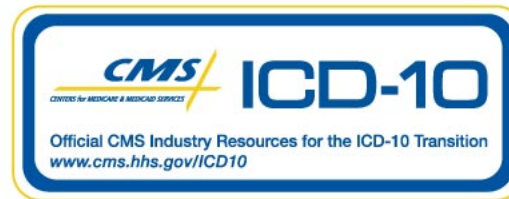


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Troponin as a Risk Factor for Mortality in Critically Ill Patients Without Acute Coronary Syndromes

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OBJECTIVES	We sought to assess the mechanism and prognostic value of elevated troponins in patients without acute coronary syndromes (ACS).
BACKGROUND	Cardiac troponins are used as specific markers for the diagnosis of ACS. Recent studies reported a considerable number of critically ill patients without ACS as being troponin-positive, especially patients with sepsis, pulmonary embolism, renal failure, and stroke.
METHODS	We analyzed 58 consecutive, critically ill patients admitted for reasons other than ACS, according to their troponin status. Thirty-day mortality, left ventricular ejection fraction (LVEF), and a panel of inflammatory cytokines were compared between troponin-positive and troponin-negative patients. Relevant coronary artery disease was excluded either by stress echocardiography or autopsy.
RESULTS	Of the 58 critically ill patients, 32 (55%) without evidence of ACS were troponin-positive. Positive troponin levels were associated with higher mortality (22.4% vs. 5.2%, $p < 0.018$) and a lower LVEF ($p = 0.0006$). Troponin-positive patients had significantly higher median levels of tumor necrosis factor (TNF)-alpha, its soluble receptor, and interleukin (IL)-6. A subgroup of 10 aplastic patients was troponin-negative at study entry. Three became troponin-positive during leukocyte recovery and subsequently died, whereas all the others stayed troponin-negative and survived. Flow-limiting coronary artery disease was not demonstrable at autopsy or stress echocardiography in 72% of troponin-positive patients.
CONCLUSIONS	Elevated troponin is a mortality risk factor for medical intensive care patients admitted for reasons other than ACS. It is associated with decreased left ventricular function and higher levels of TNF-alpha and IL-6. (J Am Coll Cardiol 2003;41:2004-9) © 2003 by the American College of Cardiology Foundation

Cardiac isoforms of troponin I (cTnI) and troponin T (cTnT) are highly sensitive and specific markers of myocardial injury. The measurement of cTnI and cTnT in blood has recently been accepted by the Joint Committee of the European Society of Cardiology and the American College of Cardiology as the standard biomarker for the diagnosis of acute myocardial infarction and by the American College of Cardiology and the American Heart Association for the diagnosis and management of unstable angina (1,2). In the setting of an acute coronary syndrome (ACS), cardiac troponins identify patients with a several-fold increased risk of death in the subsequent weeks (3). Besides this enthusiasm for troponin measurements in ACS, there have been several reports demonstrating a high incidence of elevated troponin levels in patients with sepsis and septic shock (4-9). In contrast to the extensive literature on troponins in ACS, which suggests that abnormal concentrations of

cardiac troponins always represent irreversible myocardial damage, there is evidence that cardiac troponins might be released by other mechanisms, such as reversible myocardial ischemia (10). This fits the observation that myocardial depression during sepsis is a fully reversible process in patients surviving sepsis (11). Cardiac troponins have also been reported to predict mortality in early sepsis, end-stage renal disease, acute stroke, and pulmonary embolism (5,12-14). Therefore, it is of great interest to understand the underlying mechanisms leading to elevated cardiac troponins, besides ACS. Hence, the aim of this study was to investigate the mechanism of elevated cardiac troponins in patients admitted to the intensive care unit and understand their impact for predicting mortality in patients without ACS.

METHODS

Study population. Fifty-eight critically ill patients referred to two medical intensive care units for sepsis, septic shock, systemic inflammatory response syndrome, and other severe diseases, except ACS, myocardial infarction, or recent cardiac surgery, were consecutively included within 24 h

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Abbreviations and Acronyms

- ACS = acute coronary syndromes
- cTnI = cardiac troponin I
- cTnT = cardiac troponin T
- IL = interleukin
- LVEF = left ventricular ejection fraction
- SAPS = Simplified Acute Physiology Score
- SIRS = systemic inflammatory response syndrome
- TNF = tumor necrosis factor

after admittance. Definitions of sepsis, septic shock, and systemic inflammatory response syndrome (SIRS) corresponded to the criteria of the consensus conference (15). In short, SIRS is defined as a systemic inflammatory response to a variety of clinical insults. The response is manifested by two or more of the following conditions: temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg, and white blood cell count >12,000/mm³ or <4,000/mm³. Sepsis is defined as SIRS in response to proven infection. Septic shock is defined as sepsis-induced hypotension, despite adequate fluid resuscitation needing catecholamine support.

