Clin Res Cardiol (2012) 101:375–384
DOI 10.1007/s00392-011-0403-3

ORIGINAL PAPER

Interleukin-6, -7, -8 and -10 predict outcome in acute myocardial infarction complicated by cardiogenic shock

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Received: 13 September 2011 / Accepted: 13 December 2011 / Published online: 3 January 2012
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Abstract
Background The IABP-SHOCK-trial was a morbidity-based randomized controlled trial in patients with infarction-related cardiogenic shock (CS), which used the change of the quantified degree of multiorgan failure as determined by APACHE II score over a 4-day period as primary outcome measure. The prospective hypothesis was that adding IABP therapy to "standard care" would improve CS-triggered multi organ dysfunction syndrome (MODS). The primary endpoint showed no difference between conventionally managed cardiogenic shock patients and those with IABP support. In an inflammatory marker substudy, we analysed the prognostic value of interleukin (IL)-1β, -6, -7, -8, and -10 in patients with acute myocardial infarction complicated by cardiogenic shock.
Design Inflammatory marker substudy of the prospective, randomized, controlled, open label IABP-SHOCK-trial (Clinical-Trials-gov-ID-NCT00469248).
Setting and methods A single-center study was performed in a 12-bed Intensive-Care-Unit in an university hospital in which 40 consecutive patients were enrolled with an observational period of 96 h.
Results The pro- and anti-inflammatory markers IL-6, -7, -8 and -10 showed a predictive power for mortality of infarct-related CS patients, while IL-1β did not discriminate. The maximal values during the observational period, in case of IL-7 the minimal value, showed the best power to predict mortality. Both, ROC and multivariate analyses confirmed these suggestions (area under the curve: IL-8, 0.80 $\pm$ 0.08; IL-6, 0.79 $\pm$ 0.08; IL-10, 0.76 $\pm$ 0.08; IL-7, 0.69 $\pm$ 0.08). Inflammatory markers were not affected by the presence of IABP support.
Conclusion The inflammatory response in patients with myocardial infarction complicated by cardiogenic shock, as reflected by the inflammatory markers IL-6, IL-7, IL-8 and IL-10, demonstrates a clinically relevant prognostic contribution to clinical outcome.

Keywords Cardiogenic shock · Interleukins · Inflammation · Systemic inflammatory response

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Introduction

The recently published IABP-SHOCK-Trial [1] aimed to clarify, whether adding IABP therapy to "standard care" would improve cardiogenic shock (CS) triggered multiorgan dysfunction syndrome (MODS) or failure (MOF). The

primary endpoint with respect to efficacy related to the assessment whether early use of IABP leads to a significant reduction of morbidity as quantified by the APACHE II score over the first 4 days—this could not be demonstrated. Additionally, an inflammatory marker substudy was performed.

Cardiogenic shock (CS) is the leading cause of death in patients hospitalized with acute myocardial infarction (AMI) [2–5].

Initially CS is characterized by low-cardiac output and elevated systemic vascular resistance (SVR) due to compensatory vasoconstriction. Systemic inflammation with consecutive inappropriate vasodilation will be present in many patients with CS following revascularization and might contribute to excess mortality despite vasopressor and inotropic support. Clinically, this is manifested as the SVR being in the low to normal range additionally complicating reduced cardiac output. The mechanisms of death due to CS are complex and eventually similar to that of septic shock. In addition, to hemodynamic and clinical factors, an inflammatory response, due to ischemia and reperfusion and also translocation of bacteria or their toxins, may affect the outcome of patients with CS. One group of important inflammatory mediators are interleukins. Some of these can aggravate (i.e., IL-6) and other reduce (i.e., IL-10) the inflammatory response. Interleukins are released from various cells into the blood and interstitium where they bind to interleukin receptors on cellular surfaces and can induce cellular activation. Although it is well established that high IL-6 concentrations are associated with an adverse outcome in patients with acute coronary syndrome [6–8] and especially in cardiogenic [9–11] and also septic shock [12–14], the prognostic implication of other interleukins on early mortality in patients with CS is still unclear.

Therefore, in the present study we determined the relationship between plasma levels of a defined spectrum of interleukins IL-1β, IL-6; IL-7; IL-8; IL-10 with mortality. While the main purpose of this substudy was to investigate the prognostic value of interleukin levels in patients with CS it was also of interest to determine the effect of IABP support on these inflammatory markers.

Methods

Study design, randomization and stratification

The IABP-Shock-Trial was designed to test the effect of additional IABP support in the management of patients in CS secondary to acute myocardial infarction treated effectively with early revascularization who also required dobutamine to improve LV-function and norepinephrine to increase perfusion pressure. Patients who were assigned to Group 1 were treated with percutaneous coronary intervention (PCI), pharmacological hemodynamic support (inotropic and vasopressor agents) and if necessary with respirator therapy while patients assigned to Group 2 were additionally treated with intraaortic counterpulsation (IABP). All patients who were transferred to the catheterization laboratory at Martin-Luther-University Halle-Wittenberg with an acute coronary syndrome (i.e. STEMI and NSTEMI) complicated by hemodynamic instability were considered for study participation. Study details and primary results were published recently [1].

