions of categorical variables were compared using the Fisher exact test. Group differences in continuous variables were assessed by analysis of variance for normally distributed data or the Kruskal-Wallis test for nonnormally distributed data. $P \leq .05$ was considered statistically significant. If a 3-way comparison was sig-

Table 1. Baseline Characteristics of the 297 Study Patients*

Characteristic	SIRS			P Value†
	Culture-Positive (n = 40)	Culture-Negative (n = 14)	Non-SIRS Control (n = 243)	
Age, mean ± SD, y	63 ± 10	64 ± 14	67 ± 10	.05
Male sex	78	86	65	.12
Transfer admission	53	79	54	.19
History of myocardial infarction	18	29	35	.07
History of hypertension	38	57	47	.46
History of diabetes	38	33	30	.60
History of congestive heart failure	3	0	7	.64
History of renal insufficiency	5	0	6	>.99
History of cigarette smoking	54	58	54	>.99
History of peripheral vascular disease‡	10	0	16	.78
Prior angioplasty	3	14	8	.20
Prior coronary artery bypass grafting	3	7	7	.59
Thrombolytic therapy	60	79	54	.19
Time from cardiogenic shock to diagnosis of suspected sepsis, median (IQR), d	4 (1-6)	2 (1-3)		.04
Time from myocardial infarction to cardiogenic shock, median (IQR), h	6 (4-11)	9 (4-14)	5 (2-15)	.36

Abbreviations: IQR, interquartile range; SIRS, systemic inflammatory response syndrome.

*Data are given as percentage of patients unless otherwise indicated.

†P values are for comparisons of all 3 groups, except for comparison of median time from cardiogenic shock to diagnosis of suspected sepsis. In that case, the P value is for comparison between culture-positive vs culture-negative groups.

‡Sample sizes are 31, 4, and 168 for the culture-positive, culture-negative, and control groups, respectively.

Table 2. Hemodynamic Measurements of the 297 Study Patients*

Measurement	SIRS			P Value†
	Culture-Positive (n = 40)	Culture-Negative (n = 14)	Non-SIRS Control (n = 243)	
In-hospital left ventricular ejection fraction, same day or after shock, %	30 ± 12 (n = 31)	25 ± 9 (n = 4)	28 ± 11 (n = 128)	.66
Pulmonary capillary wedge pressure, mm Hg	24 ± 7 (n = 39)	24 ± 4 (n = 11)	24 ± 8 (n = 215)	.92
Cardiac index, L/min per square meter	1.8 ± 0.6 (n = 39)	1.8 ± 0.4 (n = 11)	1.8 ± 0.6 (n = 206)	.39
Systolic blood pressure, mm Hg	85 ± 16 (n = 39)	81 ± 14 (n = 11)	89 ± 21 (n = 229)	.48
Diastolic blood pressure, mm Hg	51 ± 15 (n = 36)	51 ± 12 (n = 8)	55 ± 15 (n = 215)	.27
Heart rate, beats/min	101 ± 22 (n = 39)	108 ± 25 (n = 12)	102 ± 23 (n = 229)	.59
SVR, median (IQR), dyne/s per centimeter ⁵	1051 (862-1486) (n = 31)	1174 (705-1370) (n = 11)	1402 (1088-1807) (n = 168)	.006

Abbreviations: IQR, interquartile range; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance.

*Data are given as mean ± SD unless otherwise indicated. Values were often recorded close to shock onset (ie, 2-4 days before suspected sepsis); the most frequent forms of support were vasopressors, inotropes, and intra-aortic balloon pump support.

†P value is for comparison of all 3 groups.

nificant, pairwise comparisons were performed and adjusted using the Bonferroni method. For variables that did not apply to the control group (eg, Swan-Ganz duration, central line, central line duration, and clinical signs of sepsis), a 2-group comparison of culture-positive vs culture-negative patients was performed using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for nonnormally distributed continuous data. Logistic regression modeling predicting culture-positive SIRS (vs culture-negative SIRS or control) was performed to determine independent predictors of a subsequent positive culture. Clinical characteristics and in-hospital treatment variables with $P < .10$ were examined in univariate and multivariate modeling (Tables 1, 2, and 3). Mechanical ventilation and duration could not be included as possible predictors of culture-positive SIRS because infection and length of stay are not determined before infection; therefore, these fac-

tors could not be included as possible predictors of culture-positive SIRS. In addition, Cox regression analysis using a coronary artery bypass graft (CABG) indicator as a time-dependent covariate was performed to determine whether SVR correlated with the development of sepsis after CABG. To further assess the impact of baseline SVR on the subsequent diagnosis of SIRS, positive culture results, baseline characteristics, and 30-day mortality were compared in patients with and without low SVR (as determined by the overall median SVR [1357 dyne/s per centimeter⁵]).