Patients presenting with chest pain and one additional sign of acute coronary artery disease (dynamic ST-segment elevation or depression >1 mm on the 12-lead electrocardiogram or creatine kinase levels twice the upper limit), patients with recent cardiac surgery and those admitted to the intensive care unit only for the purpose of observation <24 h were excluded. Because of these strictly applied

exclusion criteria, the majority of the study population in our medical intensive care units consisted of patients with severe infections, and only a minority suffered from other diseases (Table 1). The local ethics committee of both hospitals approved the study. All patients, or in case of unconsciousness, their closest relative, signed a written, informed consent.

Data collection. The Simplified Acute Physiology Score II (SAPS-II) was used to analyze disease severity at study entrance (16). The original reference provides a mathematical model to calculate mortality from SAPS-II. The approximate percentages are as follows (SAPS-II/mortality): 20 points/5%, 40 points/25%, 50 points/50%, 60 points/70%, and 80 points/90%.

The left ventricular ejection fraction (LVEF) was assessed by echocardiography, using the Simpson biplane formula (17), within 24 h of study inclusion by a cardiologist blinded to the troponin levels. Patient survival was assessed 30 days after study inclusion. In case of death, an autopsy was performed. To exclude relevant coronary artery disease in troponin-positive patients, dobutamine stress echocardiography was performed according to standard procedures (18) in survivors within three months after recovery. Analysis of stress echocardiograms was performed by two experienced cardiologists.

Laboratory diagnostics. Blood samples for determination of cardiac troponins and cytokines were taken at the time of study inclusion and after 3, 12, 24, 48, 96, and 192 h. Analysis of cardiac troponins was performed from the serum on a day-to-day basis, and samples for the determination of cytokine levels were centrifuged immediately after the blood was taken and frozen at -20°C. The cTnT levels were assessed with the third-generation test (Eleclys) from Roche Diagnostics (Rotkreuz, Switzerland), and cTnI levels with a second-generation test using the AccessAnalyzer (Beckman Coulter Inc., Fullerton, California). The cutoff level was indicated as 0.1 µg/l by the manufacturer for both cTnI and cTnT and was predefined before starting the study. Patients with at least two positive troponin measurements (cTnI or cTnT) were called "troponin-positive." C-reactive protein measurement was done on an Integra 700 analyzer (Roche Diagnostics), and levels >5 mg/l were considered positive.

Tumor necrosis factor (TNF)-alpha was assessed by an enzyme-linked immunosorbent assay (ELISA) (Endogen, Boston, Massachusetts; cutoff <6.3 pg/ml). For determination of TNF-alpha receptor, an ELISA from Bender Med Systems (Vienna, Austria; cutoff <0.49 ng/ml) was used. Analyses of interleukin (IL)-1-beta, IL-6, IL-8, and soluble intercellular adhesion molecule-1 were performed with ELISA (R&D Research and Diagnostics System, Minneapolis, Minnesota). Cutoff levels were <0.1 pg/ml, <3.1 pg/ml, <0.1 pg/ml, and <300 ng/ml, respectively.

Statistical analysis. Continuous data are expressed as the mean value ± SD or as the median value with interquartile range, as appropriate. The chi-square test was used to

Table 1. Baseline Characteristics of the Study Population (n = 58)

Age (yrs)	55 ± 21
Female gender	30 (52%)
White race	53 (91%)
Body mass index (kg/m ²)	25 ± 5
SAPS-II (points)	42 ± 15
Shock requiring supportive therapy with catecholamines	24 (41%)
Main diagnoses	
SIRS/sepsis—immunocompetent	21 (36%)
SIRS/sepsis—aplastic	6 (11%)
Septic shock—immunocompetent	20 (34%)
Septic shock—aplastic	4 (7%)
Others*	7 (12%)
Troponin-positive measurement	
cTnI or cTnT	32 (55%)
cTnI	28 (48%)
cTnT	27 (47%)
Type of infection	
Bacterial, gram-positive	15 (26%)
Bacterial, gram-negative	19 (33%)
Mixed and others†	4 (7%)
Culture negative	20 (34%)

