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MACROPHAGE MIGRATION INHIBITORY FACTOR IS ASSOCIATED WITH POSITIVE CULTURES IN PATIENTS WITH SEPSIS AFTER CARDIAC SURGERY

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ABSTRACT—This prospective consecutive observational study describes the blood levels of macrophage migration inhibitory factor (MIF), other cytokines, and markers of acute-phase response in 49 consecutive patients who developed the clinical syndrome of sepsis after cardiac surgery. Before starting antimicrobial treatment, all patients underwent microbiologic screening, and blood samples were collected. These samples subsequently were assayed for MIF, macrophage chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and -10, procalcitonin (PCT), and C-reactive protein (CRP). Patients with positive cultures (n = 25) had a higher mortality ($P = 0.046$) and higher levels of MIF ($P < 0.001$) than those with negative cultures (n = 24). We could not detect significant difference between the groups concerning the levels of CRP, PCT, IL6, IL10, MCP-1, or TNF-α. MIF levels showed an area under receiver operator curve of 0.823 for the prediction of culture-proven bacterial infection, with the best cut-off value at 988.5 pg/mL. In conclusion, circulating levels of MIF could be indicated as a valuable marker of microbiologically documented sepsis in patients after cardiac surgery, which suggests that MIF may be prospectively explored as a useful diagnostic tool in this setting.

KEYWORDS—Sepsis, cardiac surgery, MIF, cytokine, microbiological screening

INTRODUCTION

Major injuries, including burns, trauma, and surgical procedures, may be followed by a complex physiological response that is clinically manifested as a systemic inflammatory response syndrome (SIRS). This syndrome can be further complicated by infection and can lead to sepsis, shock, multiple organ failure, and death (1). The host response to trauma and infection involves a complex interplay of innate immune cells that have an essential role in sensing and eliminating microorganisms (2). The cytokines and chemokines are immunomodulatory proteins that mediate this process (3). The proinflammatory cytokines signals initiate a response that, in turn, is modulated by anti-inflammatory cytokines. When orchestrated properly, these responses protect against infection, and then result in tissue repair. However, if the pro- versus anti-inflammatory interplay is uncontrolled, organ dysfunction and death may ensue (4).

SIRS, sepsis, severe sepsis, and septic shock are a continuum, sharing pathophysiologic mechanisms that can lead to multiple organ dysfunction and death (5). The initial conceptions for diagnostic criteria of sepsis (6) were especially directed to maximize its sensitivity (7) possibly because of its increasing incidence and high mortality. It was previously demonstrated that only one-half of the patients with sepsis-related syndromes remained at the same stage of the disease in the next 3 to 7 days after the diagnosis (8). As an attempt to predict outcomes and infectious complications, markers such as complement proteins (9), C-reactive protein (CRP), and procalcitonin (PCT) have been evaluated in postoperative sepsis (10), although results are still inconsistent. In spite of these tests, current recommendations reinforce the importance of early intervention, which includes prompt institution of broad-spectrum antimicrobial therapy guided by the susceptibility pattern of the customary pathogens found in the hospital (11), even though it is acknowledged that up to one-half of the patients will not have microbiological confirmation of an infection (12). Because empirical broad-spectrum therapy has potentially negative medical consequences and increases economic costs, an enhanced ability to detect infection at early stage would be a valuable advance.

Macrophage migration inhibitory factor (MIF) is a cytokine with a central role in the innate immune response (13). Different from other cytokines, MIF is constitutively expressed and stored in the anterior pituitary gland and in mononuclear cells. When stimulated by lipopolysaccharide (LPS), exotoxins, and/or proinflammatory cytokines, macrophages liberate large amounts of MIF that then exerts its powerful proinflammatory actions. MIF is also released in response to low concentrations of corticosteroids, acting as a counter-regulatory molecule, possibly providing a fine-tuning of the inflammatory response (14). Experimental models have shown that MIF is produced in sepsis, that MIF injection increases mortality, and its inhibition by anti-MIF antibodies or MIF gene deletion (15) markedly reduces cytokine production and lethality induced by LPS or gram-positive exotoxins (for review, see Ref. 16). This

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prospective observational study was designed to evaluate the discriminative power of serum levels of MIF for the early identification of microbiologically confirmed infection among patients with postoperative sepsis.

