Early prediction of outcome in score-identified, postcardiac surgical patients at high risk for sepsis, using soluble tumor necrosis factor receptor-p55 concentrations

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Objective: To investigate the prognostic value of increased serum concentrations of soluble tumor necrosis factor (TNF) receptors in patients at high risk for sepsis.

Design: Prospective study.

Setting: Cardiac surgical intensive care unit in a University Hospital.

Patients: Those 27 of 870 consecutive postcardiac surgical patients who met a previously validated high-risk criterion for imminent sepsis (Acute Physiology and Chronic Health Evaluation II [APACHE II] score of ≥24 on the first postoperative day [day 1]). In this population, systemic inflammatory response syndrome was present in 96% of the patients and the inhospital mortality rate was 30%. In addition, ten postcardiac surgical patients with an uncomplicated course (mortality rate 0%) were studied for comparison.

Interventions: Blood sampling for measurements of serum concentrations of TNF and soluble TNF receptors 55 kilodalton (TNF receptor-p55) and 75 kilodalton (TNF receptor-p75) on days 1, 2, 3, and 5.

Measurements and Main Results: Compared with the ten patients with an uncomplicated course (group A), the high-risk patients had significantly higher baseline (day 1) serum concentrations of soluble TNF receptor-p55 (9.2 vs. 4.2 ng/mL) and soluble TNF receptor-p75 (9.2 vs. 5.5 ng/mL). These high-risk patients could be further differentiated into two subgroups: one (B) with a prompt decrease in APACHE II score and a good prognosis (mortality rate 0%) and another (C) with a persisting high risk of sepsis and mortality rate (40%, $p < .05$). Although baseline APACHE II score was similar in both high-risk subgroups, soluble TNF receptor-p55 concentrations were significantly higher in subgroup C compared with subgroup B already at baseline (10.7 vs. 4.7 ng/mL). The receiver operating characteristic curve for subgroup classification by soluble TNF receptor-p55 was in a discriminating position with an area (0.773 ± 0.096), confirming soluble TNF receptor-p55 as a predictor of mortality. TNF and soluble TNF receptor-p75 concentrations were less predictive at baseline.

Conclusions: This study suggests that increased soluble TNF receptor-p55 concentrations in the serum of postcardiac surgical patients allow earlier prognostication of subsequent hospital course than APACHE II scores alone. This study further suggests that the combination of physiologic scores and cytokine receptor measurements could improve the predictive power of early postoperative risk stratification. (Crit Care Med 1996; 24:596–600)

KEY WORDS: tumor necrosis factor; tumor necrosis factor receptor; severity of illness index; sepsis; risk; predictive value of tests; heart surgery; prognosis; intensive care unit; receiver operating characteristic curve

Among the cytokines implicated in the development of sepsis and septic shock, tumor necrosis factor-α (TNF) is considered to be one of the most important endogenous mediators responsible for cytotoxicity and inflammatory changes both *in vivo* and *in vitro* (1). Naturally occurring inhibitors of TNF have been found that block these TNF-induced effects *in vitro* and *in vivo* (2–4). These host mediators have been identified as the soluble extracellular domains of the 55- and 75-kilodalton, membrane-bound TNF receptors (soluble TNF receptors-p55 and -p75) (5–7), which compete with the membrane receptors for binding of free TNF. Studies on endotoxemic human volunteers (8, 9) as well as on patients with meningococcemia (10), parasitemia (11), or clinical sepsis (12) report increased circulating concentrations of both types of soluble TNF receptors. At present, however, we are not aware of data comparing septic with other nonseptic intensive care unit (ICU) patients and systematically addressing the prognostic value of increased soluble TNF receptor concentrations in these patients.

In the present study, we investigated the relationship between serum concentrations of TNF and both types of soluble TNF receptors and their prognostic value in ICU patients who were prospectively identified by Acute Physiology and Chronic Health Evaluation II (APACHE II) (13) score to be

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at high risk for sepsis within 24 hrs after cardiac surgery (14), comparing these patients with patients who had an uncomplicated postoperative course. This cardiac surgical group is of particular interest for two reasons. First, extracorporeal circulation and its sequelae (15, 16) increase the risk of postoperative infections and subsequent morbidity and mortality (14). Second, increased cytokine concentrations may be independent of a septic process. Extracorporeal circulation per se alters the serum concentrations of inflammatory mediators, such as the complement system (15), elastase (16), and neopterin (16), as well as TNF (17). Increased TNF (and soluble TNF receptor-p55 [18]) concentrations have also been found in other cardiac diseases, such as complicated myocardial infarction (18) and heart allograft rejection (19), which are unrelated to sepsis.