*The diagnoses of these patients were two intoxications, two severe gastrointestinal bleedings, one anaphylactic shock, one pulmonary disease, and one diabetic ketoacidosis. †Two patients had mixed gram-positive and gram-negative bacterial infection, one had systemic *Candida*, and one had systemic Epstein-Barr virus infection. Data are presented as the mean value ± SD or number (%) of patients.

cTnI or cTnT = cardiac troponin I or T, respectively; SAPS-II = Simplified Acute Physiology Score II (higher scores indicate more severe illness); SIRS = systemic inflammatory response syndrome.

compare troponin-positive and -negative patients with respect to “shock” and “no shock” status. The association between LVEF and troponin levels was calculated using Spearman nonparametric correlation. Group comparisons of all continuous variables were calculated using Mann-Whitney statistics. Survival curves were prepared according to the method of Kaplan-Meier (19), and univariate survival distribution was compared by the log-rank test. Two-sided p values <0.05 were considered to be statistically significant. Statistical calculations were performed using the statistical package StatView, version 4.0 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient characteristics. The baseline clinical characteristics of the study population are presented in Table 1. Twenty-seven patients (47%) had sepsis or systemic inflammatory response syndrome, and six of them were aplastic due to chemotherapy of hematologic malignancies. Septic shock requiring supportive therapy with catecholamines was diagnosed in 24 patients (41%), and 4 of them were aplastic. The remaining seven patients (12%) were hospitalized due to a variety of conditions, such as intoxication, gastrointestinal bleeding, pulmonary disease, and diabetic coma. The severity of diseases was indicated by a high mean SAPS of 42 points at study inclusion. A causative microbial agent could be isolated in 38 (75%) of 51 patients with sepsis or septic shock. Gram-positive bacterial infection was found in 15 patients, gram-negative infection in 19, and mixed or fungal/viral infection in 4 patients. Eleven (73%) of 15 patients with gram-positive infection and 11 (58%) of 19 patients with gram-negative infection were troponin-positive.

Troponin status and mortality. Thirty-two (55%) of all 58 study patients, or 32 (63%) of 51 patients admitted for sepsis, SIRS, or septic shock, were troponin-positive. The majority of troponin-positive patients (72%) were positive for cTnT and cTnI. The remaining patients were positive for either cTnT or cTnI (Table 1). Seventeen (71%) of 24 patients with shock were troponin-positive, compared with 15 (44%) of 34 patients without shock ($p = 0.04$). The SAPS (43 ± 17 vs. 42 ± 12 ; $p = 0.74$) and age (59 ± 21 vs. 50 ± 19 ; $p = 0.08$) did not differ significantly between troponin-positive and -negative patients.

Thirty days after study inclusion, mortality was assessed in all patients according to their cardiac troponin status (Fig. 1A). A total of 16 patients (27.6%) had died. Mortality of troponin-positive patients was significantly higher than that of troponin-negative patients ($p = 0.018$). The hazard ratio to die from any cause was 4.0 (95% confidence interval 1.2 to 8.9) for troponin-positive patients. When subgroups were analyzed according to their hemodynamic status (“shock” vs. “no shock”), a significantly higher mortality ($p = 0.03$) was found only in troponin-positive patients without shock, but