MATERIALS AND METHODS

Study design

This pilot study was approved by the institutional review board and ethical committee for research, and was carried out in a research laboratory associated with the surgical intensive care unit in a tertiary care cardiology hospital. We prospectively enrolled patients who underwent cardiac operations and who met the diagnostic criteria for sepsis—SIRS plus a clinical evidence of infection (1)—after the second postoperative day. We excluded patients with neoplastic or chronic inflammatory diseases and those who were taking immunomodulatory or antimicrobial drugs.

As a component of local standard-of-care, all patients received cefazolin prophylactically, starting 2 h before surgery and ending 12 h postoperatively (17).

On the day when the diagnostic criteria of sepsis were met, informed consent was obtained, and between 12:00 a.m. and 2:00 p.m., 10 mL of peripheral blood was obtained. Serum was separated by centrifugation at 800*g* for 15 min at 4°C and was kept frozen at −70°C until assayed. Serum levels of MIF, macrophage chemoattractant protein 1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and IL-10 were assayed by enzyme-linked immunoabsorbant assay-sandwich technique (R&D Systems, Minneapolis, MN) according to the manufacturer's recommendations. CRP and PCT were assayed by immunonephelometry (Behringer Nephelometer II 2.0; Behringer, Frankfurt, Germany) and immunoluminometry (Brahms Diagnostica, Berlin, Germany), respectively.

All patients underwent microbiological screening of blood and urine. Additionally, we obtained cultures from bronchoalveolar lavage fluid in 26 patients, the drainage from surgical wounds in 10 patients, and catheter cultures of 12 patients. Catheter specimens were seeded using the Maki technique (18). Blood cultures were automatically processed for seeding (Bactec 9240; Becton Dickinson Co., Franklin Lakes, NJ), and bacterial identification and susceptibility tests (Vitek 2; Biomerieux, Durham, NC) were performed using the disk diffusion method when deemed clinically necessary (19). After microbiologic screening, all of the study received broad-spectrum antimicrobial treatment (38).

The clinical characteristics, including demographics, past medical history, present surgical intervention, and subsequent hospital course, were recorded. The preoperative risk profile of all patients was assessed by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (20). Multiple organ dysfunction (MODS) scores (21) and sequential organ dysfunction (SOFA) scores (22) were calculated using data from the 24-h time period beginning at the time of enrollment.

Statistical analysis

Data are reported as mean ± SEM or as median (quartile [Q] 1 and Q3), representing first and third quartiles, according to normal distribution or not, respectively. Differences between groups were analyzed by Mann-Whitney *U* test. Correlations were assessed by the Spearman test. Values of $P < 0.05$ were considered to be statistically significant. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic potential by means of the area under the ROC curve (AUROC) and the diagnostic accuracy of the markers at various cutoff points. The optimal cutoff was obtained by calculating the maximum value for the product of sensitivity and specificity.

RESULTS

The primary aim of this study was to evaluate the association between blood levels of MIF and the presence of positive bacterial cultures in postoperative patients with a clinical diagnosis of sepsis. Additionally, we evaluated the blood levels of other cytokines, PCT, and CRP, and assessed any possible relation between them and clinical outcomes, which was measured by the intensity of organ dysfunction and mortality.

Characteristics of the study group

Between September 2003 and May 2005, 339 patients underwent cardiac surgery with cardiopulmonary bypass. From these, 49 patients (40 after coronary artery bypass surgery and nine after valve replacement) were enrolled in the study according to the diagnostic criteria for sepsis established between the second and eighth postoperative days. These patients presented higher severity of organ dysfunction as measured by maximum MODS scores during the first 8 days postoperative (7.25 ± 0.44 versus 3.50 ± 0.23, $P < 0.001$), and also a higher mortality (34.7% versus 3.1%, $P < 0.001$) when compared with the nonseptic patients. Furthermore, no significant differences were detected concerning age, gender, APACHE II, EuroSCORE, and comorbidities, except for the higher prevalence of chronic obstructive pulmonary disease (28.6% versus 4.8%, $P < 0.01$) in patients with sepsis.