Cardiogenic shock was defined by clinical shock symptoms (signs of peripheral hypoperfusion with pale and cold extremities, oliguria) and fullfilling at least one of the following requirements:

1. systolic blood pressure $\leq$90 mmHg for 30 min
2. administration of catecholamines
3. cardiac index (CI) $\leq$2.2 l/min m^2.

Verbal or written informed consent was obtained. The trial was approved by the local Institutional Ethics Committee (Clinical Trials.gov ID NCT00469248).

Efficacy variables

Extent of cytokine release as reflected by the serum levels of investigated interleukins had been chosen as secondary endpoint. To determine the influence of systemic inflammation on mortality we correlated the interleukin levels of IL-1β, IL-6, IL-7, IL-8 and IL-10 initially (on admission, before PCI) and after 24, 48, 72 and 96 h with the clinical situation: outcome (survivors vs. non-survivors) and the presence of IABP support.

Extreme values

Over this observational period, the most extreme deviation of the investigated interleukins (maximum levels for IL-6, 8 and 10 and the minimum levels of IL-7) additionally to initial measurements was correlated with clinical situations.

Coronary angiography and percutaneous coronary intervention

All patients were treated with intravenous acetylsalicylic acid and intravenous glycoprotein-IIb-/IIIa-receptor blockers according to a weight-adjusted dose-regime for a minimum of 18–24 h. Intravenous heparin was given as a bolus and thereafter in a continuous infusion to maintain the activated partial thromboplastin time at two to three times the normal value for a minimum of 48 h. Upon PCI patients received a clopidogrel loading dose of 300 mg and commenced a maintenance dose of 75 mg daily (orally or via gastric tube).

Blood sampling for inflammatory markers

Serum samples were prepared from blood samples obtained from indwelling arterial lines on admission to our ICU or the catheterization laboratory prior to coronary intervention. Plasma and serum samples were immediately placed on ice, centrifuged within 30 min and stored at −70°C prior to analysis. Serum levels of inflammatory markers were measured by commercially available enzyme linked immunosorbent assays (ELISA, Medgenix, Ratingen, Germany).

Statistical analysis

The analysed parameters are described according to subgroups (outcome and IABP support) by mean and standard error. To investigate the relationship between the different inflammatory markers, Spearman's rank correlation coefficients were calculated. Two approaches were used to describe the discriminatory power of different interleukins as an early predictor of in-hospital mortality. First, receiver operating characteristic (ROC) curves of the initial and most extreme measurements (maximum levels for IL-6, IL-8 and IL-10; minimum levels for IL-7) during the first 4 days in hospital were calculated and presented as area under the curve [15]. Secondly, logistic regression models with a stepwise backward variable selection were used to predict in-hospital mortality on the basis of the logarithmically transformed inflammatory markers. Due to the small sample size univariate models with adjustments for the randomized treatment group, age and gender were used. To predict survival status, the prevalence of in-hospital mortality in this study (0.3) was chosen as cutpoint (as recommended in [16]).

Results

Baseline characteristics

Finally 40 patients fulfilled the inclusion criteria, in all of them demographical data and measurements of inflammatory markers were available from the time of admission and the latter named time points. In 37 patients, a complete set of samples was available for the entire observational period of 96 h. In three patients, only limited samples were available due to death. The baseline characteristics of the investigated patients are given in Table 1. Mean age was 64.2 ± 1.9 years; 21 of 40 patients required mechanical ventilation. In four patients, dialysis treatment was initiated directly after PCI and eight patients required dialysis within the next 96-h period due to acute renal failure.

InterIeukin-1β and InterIeukin-6 serum levels

IL-1β showed no or only small changes in serum levels during the observational period (Table 2) and furthermore, IL-1β levels did not differ clinically relevant between survivors and non-survivors. IL-6 levels, however, were different over the observational period of 96 h. (Table 2). Clearly, IL-6 levels were initially elevated in non-survivors (2,710 ± 2,074 vs. 373 ± 139 pg/ml) as also during the whole study period, as measured by maximum levels [i.e., 3,680 ± 1,865 pg/ml (non-survivors) vs. 562 ± 146 pg/ml (survivors)]. Interestingly, maximum IL-6 levels were not different in patients with or without IABP (Table 3).

Interleukin-7 serum levels

While IL-6, IL-8 and IL-10 showed a positive linear correlation, higher values were associated with poor prognosis, in contrast lower IL-7 levels were associated with poor prognosis. For this reason minimum levels of IL-7 and maximum levels of IL-6, IL-8 and IL-10 were investigated in different clinical settings (mortality, IABP support, age and gender). The levels of IL-7 of the treatment groups are shown in Fig. 1a. There was no clinically relevant difference between the two groups detected, either initially or over the observational period.