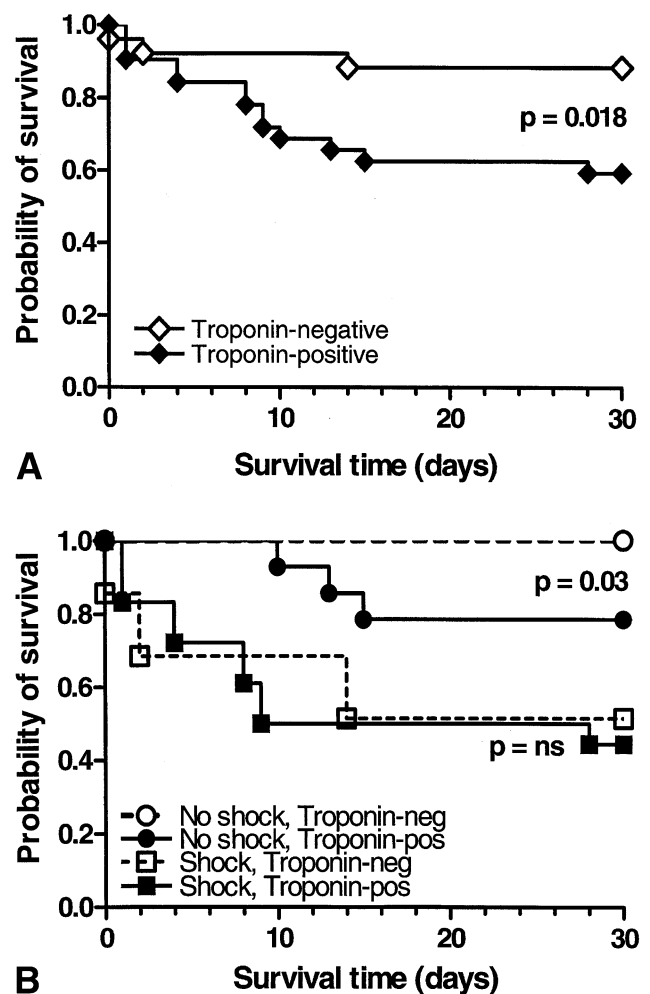


Figure 1. Kaplan-Meier survival analysis of troponin-positive and -negative patients. (A) The overall 30-day mortality was significantly higher in troponin-positive ($n = 32$) than in troponin-negative ($n = 26$) patients ($p = 0.018$). (B) When subgroups of patients with volume-refractory shock needing catecholamine therapy ($n = 24$) and patients without shock ($n = 34$) were analyzed separately, a significant difference in mortality was found in the subgroup without shock only ($p = 0.03$). ns = not significant.

not in those with volume-refractory shock receiving catecholamine therapy (Fig. 1B).

Cardiac involvement. Among the 32 troponin-positive patients, significant flow-limiting coronary artery disease could be excluded by dobutamine stress echocardiography after recovery from disease in 16 patients, by coronary angiography in one patient, and by autopsy in six cases (Table 2). In one patient, subacute myocardial infarction ($n = 1$) and high-grade coronary artery stenosis with individual cardiomyocyte necroses ($n = 1$) could be demonstrated at autopsy. One coronary angiogram and one stress echocardiogram showed evidence of an old myocardial scar, but no signs of actual ischemia. In summary, flow-limiting coronary artery disease was not demonstrable in 72% of troponin-positive patients. We found a significantly lower LVEF in cardiac troponin-positive as compared with troponin-negative patients ($48 \pm 13\%$ vs. $60 \pm 10\%$; $p =$

Table 2. Screening of Troponin-Positive Patients for Coronary Artery Disease*

	Survivors (n = 19)	Deaths (n = 13)	Total (n = 32)
Tests performed	17 (89%)	8 (62%)	25 (78%)
Test results			
Normal	15	6	21
Pathologic	2†	2‡	4
Relevant coronary artery disease			
Negative	17 (89%)	6 (46%)	23 (72%)
Positive	0	2 (15%)	2 (6%)
Patient not tested§	2 (11%)	5 (38%)	7 (22%)

*Troponin-positive surviving patients were tested by dobutamine stress echocardiography within three months after hospital discharge (n = 16) or by coronary angiography during hospitalization (n = 1). Troponin-positive patients who died were autopsied. †One patient had an inferior myocardial scar on the electrocardiogram and a corresponding occlusion of the right coronary artery on the coronary angiogram; one patient showed a myocardial scar on stress echocardiography. Because these two patients had no signs of active myocardial ischemia, they were classified as negative for relevant ischemic heart disease in the final analysis. ‡One patient had high-grade stenosis of the left circumflex artery and subacute myocardial infarction; one patient showed stenosing coronary artery disease and individual cardiomyocyte necrosis. §Stress echocardiography could not be performed in two patients because of their personal refusal. Autopsy could not be performed in five patients because of refusal by their relatives. Data represented as the number (%) of patients.

0.0006). All patients with LVEF below 45% had sepsis or septic shock and were either cTnI- or cTnT-positive. In contrast, only 19 (42%) of 45 patients with LVEF \geq 45% were troponin-positive. A statistically significant inverse correlation between cTnI levels and LVEF was found, with a relatively low correlation coefficient ($r = 0.44$, $p = 0.0006$) (Fig. 2).