Thirty-day survival was estimated using the Kaplan-Meier method. The log rank and Gehan-Wilcoxon tests were used to compare 30-day survival among the 3 groups. Because the signs of systemic inflammation necessary for physicians to suspect sepsis require time to develop, Cox regression analysis using SIRS grouping as a time-dependent covariate was performed

Table 3. In-Hospital Treatment for the 297 Study Patients*

Treatment	SIRS		Non-SIRS Control (n = 243)	P Value†
	Culture-Positive (n = 40)	Culture-Negative (n = 14)		
Early revascularization	65	36	50	.10
Coronary artery bypass grafting	40	7	23	.03
Percutaneous coronary intervention	25	43	36	.32
Vasopressors	95	86	93	.37
Inotropes	93	92	83	.26
Mechanical ventilation	93	79	81	.18
Duration of mechanical ventilation, median (IQR), d	10 (8-20)	6 (4-20)	3 (1-7)	<.001
Intra-aortic balloon pump	95	100	85	.09
Duration of intra-aortic balloon pump, median (IQR), d	3 (2-4)	5 (3-6)	3 (1-4)	.003
Pulmonary artery catheter	100	100	94	.31
Total duration of pulmonary artery catheter, median (IQR), d‡	8 (5-11)	7 (5-8)	NA	.49
Central line (other than pulmonary artery catheter)‡	68	31	NA	.03
Total duration of central line, median (IQR), d‡§	11 (6-20)	5 (3-7)	NA	.04
Length of stay, median (IQR), d	22 (9-43)	17 (11-22)	9 (1-16)	<.001

Abbreviations: IQR, interquartile range; NA, not applicable; SIRS, systemic inflammatory response syndrome.

*Data are given as percentage of patients unless otherwise indicated.

†P values are for comparisons of all 3 groups, except for comparison of pulmonary artery catheter duration, central line, and central line duration. In those cases, P values are for comparisons between culture-positive vs culture-negative groups.

‡Data were obtained from study-mandated data collection forms; therefore, no data were available for control patients.

§Sample sizes are 23 and 4 for the culture-positive and culture-negative groups, respectively.

to correct for a bias in the number of deaths between SIRS and control patients. Analyses were conducted using SAS (SAS Institute Inc, Cary, NC) and S-PLUS (Insightful, Seattle, Wash) statistical software.

RESULTS

PREVALENCE OF SUSPECTED SEPSIS AMONG PATIENTS WITH CS FOLLOWING AMI

Clinically significant signs of SIRS leading to a diagnosis of suspected sepsis were noted in 54 (18%) of 297 patients (Figure 1). Fever (94%) was the most common sign, followed by leukocytosis (72%) and localized erythema and tenderness (11%). Of these 54 patients, 40 (74%) had positive culture results and 14 (26%) did not. Five patients with positive blood culture results were judged not to have a true infection; the blood samples in all 5 cases were thought to be contaminated. Of the 40 culture-positive patients, 68% had microorganisms grown from a blood culture. The predominant pathogen isolated was *Staphylococcus aureus* (43%), followed by *Klebsiella pneumoniae* (20%), *Pseudomonas aeruginosa* (13%), and *Acinetobacter* species (10%). The median time from the diagnosis of CS to the diagnosis of suspected sepsis was 4 days and 2 days ($P=.04$), respectively, for culture-positive and culture-negative patients.

CLINICAL CHARACTERISTICS OF PATIENTS WITH SYSTEMIC INFLAMMATION

The clinical characteristics of patients with systemic inflammation are summarized in Tables 1 and 2. Patients with severe systemic inflammation (culture-positive vs culture-negative vs control) tended to be younger (63 vs

64 vs 67 years, respectively; $P=.05$). Hemodynamic variables measured close to the time of CS diagnosis were similar in the 3 groups, except for median SVR, which was significantly lower in culture-positive than control patients (1051 vs 1402 dyne/s per centimeter⁵, respectively; $P=.02$). Median SVR in culture-negative and control patients was similar. The distribution of SVR varied widely.