We are convinced that low IL-7 levels might correlate with prognosis in patients with cardiogenic shock. Thus we measured IL-7 levels in survivors and non-survivors (Fig. 1b). Interestingly, IL-7 levels on admission showed a trend to higher values in patients who did survive (i.e., initial measurement of IL-7: 5.58 ± 0.79 vs. 4.08 ± 0.84 pg/ml). This difference was observed throughout the whole period of observation. As a consequence, the extreme values showed differences between survivor and non-survivors of CS (3.85 ± 0.42 vs. 2.39 ± 0.17 pg/ml),

Interleukin-8 serum levels

IL-8 levels in CS Patients are shown in Fig. 2a. There was no clinically relevant difference between the two groups (IABP and no IABP) initially and over the 96-h observational period (Fig. 2a).

Corresponding to the discriminating power of IL-6, IL-8 showed initially lower levels in survivors as compared to non-survivors (IL-8 2.9 ± 0.8 vs. 9.4 ± 3.7 pg/dl). This difference was observed over the whole time period (Fig. 2b). Maximal values were clinically relevant different in comparison of survivors and non-survivors (IL-8 3.2 ± 0.7 vs. 14.4 ± 5.2 pg/dl).

Table 1 Initial patient characteristics

Characteristics	Survivor ($n = 27$)	Non-survivors ($n = 13$)	IABP group ($n = 19$)[a]	No IABP group ($n = 21$)[a]
Gender (male/female)	21 (78%)/6 (22%)	10 (77%)/3 (23%)	14 (74%)/5 (26%)	17 (81%)/4 (19%)
Age, years, mean (range)	62.4 (38–82)	67.9 (44–82)	62.1 (38–82)	66.1 (49–82)
Previous AMI, *n* (%)	5 (18%)	4 (31%)	4 (21%)	5 (24%)
Known heart failure, *n* (%)	4 (15%)	4 (31%)	5 (26%)	3 (14%)
STEMI, *n* (%)	18 (67%)	8 (62%)	10 (53%)	16 (76%)
PTCA/Stent, *n* (%)	24 (89%)/22 (82%)	12 (92%)/12 (92%)	18 (95%)/16 (84%)	18 (86%)/18 (86%)
CI (l/min/m^2)	2.1 ± 0.2	1.9 ± 0.3	2.3 ± 0.2	1.7 ± 0.1
PCWP in mmHg (mean value)	18.1 ± 1.3	16.5 ± 1.6	20.1 ± 1.2	14.8 ± 1.3
Ventilation, *n* (%)	12 (44%)	9 (69%)	7 (37%)	14 (67%)
Diabetes, *n* (%)	13 (48%)	7 (54%)	10 (53%)	10 (48%)
IABP, *n* (%)	12 (44%)	7 (54%)	19 (100%)	1 (5%)*
Dialysis initial	1 (4%)	3 (23%)	2 (10%)	2 (10%)
Dialysis in 96 h	1 (4%)	7 (54%)	3 (16%)	5 (24%)

[a] One pat. was cross over

Table 2 Interleukin-1β, and interleukin-6 for survivors and non-survivors between initial (on admission to hospital) and day 4

	Initial ($n = 40$)	24 h ($n = 40$)	48 h ($n = 38$)	72 h ($n = 38$)	96 h ($n = 37$)	Delta (initial to 96 h)	Maximum over 96 h
IL-1β							
Alive ($n = 27$)	2.27 ± 0.24	1.98 ± 0.03	1.95 ± 0.00	1.95 ± 0.00	1.95 ± 0.00	0.56 ± 0.41	2.30 ± 0.24
Dead ($n = 13$)	3.24 ± 0.76	2.22 ± 0.27	2.24 ± 0.29	1.95 ± 0.00	1.96 ± 0.01	1.27 ± 0.90	3.24 ± 0.76
Total ($n = 40$)	2.58 ± 0.30	2.05 ± 0.08	2.03 ± 0.08	1.95 ± 0.00	1.95 ± 0.00	0.84 ± 0.43	2.60 ± 0.29
IL-6							
Alive ($n = 27$)	373.2 ± 139.5	287.7 ± 80.6	189.0 ± 58.3	183.7 ± 47.4	168.5 ± 48.7	323.2 ± 238.1	562.3 ± 145.6
Dead ($n = 13$)	2710.1 ± 2073.5	1393.0 ± 614.9	930.7 ± 345.8	809.2 ± 283.2	645.5 ± 437.3	502.5 ± 320.7	3679.4 ± 1865.1
Total ($n = 40$)	1067.9 ± 629.5	616.3 ± 203.7	391.3 ± 115.5	420.9 ± 122.5	359.3 ± 178.3	390.4 ± 187.9	1546.6 ± 627.0

Table 3 Comparisons of IL-1β and IL-6 levels for various conditions in CS patients following PCI