Cytokine levels. The median cytokine levels in cardiac troponin-positive and -negative patients are presented in Table 3. Troponin-positive patients showed significantly

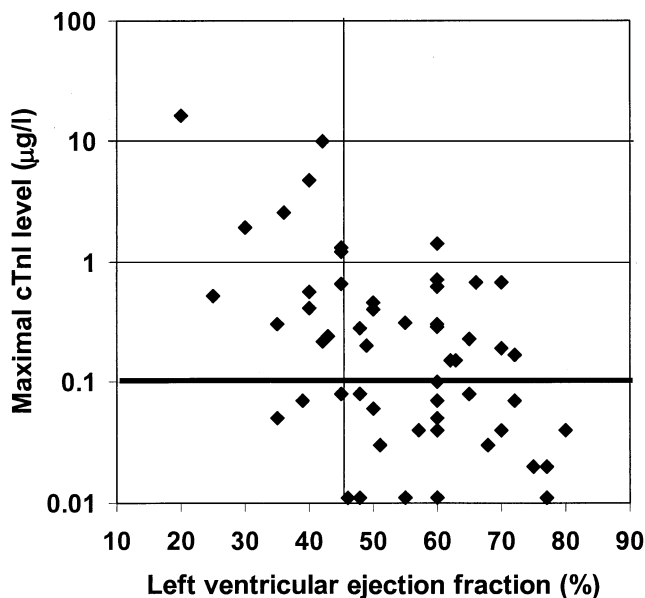


Figure 2. Relationship between left ventricular ejection fraction (LVEF) and peak cardiac troponin I (cTnI) level. A significantly lower LVEF was found in troponin-positive versus -negative patients ($r = 0.44$, $p = 0.0006$). All patients with LVEF $<$ 45% (left of thin vertical line) had sepsis or septic shock, and 11 of 13 were troponin-positive. The normal cutoff level for cTnI is indicated at 0.1 μ g/l by a bold horizontal line.

higher levels of TNF-alpha ($p = 0.0007$), its soluble receptor ($p < 0.0001$), IL-6 ($p = 0.0007$), and C-reactive protein ($p = 0.0002$). In contrast, there was no difference in the median levels of IL-1-beta ($p = 0.11$), IL-8 ($p = 0.26$), and soluble intercellular adhesion molecule-1 ($p = 0.07$). Subgroup analyses revealed that the observed median cytokine level difference between troponin-positive and -negative patients was mainly generated by the subgroup of patients without volume-refractory shock. Significantly higher levels of TNF-alpha, its soluble receptor, IL-6, and C-reactive protein for troponin-positive compared with troponin-negative patients were found in the subgroup with sepsis or SIRS, but not in those patients with volume-refractory septic shock (Table 3).

Role of neutrophilic granulocytes. All 10 aplastic patients with sepsis or septic shock were troponin-negative at the time of study entrance. Three of them became troponin-positive shortly after leukocyte recovery and subsequently died. In contrast, all others remained troponin-negative and survived.

DISCUSSION

In the present study, 32 (55%) of 58 critically ill patients consecutively admitted to two medical intensive care units due to severe illnesses other than ACS, or 32 (63%) of 51 patients admitted for sepsis, SIRS, or septic shock, were troponin-positive. Mortality was fourfold higher and LVEF significantly lower in troponin-positive patients as compared with troponin-negative patients. To our knowledge, this is the first study that attempted to systematically exclude significant coronary artery disease by autopsy or stress echocardiography in the majority of troponin-positive patients. Remote stress echocardiography cannot definitively exclude microembolism from non-flow-limiting unstable plaques as a cause for elevated troponins. However, ethical considerations did not allow us to perform coronary angiography in every one of these severely ill patients to check this hypothesis for troponin release. Our data indicate that troponin elevation may be used as a new mortality risk factor for intensive care patients without coronary artery disease. It is noteworthy that there was no significant difference in the SAPS between troponin-positive and -negative patients, although a significantly higher percentage of patients presenting with shock, compared with those without shock, were troponin-positive. This was surprising. According to our results, troponin in intensive care patients gives additional prognostic information beyond conventional risk scoring.