Most of these data, including SVR, were recorded while support measures were in use. For example, vasopressor drugs were used in 93% of patients. Cardiogenic shock occurred within 14 hours of the index myocardial infarction in most patients, and the diagnosis of suspected sepsis was usually made days after the CS diagnosis. In **Figure 2**, a scatterplot depicts the timing of suspected sepsis during the hospital stay and the timing of revascularization. Notably, approximately 40% of the patients who were culture-positive had undergone CABG surgery. Timing and SVR data were available for 40 culture-positive or culture-negative patients. Most of the culture-positive patients in this subset had received a diagnosis of sepsis days after the onset of CS; the hemodynamic measurements, including SVR, were obtained near the onset of shock. Therefore, in most cases, hemodynamic data were obtained several days before sepsis was clinically suspected.

IN-HOSPITAL TREATMENT

The proportions of patients randomly assigned to the early revascularization arm of the SHOCK trial were similar among the study groups (culture-positive vs culture-negative vs control) (65% vs 36% vs 50%, respectively; $P=.10$) (Table 3). Differences occurred in the percentages of patients who underwent CABG surgery (40% vs

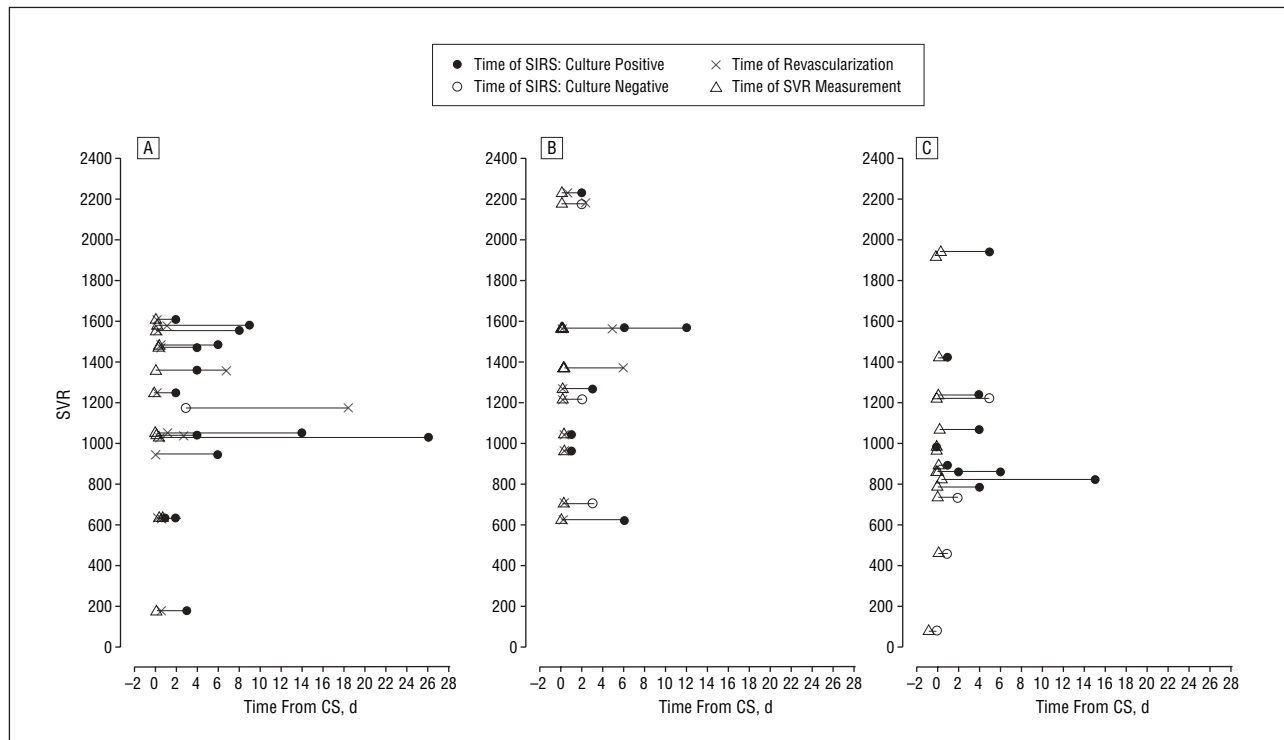


Figure 2. Scatterplot of timing of invasive procedures and systemic inflammatory response syndrome (SIRS) by systemic vascular resistance (SVR), separated by type of revascularization performed. A, Patients who underwent coronary artery bypass graft. B, Patients who underwent percutaneous coronary intervention. C, Patients who did not undergo revascularization.