Consistent with other experience (23), pneumonia was the most frequent clinically diagnosed infection (35 patients), followed by infections related to urinary tract (six patients), vascular catheter (five patients), and surgical wounds (three patients). Preoperative risk stratification as measured by the EuroSCORE was similar between patients with positive and negative cultures. The pooled mean score for EuroSCORE was 6.3 ± 0.50. Using the variables obtained at the day when sepsis was detected, global values for MODS were 6.1 ± 0.84, and for SOFA were 6.2 ± 0.77. Although all of these patients met the clinical criteria for sepsis, the results of the microbiological screening were negative in 24 patients (49%) and positive in 25 patients (51%). Positive cultures were obtained from respiratory secretions in 19 patients, from vascular catheters in two patients, peripheral blood from blood in seven patients, and from urine in eight patients. The responsible organisms were gram-negative in 18 cases and gram-positive cocci in seven cases.

Mortality and organ dysfunction

The overall mortality observed was 34.7% (17/49). Among the patients with positive cultures, there were 12 deaths out of 25 patients (48%) compared with five deaths among the 24 patients (20.8%) that comprised the negative culture group ($P = 0.046$) (Table 1). Serum levels of PCT were significantly higher among nonsurviving patients ($P = 0.007$), with an AUROC of 0.656 ± 0.074. No significant association could be detected between the blood levels of any other cytokine assayed, or CRP, and the mortality or the intensity of organ dysfunction as measured by MODS and SOFA scores.

Interrelationship between sepsis markers and cytokine levels

Few patients exhibited detectable levels of IL-10 and TNF-α. Nevertheless, when detectable, the levels of IL-10 and TNF-α were associated with each other ($P = 0.003$, rho = 0.650). The levels of IL-6 (60.6 [35.3–116.8] pg/mL] correlated ($P = 0.01$, rho = 0.468) with MCP-1 levels (105.0 [19.61–178.4] pg/mL) and ($P = 0.009$, rho = 0.368) with PCT levels (0.63 [0.21–2.60 ng/mL] pg/mL). Likewise, the PCT levels correlated with MCP-1 levels ($P < 0.0001$, rho = 0.517).

Microbiological screening

With the exception of MIF, none of the markers showed significant differences between the groups with positive and negative cultures, as shown in Table 2 Notably, the MCP-1 levels did not discriminate between the groups, although there

TABLE 1. **General characteristics of the patients enrolled sorted by microbiologic outcomes**

	Group PC	Group NC	Total	*P*
Age (years)	70.7 ± 1.9	69.5 ± 1.9	70.1 ± 1.2	NS
Men	17/25 (68.0%)	16/24 (66.6%)	33/49 (67.3%)	NS
APACHE II*	15.8 ± 0.7	15.3 ± 0.6	15.5 ± 0.5	NS
MODS†	5.6 ± 1.07	6.6 ± 1.36	6.1 ± 0.84	NS
SOFA†	6.0 ± 0.69	6.4 ± 1.43	6.2 ± 0.77	NS
EuroSCORE	6.1 ± 0.82	6.5 ± 0.65	6.3 ± 0.50	NS
Mortality	12/25 (48%)	5/24 (20.8%)	17/49 (34.7%)	0.046
Chronic obstructive pulmonary disease	8/25 (32.0%)	6/24 (25.0%)	14/49 (28.6%)	NS
Diabetes mellitus	7/25 (28.0%)	8/24 (33.3%)	15/49 (30.6%)	NS
Hypertension	18/25 (72.0%)	14/24 (58.3%)	32/49 (65.3%)	NS
Thyroid disease	2/25 (8.0%)	1/24 (4.2%)	3/49 (4.1%)	NS

*At admission in the surgical intensive care unit; †when sepsis was clinically established.
PC, patients with positive cultures; NC, patients with negative cultures.

was a trend for them to be lower in the group with positive cultures (34.1 [14.3–127.4] pg/mL) compared with the group with negative cultures (135.9 [49.9–224.2] pg/mL; $P = 0.06$).