Our data show that even at similar initial high risk, as assessed by the APACHE II score, one subgroup of patients was amenable to recovery while the other had a high mortality rate. The combination of the APACHE II score with soluble TNF receptor-p55 serum concentrations appears to allow the early delineation of these two subgroups.

MATERIALS AND METHODS

Patients. Postcardiac surgical ICU patients (n = 27) who fulfilled the previously validated high-risk criterion for postoperative sepsis (APACHE II score of ≥24 on the first postoperative day ["day 1"] [14]) were included into the study. This group was prospectively selected from 870 patients undergoing elective open-heart surgery (excluding transplantation) on the basis of microcomputer-assisted APACHE II scoring (20). The initial blood samples were collected on day 1. Simultaneously, conventional sepsis criteria (Elebute sepsis scores [21] and systemic inflammatory response syndrome [22]) were recorded. All patients were subsequently administered polyvalent immunoglobulins in addition to antibiotics. Blood sampling and APACHE II scoring were repeated on days 2, 3, and 5.

In addition to the high-risk group, ten consecutive postcardiac surgical patients at low risk for sepsis (APACHE II score of <19 on day 1 [14]) during the above period of risk screening were monitored for comparison (days 1 through 3).

Mortality rate was defined as inhospital mortality rate. All patients had given informed consent. The study was approved by the University of Munich Medical Faculty Ethics Committee.

Sampling and Assays. After blood sampling, serum was obtained by centrifugation (2000 *g* for 15 mins) at room temperature. Aliquots were stored at –30°C until analysis. TNF serum concentrations were determined in duplicate by enzyme immunoassay (EASIA®, Medgenix, Ratingen, Germany). TNF concentrations were measured as total TNF, including the free and receptor-bound molecule, with a detection limit of 5 pg/mL. Concentrations of soluble TNF receptors-p55 and -p75 were measured with enzyme-bound immunologic assays (10). We used the recently available automatic measurements on Cobascore® (ELISA, Hoffmann-La Roche, Basel, Switzerland), which utilizes the purified monoclonal mouse antibody clones utr-4 (against soluble TNF receptor-p55) and htr-20 (against soluble TNF receptor-p75) coated on plastic beds. The soluble TNF receptor assays detect only functionally active receptor fragments, using enzyme-labeled recombinant human TNF as a substrate. Concentrations of ≤10 ng/mL of TNF in plasma did not interfere with the assay (11). The lower detection limit was about 100 pg/mL for both soluble TNF receptors.

Statistical Analysis. Differences between groups were statistically analyzed using the chi-square test with Yates correction for categorical variables. For continuous variables, the Student's *t*-test for unpaired data or the Mann-Whitney test were used, where appropriate. Correlations were assessed by means of Pearson's coefficient. The areas under the receiver operating characteristic curves were determined (mean ± SEM) and compared, according to the method of Hanley and McNeil (23, 24). All other values are given as mean and 95% confidence intervals for the mean. A $p < .05$ was considered statistically significant.

RESULTS

In the 27 patients who were scored as being at high risk for sepsis, mean APACHE II scores on day 1 were 27.3 (25.7 to 28.9) compared with 8.5 (5.8 to 11.2) in the low-risk group. The high-risk group presented significantly ($p < .0001$) higher mean Elebute sepsis scores: 12.4 (11.6 to 13.2) vs. 3.8 (2.7 to 4.9). Systemic inflammatory response syndrome was present in all but one of the high-risk patients (96%). Mortality rate in the high-risk population was 30% (low risk = 0%).