	Initial IL-1β	Max IL-1β (until 96 h)	Initial IL-6	Max IL-6 (until 96 h)
IABP treatment				
IABP ($n = 19$)	2.54 ± 0.47	2.54 ± 0.47	375.0 ± 169.1	1036.7 ± 422.8
No IABP ($n = 21$)	2.61 ± 0.38	2.65 ± 0.38	1656.9 ± 1152.7	2005.6 ± 1134.6
Gender				
Male ($n = 31$)	2.51 ± 0.32	2.54 ± 0.32	1176.4 ± 797.5	1762.6 ± 785.5
Female ($n = 9$)	2.82 ± 0.76	2.82 ± 0.76	674.8 ± 419.2	736.7 ± 407.9
Age groups				
<75 years ($n = 33$)	2.35 ± 0.23	2.37 ± 0.23	438.6 ± 141.3	741.1 ± 155.8
≥75 years ($n = 7$)	3.80 ± 1.38	3.80 ± 1.33	5095.5 ± 4550.9	5842.9 ± 3638.4

Interleukin-10 serum levels

IL-10 levels are shown in Fig. 3. There was no clinically relevant difference between CS patients treated with or without IABP either initially or over the observation period (Fig. 3a).

Since elevated IL-10 levels might correlate with prognosis in patients with cardiogenic shock we determined IL-10 levels in survivors and non-survivors (Fig. 3b). Corresponding to the discriminatory power of IL-6 the anti-inflammatory IL-10 even initially showed higher levels in non-survivors (i.e., 41.3 ± 20.7 vs. 72.4 ± 22.8 pg/dl), while this discriminatory power

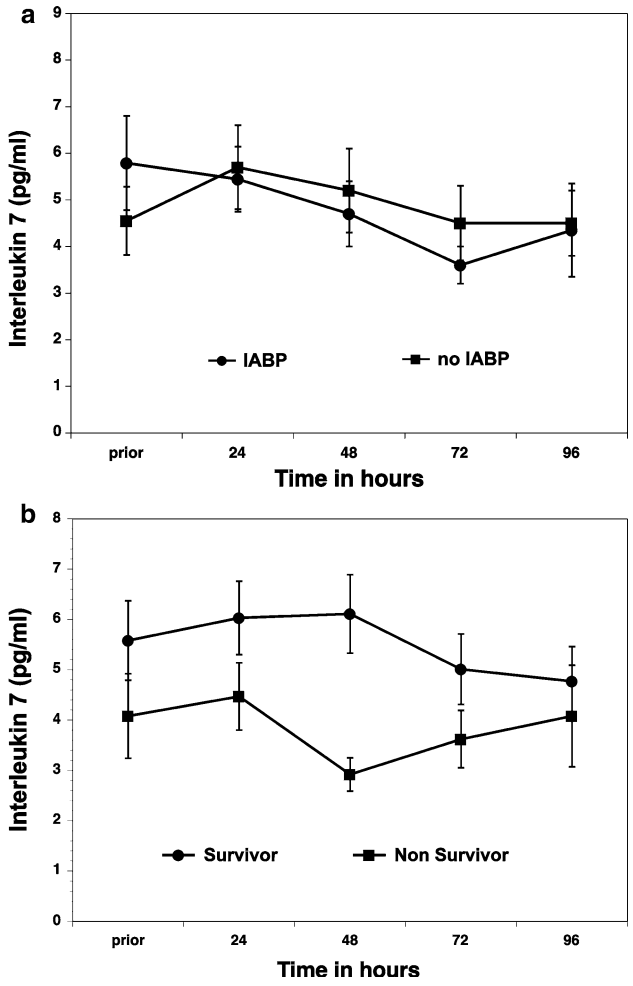

Fig. 1 **a**, **b** Interleukin-7 levels in patients with cardiogenic shock. **a** All patients with CS following MI (STEMI and NSTEMI) underwent revascularization of infarction-related artery and were randomized to IABP insertion or not IABP (i.e. dobutamine and norepinephrine treatment alone). IL-7 levels were measured initially and up to 96 h after IABP. **b** Since elevated IL-7 levels might be associated with prognosis in patients with cardiogenic shock we determined IL-7 levels in survivors and non-survivors