Blood levels of MIF ranged from 39.7 to 8490.4 pg/mL, with median values of 1152.8 (198.3–3409.3) pg/mL. As shown in Figure 1, significantly higher levels of MIF ($P < 0.001$) were detected among patients with positive cultures (1632.2 [1264.2–5767.3] pg/mL) compared with those with negative cultures (379.90 [100.9–1344.1] pg/mL). Among the cytokines tested, MIF levels showed the best performance for the early detection of positive-culture cases, with AUROC of 0.823 ± 0.06. The optimum cutoff value was of 988.5 pg/mL, generating a positive likelihood ratio (LR+) of 3.36 and a negative likelihood ratio (LR−) of 0.21 in the prediction of positive cultures. The lowest value of MIF detected in a patient with positive cultures was 709.4 pg/mL (Table 3).

DISCUSSION

The high prevalence of SIRS after major surgical procedures or trauma makes the diagnosis of infection a major challenge in the surgical intensive care setting, particularly after cardiac surgery (24). Moreover, the likelihood of infection is increased in this setting as the result of many factors, including the presence of indwelling devices, surgical wounds, and pulmonary edema (25). Early diagnosis and treatment can improve patient outcomes and decrease medical costs (26). For these reasons, most patients with SIRS and a potential source of infection are currently treated as if they have bacterial sepsis. In the postoperative setting, especially after cardiac surgery, the high prevalence of SIRS associated with multiple potential reasons for clinical signs that could be misinterpreted as infection might make one to inquire how suitable are the current diagnostic criteria of sepsis (1) based on ''clinical evidence of infection'' instead of microbiologically documented infection. To address this point, the development of diagnostic markers of microbiologically proven sepsis would be likely to facilitate the management of patients in this setting, especially concerning the decision to start empirical antimicrobial therapy. The results presented here may be potentially important to help early identification of patients with proven infection in this population.

Experimental models have shown that microbial agents and LPS inoculation can promote marked rising in cytokine blood levels (27). Despite of many common mechanisms, different cytokine profiles were observed, comparing experimental models of systemic inflammation (28) and sepsis caused by different microorganisms (2).

An essential component of the LPS receptor complex is toll-like receptor 4, a signal-transducing transmembrane protein whose expression is upregulated by MIF (29). It has been experimentally demonstrated that MIF production can be induced by endotoxin inoculation, with elevated blood levels observed 6 h after the injection (30). We (31) and others (32) have previously shown that cardiac surgery under cardiopulmonary bypass results in a transient rise in blood levels of MIF, which return to baseline levels 24 h after the procedure. In the present study, this early effect of surgical trauma on the blood levels of MIF was controlled for by including patients beginning at least 2 days after surgery. Our results demonstrated that when the diagnostic criteria of sepsis were met, the MIF levels in the blood exhibited discriminative power for the early detection of documented bacterial sepsis (AUROC = 0.823). The limited magnitude of the likelihood ratios

TABLE 2. **Levels of inflammatory markers sorted by microbiological outcomes**

	Group PC	Group NC	*P*
MIF (pg/mL)	1632.2 (1264.2–5767.3)	379.90 (100.9–1344.1)	<0.001
MCP-1 (pg/mL)	34.1 (14.3–127.4)	135.9 (49.9–224.2)	NS (0.061)
IL-6 (pg/mL)	50.0 (34.0–114.4)	76.0 (29.1–139.3)	NS (0.857)
IL-10 (pg/mL)	0 (0–19.2)	0 (0–1.5)	NS (0.926)
TNF-α (pg/mL)	0 (0–0)	0 (0–0)	NS (1.000)
CRP (mg/L)	101.0 (81.0–186.0)	78.0 (44.5–180.3)	NS (0.949)
PCT (ng/mL)	0.6 (0.2–2.3)	1.1 (0.2–5.1)	NS (0.802)

Values are presented as medians (Q1 and Q3), representing first and third quartiles, respectively.
PC, patients with positive cultures; NC, patients with negative cultures.