7% vs 23%; $P=.03$). Culture-positive patients underwent CABG at a higher rate than culture-negative patients, although pairwise comparisons showed no statistically significant difference. Culture-positive patients also had a higher rate of central venous access by means other than a pulmonary artery catheter (68% vs 31%; $P=.03$), as well as a longer median duration of central venous access (11 vs 5 days; $P=.04$). No statistically significant differences occurred in durations of the pulmonary artery catheter and central line as well as the frequency of catheter changes between culture-positive and culture-negative patients.

PREDICTORS OF SIRS

Logistic regression modeling was performed to determine the predictors of culture-positive SIRS. Univariately, older age (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.52-0.97; $P=.03$) and a history of prior myocardial infarction (OR, 0.40; 95% CI, 0.17-0.94; $P=.04$) were associated with a decreased risk of culture-positive SIRS, whereas lower SVR near the onset of shock (OR per decrease of 200 dyne/s per centimeter⁵, 1.20; 95% CI, 1.03-1.39; $P=.02$) and CABG surgery (OR, 2.29; 95% CI, 1.14-4.59; $P=.02$) was associated with an increased risk. Multivariate modeling showed that lower SVR was a significant independent predictor of culture-positive SIRS after controlling for age and CABG (**Table 4**). For each decrease in SVR of 200 dyne/s per centimeter⁵, the risk of culture-positive SIRS increased 1.21 times (95% CI, 1.04-1.40).

To investigate whether early low SVR values correlated with the development of systemic inflammation after CABG,

Table 4. Logistic Regression Model for Predictors of Culture-Positive SIRS for 210 Study Patients

Predictor	OR for Culture-Positive SIRS (95% CI)	P Value
Age*	0.67 (0.45-1.00)	.047
Coronary artery bypass grafting (yes vs no)	3.01 (1.32-6.86)	.009
SVR†	1.21 (1.04-1.40)	.01

Abbreviations: CI, confidence interval; OR, odds ratio; SVR, systemic vascular resistance.

*The OR and 95% CI for age are in 10-year increments.

†The OR and 95% CI are for each decrease in SVR of 200 dyne/s per centimeter⁵.

we modeled time to sepsis with continuous SVR as a covariate, controlling for CABG as a time-dependent covariate. The risk of subsequent systemic inflammation syndrome increased for lower SVR values, measured near shock onset (hazard ratio per decrease of 200 dyne/s per centimeter⁵, 1.21; 95% CI, 1.07-1.37; $P=.003$).

OUTCOMES

Unadjusted, 30-day survival for the culture-positive and culture-negative patients was 55% (95% CI, 40%-70%) and 64% (95% CI, 39%-89%), respectively. The control patients had the lowest survival among the 3 groups (47%; 95% CI, 41%-53%); this was established by comparison using the Gehan-Wilcoxon test, which placed more weight

Table 5. Time-Dependent Cox Regression for 30-Day Survival by SIRS Grouping After Age Adjustment in the 297 Study Patients

Covariate*	Hazard Ratio for Mortality (95% CI)	P Value†
Overall association between survival and SIRS grouping		.008
Culture-positive vs non-SIRS control	2.22 (1.32-3.76)	.008
Culture-negative vs non-SIRS control	1.36 (0.55-3.37)	>.99
Culture-positive vs SIRS culture-negative	1.64 (0.61-4.42)	.99
Age‡	1.38 (1.17-1.61)†	<.001

Abbreviations: CI, confidence interval; SIRS, systemic inflammatory response syndrome.

*Hazard ratio for combined SIRS group (culture-positive and culture-negative) vs non-SIRS control group was 1.95 (95% CI, 1.21-3.13; $P = .006$).

†Hazard ratio and 95% CI for age are in 10-year increments.

on events that occurred early after randomization ($P = .02$). However, no association existed between patient group and overall survival (log rank; $P = .10$).