By means of sequential APACHE II scoring, the high-risk patients could be retrospectively differentiated into two subgroups (Fig. 1, *top left*, *B* and *C*). In one subgroup (B), there was a prompt decrease in APACHE II scores toward low-risk values (A), which was associated with good prognosis (mortality rate 0%). In the other subgroup (C), there was a persisting score-quantified high risk of sepsis during the first postoperative days and a resulting increase in mortality rate (40%, $p < .05$). The APACHE II score's discriminatory power between survivors and nonsurvivors was significant on day 3 (chi-square 7.404, $p < .01$; receiver operating characteristic area 0.809 ± 0.085) and day 5 (chi-square 10.028, $p < .005$; receiver operating characteristic area 0.876 ± 0.070).

Compared with low-risk patients, the group of score-classified patients at high risk for sepsis as a whole displayed higher mean baseline (day 1) serum concentrations for TNF and both types of soluble TNF receptors (Table 1). Within the high-risk group, all three parameters were significantly higher on day 1 in nonsurvivors compared with survivors (Table 1).

Even though patients in both high-risk subgroups (B and C) had similar APACHE II scores on day 1, subgroup C had higher soluble TNF receptor-p55 and TNF concentrations as compared with subgroup B (Fig. 1). On day 2, TNF and both types of soluble TNF receptors were significantly higher in subgroup C compared with B. The mean peak concentrations in subgroup C were observed on day 2 for TNF and on day 3 for both soluble TNF receptors. On day 5, a decrease in TNF and both soluble TNF receptors was noted in subgroup C, despite

unchanged APACHE II scores (Fig. 1). On all days of monitoring, subgroup B displayed similar TNF and soluble TNF receptor concentrations to those concentrations of the low-risk patients (Fig. 1, A).

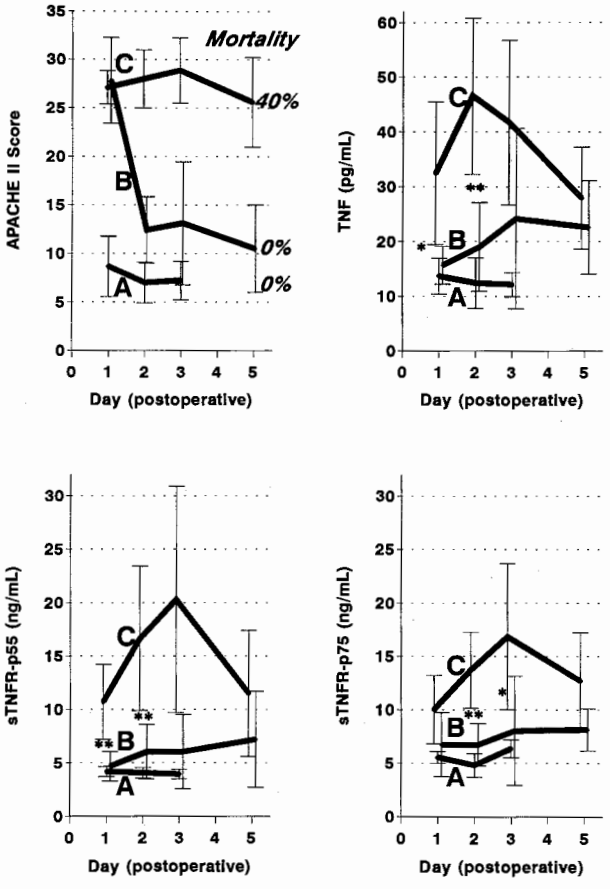

Figure 1. Patients after cardiac surgery. Early postoperative course of Acute Physiology and Chronic Health Evaluation II (*APACHE II*) scores, tumor necrosis factor (*TNF*), and soluble TNF receptors 55 kilodalton (*sTNFR-p55*) and 75 kilodalton (*sTNFR-p75*) serum concentrations. Classification into three subgroups according to baseline and subsequent APACHE II scores (*top left*): *A*) low-risk controls (n = 10); *B*) high-risk, improving (n = 7); *C*) high-risk, persisting during the first days (n = 20). Asterisks (*$p < .05$; **$p < .005$) indicate significant differences between subgroups *C* and *B*. On day 5, samples for TNF and soluble TNF receptor measurements in subgroup *C* were available only for 12 patients. For further details, see text. Data are mean ± 95% confidence intervals for the mean.