In troponin-positive patients, the median levels of TNF-alpha, its soluble receptor, and IL-6 levels were significantly higher than those of troponin-negative patients. These findings suggest but cannot prove, due to the observational study design, that myocardial depression with elevation of cardiac troponins might be mediated by TNF-alpha. This hypothesis is supported by in vitro studies showing that

Table 3. Cytokine and C-Reactive Protein Levels of Troponin-Positive Versus Troponin-Negative Patients*

Variable	Patients With Septic Shock			Patients With SIRS Sepsis Without Shock			Total Patients		
	Troponin Positive (n = 18)	Troponin Negative (n = 6)	p Value	Troponin Positive (n = 14)	Troponin Negative (n = 13)	p Value	Troponin Positive (n = 32)	Troponin Negative (n = 26)	p Value
Cytokine									
Tumor necrosis factor- α (pg/ml)	14.8 (11.5-53.4)	14.9 (10.4-32.6)	0.65	10.6 (5.8-15.7)	4.4 (2.7-8.0)	0.02	13.0 (9.2-26.6)	5.7 (2.6-11.3)	0.0007
Soluble tumor necrosis factor- α receptor (ng/ml)	1.40 (0.86-3.15)	1.44 (0.68-2.07)	0.78	0.71 (0.53-1.80)	0.40 (0.27-0.47)	0.003	1.05 (0.67-2.85)	0.43 (0.30-0.68)	< 0.0001
Interleukin-1-beta (pg/ml)	0.35 (0-7.78)	1.03 (0.13-3.91)	0.92	0.70 (0.10-5.25)	0.10 (0-0.70)	0.21	0.65 (0-5.38)	0.1 (0-1.56)	0.11
Interleukin-6 (pg/ml)	830 (99-6,786)	5311 (250-17,564)	0.52	72 (57-364)	27 (19-37)	0.006	358 (68-1,281)	29 (21-89)	0.0007
Interleukin-8 (pg/ml)	141 (61-694)	1242 (63-8,020)	0.68	54 (38-202)	59 (51-87)	0.86	85 (49-474)	65 (38-126)	0.26
Soluble intercellular adhesion molecule-1 (ng/ml)	2018 (948-2,307)	1124 (1,030-1,239)	0.23	852 (447-1,056)	458 (295-1,202)	0.48	1056 (625-2,059)	969 (325-1,298)	0.07
C-reactive protein (mg/l)	279 (189-317)	218 (184-259)	0.23	221 (178-259)	118 (84-177)	0.016	258 (181-321)	144 (69-193)	0.0002

*Median values over time were calculated for each patient, and the median value (interquartile range) per group is indicated. The upper normal values are indicated as follows: tumor necrosis factor- α <6.3 pg/ml, soluble tumor necrosis factor- α receptor <0.49 ng/ml, interleukin-1-beta <0.1 pg/ml, interleukin-6 <3.1 pg/ml, interleukin-8 <0.1 pg/ml, soluble intercellular adhesion molecule-1 <300 ng/ml, C-reactive protein <5 mg/l. SIRS = systemic inflammatory response syndrome.

TNF- α leads to reduced contractility of cardiomyocytes (20). Although clinical trials with anti-TNF antibodies or p55 TNF receptor fusion protein in patients with severe sepsis failed to improve survival (21-23), this does not exclude that elevated TNF- α blood levels may cause myocardial damage and hence contribute to the poor survival in these patients. However, as suggested in a previous review (24), our results also indicate that neither the systemic inflammatory response to sepsis nor troponin positivity is sufficient to explain circulatory shock in patients with severe sepsis.

Ten of our patients developed sepsis or septic shock while they had aplasia. At recruitment, all were troponin-negative. During leukocyte recovery, three of them became troponin-positive and subsequently died, whereas all the others stayed troponin-negative and survived. This observation suggests that, in addition to TNF- α , mediators produced by young and highly activated neutrophilic granulocytes may cause troponin elevation in patients with sepsis or septic shock. In healthy volunteers, it has been reported that pretreatment with granulocyte colony-stimulating factor considerably increased the plasma levels of TNF- α , its soluble receptor, and IL-6 on administration of endotoxin (25). Further studies are warranted to confirm this new possible interaction between young highly active granulocytes and myocardial damage in a larger patient population. These findings might be relevant for all septic patients receiving granulocyte colony-stimulating factor during aplasia.

Based on the findings of Piper et al. (26), who showed cardiac enzyme release without cell necrosis after reversible ischemia in vitro, we speculate that TNF- α and mediators produced by neutrophilic granulocytes may lead to an increased permeability of the cardiomyocyte membrane for macromolecules and therefore leakage of troponin without myocyte necrosis (10).

Conclusions. We found a significantly higher mortality of cardiac troponin-positive patients admitted to medical intensive care units for reasons other than ACS. Our data show an association between troponin positivity and TNF- α , IL-6, and left ventricular dysfunction. Further studies in larger patient populations must establish whether elevated troponin may be used as an independent mortality risk factor for intensive care patients without ACS.

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