Only 1 patient in each of the 2 SIRS subgroups (3% of culture-positive patients and 7% of culture-negative patients) died early (ie, within 48 hours of randomization) compared with 74 control patients (30%). This may have been because infections take time to develop and physicians can diagnose suspected sepsis in the setting of AMI only after time in the coronary care unit or intensive care unit has elapsed. To correct for this bias and assess the effect of SIRS and infection on those who survived long enough for an infection to develop, we performed a survival analysis with a time-dependent covariate for SIRS grouping. A significant difference was found between the SIRS groupings ($P = .04$); the culture-positive group had a significantly higher hazard of death than the non-SIRS controls (hazard ratio, 1.96; 95% CI, 1.16-3.30; $P = .04$). Since the patients with SIRS were significantly younger, this analysis was also adjusted for age (Table 5). Even then, severe systemic inflammation status remained a significant predictor of death, with the culture-positive patients having a 2.22-fold greater hazard of death than control patients, and the difference among the 3 groups was even greater ($P = .008$).

When patients with lower SVR (patients with SVR below the median value) were compared with those with higher SVR (patients with SVR above the median value), 2 of the variables examined were statistically significant: sex ($P = .04$) and median time from myocardial infarction to CS ($P = .01$). The total duration of pulmonary artery catheter was similar for low vs high SVR ($P = .68$). Although not statistically significant, 30-day mortality for patients in the low SVR group tended to be higher (61% vs 49%; $P = .10$) (Table 6).

COMMENT

In the SHOCK trial, almost one fifth of randomized patients with CS showed signs of severe systemic inflam-

Table 6. Baseline Characteristics and Outcome by SVR Near-Shock Onset or at Randomization*

Characteristic	Low SVR (n = 105)	High SVR (n = 105)	P Value
Age, mean \pm SD, y	66 \pm 10	67 \pm 11	.32
Male sex	72	58	.04
Transfer admission	54	58	.68
History of myocardial infarction	24	35	.10
History of hypertension	41	52	.16
History of diabetes	26	30	.64
History of congestive heart failure	4	7	.54
History of renal insufficiency	6	4	.54
History of cigarette smoking	59	45	.06
History of peripheral vascular disease‡	19	10	.16
Prior angioplasty	4	10	.10
Prior coronary artery bypass grafting	4	10	.16
Thrombolytic therapy	54	63	.26
Time from myocardial infarction to cardiogenic shock, median (IQR), h	4 (2-12)	8 (4-17)	.01
SIRS grouping			.05
Culture-positive	19	10	
Culture-negative	8	3	
Non-SIRS	73	87	
30-Day mortality	61	49	.10
Total duration of pulmonary artery catheter, median (IQR), d‡	7 (5-11)	8 (6-13)	.68

Abbreviations: IQR, interquartile range; SVR, systemic vascular resistance. *Data are given as percentage of patients unless otherwise indicated. Low SVR is defined as an SVR of lower than 1357; high SVR is defined as an SVR of 1357 or higher.

†Sample sizes are 74 and 71 for the low SVR and high SVR groups, respectively.

‡Sample sizes are 26 and 11 for the low SVR and high SVR groups, respectively.

mation, leading to a diagnosis of suspected sepsis. These patients had intensive workups for potential infectious sources. Seventy-four percent had positive culture results; of these, 68% had positive blood culture findings. Low initial SVR at the time of shock diagnosis was independently associated with the subsequent development of positive culture results.

The 30-day survival rate for these patients who showed signs of systemic inflammation was 57%, and survival in the SIRS subgroups was better than in the control group. However, there were many more early deaths in the control group than in the groups with severe systemic inflammation. Most deaths related to AMI complicated by CS are known to occur within the first 48 hours, mainly as a result of systemic hypoperfusion secondary to reduced cardiac output,¹⁴ whereas sepsis usually develops in patients who live longer than 48 hours.

The time-dependent model that we created to correct for the survivor bias in our study demonstrated worse survival for the culture-positive group than for the control group. Moreover, even though patients in both SIRS groups were younger, SIRS status remained a significant predictor of increased risk of death after adjustment for age.