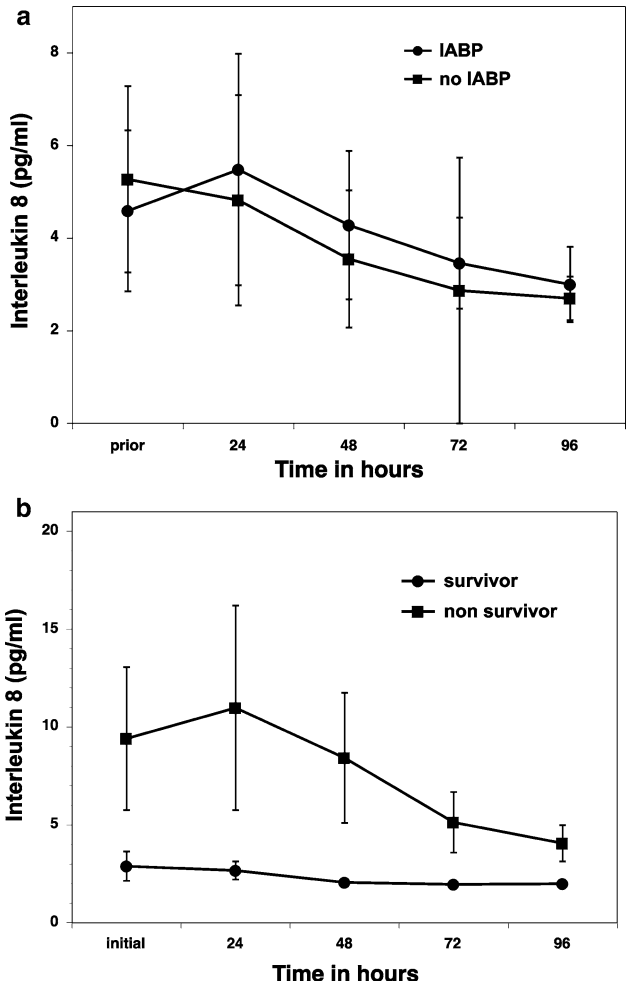

Fig. 2 **a**, **b** Interleukin-8 levels in patients with cardiogenic shock. **a** All patients with CS following MI (STEMI and NSTEMI) underwent revascularization of infarction-related artery and were randomized to IABP insertion or not IABP (i.e., dobutamine and norepinephrine treatment alone). IL-6 levels were measured initially and up to 96 h after IABP. **b** Since elevated IL-8 levels might be associated with prognosis in patients with cardiogenic shock we determined IL-8 levels in survivors and non-survivors. Clearly, IL-8 levels were much lower in patients surviving cardiogenic shock

was confirmed over time by IL-10 levels higher in non-survivors (i.e., max levels 42.7 ± 20.6 vs. 158.4 ± 98.1 pg/ml).

Interleukin serum levels (IL-7, IL-8, IL-10) according to gender and age

Neither the initial nor the extreme levels of IL-7, IL-8, and IL-10 over the observational period showed any clinically relevant difference between these investigated gender or age groups (Table 4).

Receiver operator characteristics of interleukins in patients with cardiogenic shock

The tables of rank correlation coefficients of initial and extreme values (maximum levels; minimum levels for IL-7) demonstrate a high correlation between IL-1β, IL-6, IL-8 and IL-10 (Tables 5, 6). IL-7 showed only weak correlations with this group of parameters.

To compare the predictive power for survival between baseline value and the most extreme value over the 96-h time course, we performed independent ROC analyses (Table 7) for four markers (i.e., IL-6, IL-7, IL-8, and IL-10) using baseline and maximum levels. The maximum levels of IL-8 showed the highest diagnostic accuracy with an area under the curve (AUC) of 0.80 ± 0.08, followed by IL-6 (AUC 0.79 ± 0.08), IL-10 (AUC 0.76 ± 0.08) and minimal levels of IL-7 (AUC 0.69 ± 0.08). The baseline values had only lower predictive power in all investigated parameters (Table 7). Multivariate analyses with the

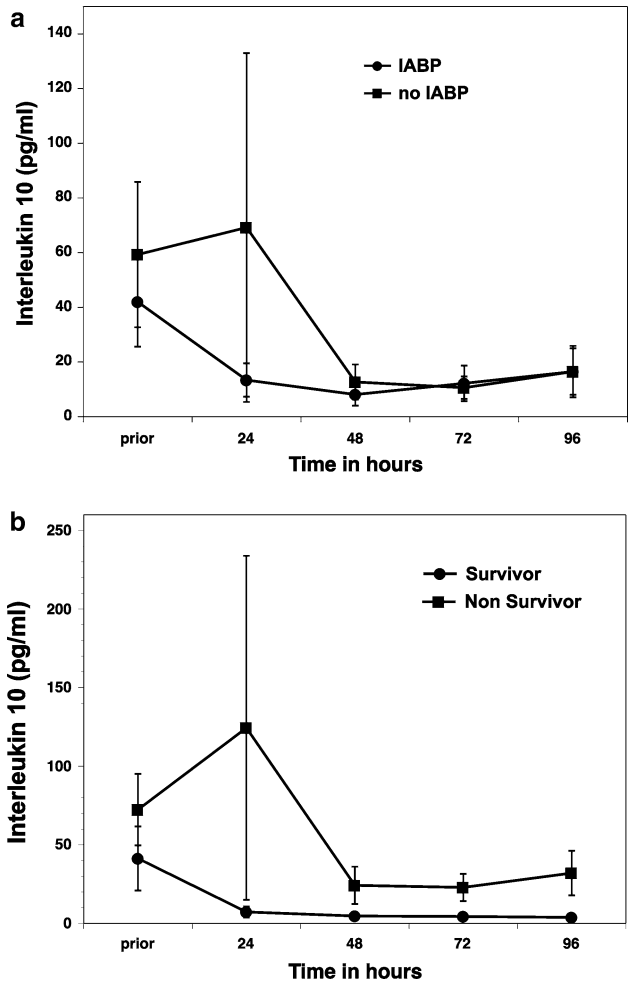

Fig. 3 **a**, **b** Interleukin-10 levels in patients with cardiogenic shock. **a** All patients with CS following MI (STEMI and NSTEMI) underwent revascularization of infarction-related artery and were randomized to IABP insertion or not IABP (i.e., dobutamine and norepinephrine treatment alone). IL-10 levels were measured initially and up to 96 h after IABP. **b** Since elevated IL-10 levels might be associated with prognosis in patients with cardiogenic shock we determined IL-10 levels in survivors and non-survivors. Clearly, IL-10 levels were much lower in patients surviving cardiogenic shock

possible confounders age, gender and IABP confirmed a predictive ability of these four inflammatory markers.