Receiver operating characteristic curves for correct classification into subgroups B and C on day 1 gave the largest area for soluble TNF receptor-p55 (0.773 ± 0.096), compared with TNF (0.668 ± 0.100), soluble TNF receptor-p75 (0.644 ± 0.118, $p < .05$), and the APACHE II score (0.500 ± 0.132, $p < .05$). Accordingly, the best Youden index (25) for correct subgroup classification at baseline of 0.61 was achieved by soluble TNF receptor-p55 (cutoff value ≥6.5 ng/mL, chi-square 4.532, $p < .05$) compared with 0.55 for TNF (cutoff value >26.2 pg/mL, chi-square 4.418, $p < .05$) and with 0.33 for soluble TNF receptor-p75 (cutoff value ≥8.4 ng/mL, chi-square 0.914, $p = .34$). At this soluble TNF receptor-p55 cutoff point, the positive-predictive value for classification into subgroup C was particularly high (100%; negative predictive value 46%). The respective values were 100% and 44% for TNF and 90% and 36% for soluble TNF receptor-p75.

During the first three postoperative days, both types of soluble TNF receptors correlated significantly ($p < .0001$) with the TNF concentrations (soluble TNF receptor-p55: $r^2 = .61$; soluble TNF receptor-p75: $r^2 = .69$), with a maximum on day 3 (soluble TNF receptor-p55: $r^2 = .83$; soluble TNF receptor-p75: $r^2 = .86$). No correlation of these parameters with the APACHE II score was noted on day 1. From day 2 on, TNF and both types of soluble TNF receptors correlated with the APACHE II score. The best correlation was found on day 2 for TNF ($r^2 = .44$) and on day 3 for soluble TNF receptor-p55 ($r^2 = .49$) and soluble TNF receptor-p75 ($r^2 = .50$) (all $p < .001$). On the first 2 days, there was a tendency in subgroup C that survivors had higher molar soluble TNF receptor/TNF ratios than nonsurvivors (for soluble TNF receptor-p55: day 1, 174 vs. 99; day 2, 148 vs. 83; for soluble TNF receptor-p75: day 1, 111 vs. 78; day 2, 95 vs. 56).

DISCUSSION

In sepsis, TNF itself induces its own soluble receptors in a dose-effect relationship (12). The serum concentrations of soluble TNF receptor-p55 and soluble TNF receptor-p75 in sepsis (12) or parasitemia (11) significantly correlate with the immunoreactive (total) TNF concentrations. Our study primarily aimed to address this relationship, particularly the prognostic value of increased concentrations of soluble TNF receptors in a well-defined postoperative patient population at high risk for sepsis.

The increase in serum concentrations of both soluble TNF receptors in these high-risk patients was similar to that increase reported in patients with clinical sepsis (12). Likewise, the release of soluble TNF receptor-p55 and soluble TNF receptor-p75 significantly correlated with total TNF concentrations. In the high-risk group, the TNF peak concentration preceded

Table 1. Baseline serum tumor necrosis factor (TNF) and soluble TNF receptor concentrations according to postoperative risk for sepsis and to prognosis

Parameter	All Low-Risk Patients (n = 10)	All High-Risk Patients (n = 27)	*p* Value	High-Risk Survivors (n = 19)	High-Risk Nonsurvivors (n = 8)	*p* Value
TNF (pg/mL)	13.7 (10.4–17.0)	28.1 (18.2–38.0)	<.05	21.2 (11.5–30.9)	44.5 (20.3–68.7)	<.05
sTNFR-p55 (ng/mL)	4.2 (3.7–4.7)	9.2 (6.4–12.0)	<.01	7.4 (3.9–10.9)	13.5 (9.7–17.3)	<.005
sTNFR-p75 (ng/mL)	5.5 (4.9–6.1)	9.2 (6.7–11.7)	<.01	7.3 (4.7–9.9)	13.9 (9.5–18.3)	<.005

sTNFR-p55, soluble 55 kilodalton TNF receptor; sTNFR-p75, soluble 75 kilodalton TNF receptor.
Values are mean with confidence intervals in parentheses.

those concentrations of both soluble TNF receptors. Baseline TNF and soluble TNF receptors were significantly higher in the patients at high risk for sepsis compared with our postcardiac surgical low-risk group. Nonetheless, these postoperative low-risk ICU patients still had higher soluble TNF receptor concentrations than those concentrations reported for healthy controls. Our data on healthy controls (soluble TNF receptor-p55 1.3 ± 0.8 ng/mL, soluble TNF receptor-p75 0.9 ± 0.7 ng/mL, n = 50) are in accordance with previously published observations (12). Extracorporeal circulation, which was employed in all our cardiac surgical patients, may cause this increase in TNF concentrations (17). Taken together, these data seem to support the concept that TNF concentrations themselves induce and regulate soluble TNF receptors and that such a mechanism may operate also in inflammatory states other than sepsis.