In the classic paradigm of CS, the depression of cardiac output after AMI causes intense systemic vasoconstriction and an initial elevation of SVR. This was not ob-

served in the SHOCK trial, even in patients without sepsis. All patient groups had similar mean heart rates and cardiac indexes, but the median SVR was significantly lower in patients with SIRS despite a high rate of vasopressor drug use. What is striking is that in patients who had signs of severe systemic inflammation, SVR was lower at the onset of shock, preceding the clinical diagnosis of suspected sepsis by 2 days (culture-positive) or 4 days (culture-negative). These lower SVRs occurred early during shock, remote from the time of sepsis diagnosis, and would not likely have been due to nosocomial infection. It appears that a systemic inflammatory response was present soon after shock onset (ie, at the time of initial hemodynamic measurements) and that this was an independent risk factor for later development of positive culture results.

An obvious confounding factor in this study was the high incidence of CABG in the culture-positive SIRS group, possibly due to the larger number of catheters used in those patients for longer times during the postoperative period. It is also possible that the systemic inflammatory response in some of these cases was due to the CABG procedure itself and the accompanying cardiopulmonary bypass. Signs of systemic inflammation and a marked increase in cytokine levels have been observed after CABG surgery.^{4,15} However, the increased risk of systemic inflammation and culture-positive SIRS with lower SVR independent of the time of CABG surgery supports the following unifying hypothesis: low SVR predisposes patients with SIRS to endothelial damage, resulting from the increased presence of inflammatory mediators and a leakage syndrome in which normal barriers against infection are disrupted. When comparing patients with lower SVR vs higher SVR, those with lower SVR developed positive culture results whether they had received a CABG or not, and these patients tended to have a worse outcome.

Previously, on the basis of observations in nonhypotensive patients with CS, we have stressed the importance of being able to constrict the vessels in vascular beds to compensate for reduced cardiac output.⁵ The mismatch of depression of myocardial function and inappropriate vasodilation may result in CS in many patients.^{16,17} Emerging evidence suggests that expression of high levels of inducible NO synthase is due to the release of inflammatory mediators during AMI. High levels of NO and peroxynitrites lead to inappropriate vasodilation and further myocardial depression, thus playing an important role in the pathogenesis and persistence of shock.^{4,7} In such settings, administration of NO synthase inhibitors may improve clinical and hemodynamic outcomes.^{18,19}

We postulate that the early low SVR we observed before clinical diagnosis of suspected sepsis in some patients partially reflected the induction of NO-mediated vasodilation in the setting of AMI complicated by CS.^{3,18,19} Patients who showed signs of inflammation also tended to be younger, which suggests that systemic inflammation may contribute more strongly to the pathogenesis of shock in younger patients who present with refractory CS. Support for this comes from the recent observation that inhibition of the post-myocardial infarction inflammatory cascade by a C5 inhibitor reduces the com-

posite of shock and death after percutaneous coronary intervention for AMI.²⁰ Additionally, the SVR seen in the control group was inappropriately low for patients with CS who were receiving large doses of vasopressors and thus should have been exhibiting peripheral vasoconstriction. These patients likely had SIRS to some degree, but this information was not collected for all patients; it was obtained only for those with suspected sepsis. A study of patients with unstable angina provides evidence that circulating lymphocytes are activated and that an immunologic reaction precedes the occurrence of unstable ischemic symptoms.²¹ Inflammatory marker levels are more markedly elevated in the setting of substantial myocardial necrosis, compared with unstable angina, and are further elevated in patients with CS. Inflammatory marker levels were initially high in patients with uncomplicated myocardial infarction at presentation who underwent primary percutaneous coronary intervention and later developed CS²²; these levels were elevated to the same degree in established CS as in septic shock.²³

Our analysis has several limitations. First, no standardized diagnostic test for sepsis was used in the SHOCK trial. Second, evidence of systemic inflammation was not prospectively collected on all patients, and data on leukocyte counts or serologic inflammatory markers (eg, C-reactive protein) were not available. Many in the control group likely had evidence of inflammation as well but did not develop a constellation that led to a clinical diagnosis of suspected sepsis. Finally, duration and frequency of catheter changes were not available in the control group, since a protocol-mandated form was not completed for these patients.

Almost one fifth of patients with CS had severe systemic inflammation that led to a diagnosis of suspected sepsis. Culture-positive patients were at significantly higher risk for death than control patients after correction for a survivor bias. Approximately three fourths of patients who had a subsequent positive culture result presented with an initially low SVR, suggesting that inappropriate vasodilation may play an important role in CS and is a risk factor for the development of positive culture results. Further investigation is needed to elucidate the role of systemic inflammation in the pathogenesis and persistence of CS and the efficacy of therapies that target the disease pathways.

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