Discussion

While chronic low-grade systemic inflammation is a key component in atherogenesis on one hand, decreased heart rate variability, a strong predictor of cardiovascular events, on the other hand has been associated with elevated inflammatory markers like C-reactive protein and IL-6. Recent studies could demonstrate that reduced cardiac autonomic control is associated with increased systemic inflammation even in patients with stable coronary heart disease [17].

While the data of our present study showed no impact of the IABP support on interleukins, the levels of the inflammatory interleukins IL-6, Il-7, IL-8 and IL-10 demonstrated a predictive value regarding outcome.

The investigated interleukins give insights into the expression and release of a broad spectrum of important inflammatory markers in patients with AMI complicated CS.

Sepsis is a complex syndrome that develops when the initial, appropriate host response to an infection becomes amplified and then dysregulated [18–22]. Depending on their effects, cytokines have been classified on the basis of their biological responses as pro- or anti-inflammatory mediators. Important cytokines are interleukins, growth hormones, interferons (IFN) and tumor necrosis factors—alpha or beta (TNF). The functions of some cytokines such as IL-1β, IL-2, IL-4, IL-5, IL-6 and IL-10 are closely associated with the interactions between B and T cells. Interleukins are known as prognostic markers in acute coronary syndrome, cardiac arrest, heart failure, sepsis and other conditions of multiorgan dysfunction/failure [13, 23–26]. So far, there are limited data available from prospective trials investigating the diagnostic and prognostic value of various interleukins in cardiogenic shock. Only a few studies have demonstrated the discriminatory power of pro-inflammatory markers such as IL-6 in cohort studies [8, 9]. Geppert et al. demonstrated that once MOF is present, patients with CS exhibit similarly high IL-6 levels as patients with septic shock. High IL-6 levels in CS patients are associated with the progression to MOF and a worse outcome (i.e., increased mortality) [10]. Debrunner et al. have shown that inflammation-associated cytokines such as TNF-α, IL-6 and IL-1β are clinically relevant elevated in patients with MI complicated by CS. Among patients with cardiogenic shock IL-1β levels appeared to be a useful diagnostic marker for early identification of patients developing SIRS and increased mortality [9]. In 20% of these patients Kohsaka et al. detected clinical signs of severe systemic inflammation shown by fever or leukocytosis, which led to subsequent diagnosis of sepsis. CS patients who were identified as septic with a gram positive culture had a twofold increased risk of death [11]. In line with this, low SVR at the onset of shock in patients with culture-positive systemic inflammation suggests an inappropriate vasodilation which may play an important role in the pathogenesis and persistence of shock. In our view, patients with cardiogenic shock are likely to develop a sepsis-like syndrome within 48–96 h following the beginning of CS. This can be explained due to the inflammatory response following ischemia and reperfusion or as a consequence to bacteriaemia in combination with endo- and exotoxin release. Indeed, bacterial translocation might be facilitated due to increased intestine permeability following

Table 4 Comparisons of IL-7, IL-8 and IL-10 levels for various conditions in CS patients following PCI

	Initial IL-7	Max IL-7 (until 96 h)	Initial IL-8	Max IL-8 (until 96 h)	Initial IL-10	Max IL-10 (until 96 h)
Gender						
Male ($n = 31$)	4.97 ± .58	3.50 ± .37	4.82 ± 1.58	6.91 ± 2.32	37.2 ± 11.1	72.14 ± 40.6
Female ($n = 9$)	5.64 ± 1.96	2.97 ± .50	5.44 ± 2.25	5.96 ± 2.16	103.5 ± 62.9	105.71 ± 62.4
Age groups						
<75 years ($n = 33$)	5.43 ± .69	3.43 ± .33	3.99 ± 1.07	6.02 ± 1.94	47.6 ± 18.0	80.9 ± 40.4
≥75 years ($n = 7$)	3.40 ± .91	3.17 ± .96	10.03 ± 6.22	10.35 ± 6.15	70.0 ± 33.2	70.0 ± 33.2

No clinically relevant differences between groups were observed in the IL-7, IL-8, and IL-10 initial value and maximal deviations levels (maximal levels: IL-8 and IL-10; minimal levels: IL-7)

Table 5 Spearman's rank correlation coefficients between initial measurements of interleukins

	Initial IL-1β	Initial IL-6	Initial IL-7	Initial IL-8	Initial IL-10
Initial IL-1β	1.000	0.509	−0.009	0.503	0.517
Initial IL-6		1.000	0.130	0.392	0.496
Initial IL-7			1.000	−0.029	0.315
Initial IL-8				1.000	0.582
Initial IL-10					1.000

Table 6 Spearman's rank correlation coefficients between most extreme measurements of interleukins over the first 96 h after randomization

	Max IL-1β	Max IL-6	min IL-7	Max IL-8	Max IL-10
Max IL-1β	1.000	0.455	0.136	0.372	0.489
Max IL-6	*	1.000	−0.095	0.708	0.477
Min IL-7			1.000	−0.280	0.223
Max IL-8				1.000	0.561
Max IL-10					1.000

CS. In this line, Kohsaka et al. demonstrated that clinical sepsis is common after cardiogenic shock (18%) complicating acute myocardial infarction, particularly in patients who received prolonged IABP support or had multiple central catheters [27].