The major finding of our study was, however, that within the patient group at high risk for sepsis, the presence of increased soluble TNF receptor-p55 serum concentrations very early predicted the severity of the subsequent course and prognosis. Thus, already on the first postoperative day, soluble TNF receptor-p55 concentrations of ≥6.5 ng/mL identified all patients with a persisting severe course and a significantly increased mortality rate, despite early initiation of sepsis therapy (antibiotics plus immunoglobulin). The receiver operating characteristic curve for the soluble TNF receptor-p55 was discriminatory on day 1 and the area under the curve confirmed soluble TNF receptor-p55 as a predictor of mortality, as compared with soluble TNF receptor-p75. An intriguing finding was that even though APACHE II has a good mortality predictive value in postcardiac surgical patients (14), soluble TNF receptor-p55 concentrations further distinguished between the two high-risk subgroups, even at an earlier stage. It is conceivable that the rapid improvement noted in some of our patients was due to successful early treatment. Conversely, the persisting high-grade disease severity in the remainder of patients could have been caused by a pretreatment hyperinflammatory state that is best indicated by increased soluble TNF receptor-p55 concentrations but less reflected by the initial routine clinical variables included in the APACHE II score. Thus, soluble TNF receptor-p55 concentrations on the first postoperative day seem to quantitatively mirror the severity of the inflammatory state and the subsequent course of the disease. The prognostic value of increased concentrations of soluble TNF receptors in our study is reflective of the prognostic value of high concentrations of soluble TNF receptors in children with severe meningococcemia with fatal outcome (10). A recent preliminary report (26) communicated similar results for soluble TNF receptor-p55 in adults with sepsis. The discrepancy between our data and the data of other researchers (8, 12) may be due to the different timing of sample collections, and to the selection criterion of including septic patients in the study without risk stratification.

In our study, the baseline soluble TNF receptor-p75 (and TNF) concentrations were less predictive for prognosis. The physiologic significance of the presence of the two receptors remains poorly understood (27). Whether the differences in the release of these receptors and their biological properties are responsible for a better predictive value of soluble TNF receptor-p55 in our patients remains to be clarified. The reason for the decrease in both concentrations of soluble TNF receptors on day 5 in our high-risk subgroup C, despite persisting high APACHE II scores, remains uncertain. Whether their intracellular mobilization and subsequent depletion of storage pools (28) is responsible for this effect remains unclear.

The clinical significance of increased serum soluble TNF receptor-p55 values may prove a useful approach for early sepsis severity and mortality risk stratification, in addition to APACHE II scores. Even though APACHE II scores of ≥24 on the first day after cardiac surgery identified patients at high risk for sepsis where early treatment is desirable (14), our data showed that score assessment combined with soluble TNF receptor-p55 measurements can improve the predictive power. In particular, soluble TNF receptor-p55 concentrations of >6.5 ng/mL on the first postoperative day may permit an early identification of the subgroup with a hyperinflammatory response and an increased mortality rate, which would require further sepsis therapy in addition to the treatment regimen already being used in our study. Thus, combination of physiologic scores (first step) and cytokine receptor measurements (second step) for risk stratification may prove useful for a more specific initiation of supplemental sepsis therapy. Even though soluble TNF receptors are present in high molar excess over TNF (90-fold in the study by van der Poll [12], ≤99-fold in the nonsurvivors in our study), this excess may still be insufficient in severe cases to prevent the lethal consequences of high blood concentrations of TNF (12). New treatment approaches that deserve consideration are either to increase concentrations of soluble TNF receptors by exogenous administration of recombinant soluble TNF receptors (8, 29) or to neutralize TNF concentrations by TNF antibodies (30). This hypothesis will have to be established by future clinical studies.

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