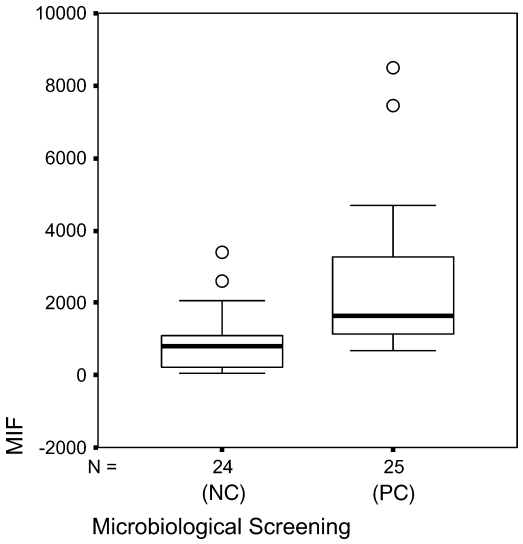

FIG. 1. **Serum levels of MIF sorted by microbiological outcomes.** (PC, patients with positive cultures; NC, patients with negative cultures)

TABLE 3. **Cutoff values of MIF for the prediction of positive bacterial cultures in patients with a clinical diagnosis of sepsis**

Cutoff values of MIF	Sensitivity	Specificity	LR+	LR−
988 pg/mL	0.840	0.750	3.36	0.21
900 pg/mL	0.880	0.625	2.37	0.26
709 pg/mL	1.000	0.458	1.85	<0.01

generates a small but perhaps important improvement in diagnostic ability. Most likely, the most important finding is that positive cultures did not occur in cases with MIF levels lower than 709 pg/mL, making this a potentially valuable cutoff point in predicting whether patients with clinical sepsis will have negative cultures. Although the plasma levels of MIF did not discriminate severe sepsis with positive culture from surgical trauma (33), higher levels of MIF were associated with positive cultures in trauma patients (34). To our knowledge, this is the first description of MIF as an early marker of postoperative infection in a specific population of surgical patients who met the clinical diagnostic criteria for sepsis.

Current practice guidelines use the results of bacterial cultures to dictate antibiotic therapy in patients with SIRS. If cultures are negative, antibiotics may be stopped; if they are positive, broad-spectrum empirical therapy is discontinued and replaced by antibiotics that are specific for the identified organism (11). However, a common dilemma rises when critical patients in whom there is clinical suspicion of infection have negative microbiological results. In this circumstance, it is common to choose to maintain broad-spectrum empirical antimicrobial treatment. However, the potentially detrimental effects of unnecessary use of wide-spectrum antimicrobials such as superinfection by resistant pathogens sign that diagnostic tests as circulating levels of MIF could be clinically useful to supplement bacterial cultures.

High blood levels of MIF in samples obtained early after intensive care unit admission have been associated with poor outcome in sepsis (35, 36). In the present study, in spite of the higher mortality among patients with positive cultures (which was predicted by MIF levels), we did not find a direct correlation between MIF and mortality. The reason for this discrepancy is not clear, but could be related to differences in the characteristics of the patients included in this study, especially to the surgical intervention.

As previously described (10, 37), the present study has shown that high blood levels of PCT are associated with a poor outcome.

An interesting and consistent relationship was observed among IL-6, MCP-1, and PCT that is consistent with the previous demonstration that IL-6 induces the expression of MCP-1 (38) and PCT (21).

Considering the limitations related to the small population included in this pilot study, we found that MIF levels could be an accurate marker for the early detection of infection among patients who developed sepsis after cardiac surgery. Moreover, MIF levels lower than 709 pg/mL were highly suggestive that cultures would be negative. The reproduction of these results in future prospective investigations including larger and different populations are necessary to clinically validate the discriminative power of MIF in detecting microbiologically documented infection in patients with sepsis, which could reduce the biologic and economic costs of postoperative sepsis.

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