Nevertheless, the present prospective randomized controlled trial has performed a detailed analysis of a broad panel of interleukins in CS patients for the first time.

Interleukins and inflammation

While IL-6, IL-7, IL-8 are well described as pro-inflammatory cytokines, IL-10 predominantly acts as an anti-inflammatory cytokine. IL-10 has pleiotropic effects in immunoregulation and inflammation. It down regulates the expression of TH1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production [28]. Although there have been published encouraging data reporting beneficial effects after administration of bone marrow stem cells in acute myocardial infarction, recent studies observed no significant effects on levels of natriuretic peptides or inflammatory markers like IL-6 [29].

Table 7 ROC analyses with area under the curves (AUC) and their standard error of IL-6, IL-7, IL-8, and IL-10, initial and most extreme values over 96 h

	Area under the curve (AUC) ± standard error	
	Initial	Most extreme
IL-6	0.720 ± 0.085	0.788 ± 0.085
IL-7	0.583 ± 0.095	0.691 ± 0.084
IL-8	0.667 ± 0.102	0.804 ± 0.079
IL-10	0.745 ± 0.081	0.763 ± 0.080

Interleukins and IABP

It is well documented that artificial surfaces in contact to blood cells can stimulate an inflammatory response [30–32]. Thus we tried to determine the potential impact of IABP support on systemic inflammation in CS. IABP

support of CS patients was not shown to significantly affect the levels of the investigated cytokines. We could demonstrate that IABP-use shows no clinically relevant impact on the systemic inflammatory response: neither the investigated cytokines IL-1β, IL-6, IL-7 IL-8, and IL-10 have been triggered to elevated serum levels by intraaortic counterpulsation nor did stabilized hemodynamics by IABP support induce a reduction of the inflammatory response. So the authors conclude that the artificial surface as represented by the IABP balloon seems to be too small for systemic stimulation of circulating blood cells inducing systemic inflammatory response and that on the other hand the limited hemodynamic macrocirculatory effects cannot prevent ischemia/reperfusion injuries by CS. The impaired microcirculation induced by CS and the corresponding therapeutic interventions like the use of vasopressors might in part explain these phenomena. Steinvil et al. [33] could recently demonstrate in patients with acute coronary syndromes a correlation between the time from symptom onset to the appearance of an inflammatory response and aggregated erythrocytes in the peripheral blood. In the setting of elective PCI an improved sublingual microcirculatory flow could be observed after initiation of IABP support [34]. In contrast to the setting of elective PCI, the vasopressor therapy in CS patients seems to prevent the transmission of beneficial macrocirculatory hemodynamic effects of IABP support to microcirculation. In patients deemed ready for discontinuing IABP support according to current practice an increase of microcirculatory flow of small vessels after ceasing IABP therapy could be observed. The authors speculated whether this observation may indicate that IABP impairs microvascular perfusion in recovered patients [35].

Interleukins and survival in CS patients—ROC analysis

Interestingly, four of the investigated interleukins, which were studied in detail (IL-6, IL-7, IL-8 and IL-10) are suitable to discriminate survivors and non-survivors in septic patients [36]. While these four interleukins are suitable markers for prognosis in CS, IL-8 according to the ROC analysis seems to have the highest predictive value, while IL-10, although seen as an anti-inflammatory marker, surprisingly shows nearly a comparable prognostic value.

ROC analyses for IL-6, IL-7, IL-8, and IL-10 in CS patients were performed for baseline and maximal levels during the observational period. The most extreme levels of the four interleukins showed considerable better diagnostic accuracy. However, of the four, maximal levels of IL-8 showed the best predictive value. Therefore, our data in CS patients are in contrast to previous studies in septic patients where IL-6 had the best diagnostic accuracy. In addition, with our study we were able to increase the pathophysiological understanding regarding the elevation of IL-7, IL-8 and IL-10 upon PCI in CS patients.

Interleukins regarding gender and age

In contrast to septic patients [37], we did not detect any differences of these interleukins with respect to gender or age. It has been previously shown that there is an immune senescence reducing interleukin expression in elderly patients [38–40]. However, the elderly CS patients in our study did not show reduced interleukin expression or release upon PCI.

Comparison of interleukin levels in sepsis and cardiogenic shock

MOF is of predictve value in CS and also in septic shock. One important cause might be systemic inflammation due to impaired microcirculation upon ischemia and reperfusion. In this regard, Geppert et al. [10] have shown that patients with CS and MOF exhibited similar IL-6 levels like patients with septic shock. In a prospective randomized animal study, the role of inflammatory cytokines in the pathogenesis of sepsis-induced circulatory failure with downregulation of angiotensin-II-type-I-(AT(1))-receptors has been shown. Inhibition of several cytokines attenuated AT-1 receptor down regulation and prevented septic circulatory failure [41]. This might implicate that therapeutic control of inflammation is important for hemodynamic stability in both, cardiogenic and septic shock. Although we could not see relevant changes in IL-1β in our investigated population, the data published by Cha et al. [42] provide strong evidence that TLR4 causes impairment of post-ischemic myocardial function through TNF- and IL-1 production.

Limitations of this study

This inflammatory marker study has been properly conducted under the conditions of a randomized controlled trial, so that we can provide valuable data to identify prognostic markers for decision making on the ICU. Although a higher number of patients might have been helpful, we expect confirmation of our presented data by larger clinical trials involving increased patient numbers.

Clinical perspectives

Many clinical investigations have focused on cytokines in inflammatory diseases such as heart failure, CS or sepsis. The main purpose of this study was to assess the prognostic value of systemic inflammation (i.e., interleukin expression) upon cardiogenic shock complicating acute

myocardial infarction. In our study, we were able to demonstrate that IL-6, IL-7, IL-8, and IL-10 substantially contribute to development, progression and outcome in CS. However, in consideration of pathophysiological reservations, over the time period inflammatory markers may not be as reliable or helpful as seen in septic patients. In addition, even inhibition of inflammation was not really therapeutically effective in CS patients [43–45].

Although the first phase of cardiogenic shock is commonly accompanied by compensatory vasoconstriction, recent studies have shown that during the following phases of cardiogenic shock inappropriate vasodilation due to ischemia/reperfusion or inflammation might occur [46, 47]. This might explain the persisting hemodynamic instability and may demand increased doses of inotropes and vasopressors.

Cytokine-monitoring of prognosis by initial and serial cytokine levels

Our present data confirm the clinically relevant contribution of inflammation in CS. In addition, we could demonstrate that IL-6, IL-7, IL-8, and IL-10 are useful markers in CS patients to predict prognosis in infarct-related cardiogenic shock. For clinical decision making initial interleukin levels (without influence of therapeutic measures) may be helpful for the first estimation of individual patient prognosis, while the evaluation of the prognostic impact of therapeutic measures by serial interleukin measurements seems not to be as good for clinical practice. In contrast, serial determination of the APACHE II score seems to be more reliable for prognosis evaluation in daily practice on the ICU. The SBITS-trial showed a significant prognostic impact of the declining of the APACHE II score from initial to day 4 in septic patients [48]. The prognostic impact of the APACHE II score in CS patients has been shown by the IABP SHOCK-Trial [1]. Regarding the expanding costs of escalating therapy in cardiogenic shock inflammatory markers can be used as a tool in addition to clinical parameters, hemodynamics and scoring systems for the necessary prognostic assessment on ICU to evaluate which individual patient might benefit from escalating therapeutic measures like extracorporeal membrane oxygenation or left ventricular assist devices.

On the background of these present findings initial interleukin measurements combined with daily determination of the degree of organ failure with the APACHE II score seems to be a valuable strategy for an individual prognosis estimation in CS patients on the ICU.

Conflict of interest The authors declare the following relations: R.P., K.W., and M.B. received lecture fees from Datascope Inc. The IABP-Shock-Trial was supported by an unrestricted grant from Datascope Inc.

References

1. Prondzinsky R, Lemm H, Swyter M, Wegener N, Unverzagt S, Carter JM, Russ M, Schlitt A, Buerke U, Christoph A, Schmidt H, Winkler M, Thiery J, Werdan K, Buerke M (2010) Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. Crit Care Med 38:152–160
2. Hochman JS, Sleeper LA, Webb JG et al (1999) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med 341:625–634
3. Ruiz-Bailen M, Rucabado-Aguilar L, Exposito-Ruiz M et al (2009) Cardiogenic shock in acute coronary syndrome. Med Sci Monit 15:RA57–RA66
4. Kouraki K, Schneider S, Uebis R, Tebbe U, Klein HH, Janssens U, Zahn R, Senges J, Zeymer U (2011) Characteristics and clinical outcome of 458 patients with acute myocardial infarction requiring mechanical ventilation. Results of the BEAT registry of the ALKK-study group. Clin Res Cardiol 100(3):235–239
5. Liebetrau C, Szardien S, Rixe J, Woelken M, Rolf A, Bauer T, Nef H, Möllmann H, Hamm C, Weber M (2011) Direct admission versus transfer of AMI patients for primary PCI. Clin Res Cardiol 100(3):217–225
6. Mielniczuk LM, Pfeffer MA, Lewis EF, Blazing MA, de Lemos JA, Mohanavelu S, Rouleau J, Fox K, Pedersen TR, Califf RM (2009) Acute decline in renal function, inflammation, and cardiovascular risk after an acute coronary syndrome. Clin J Am Soc Nephrol 4:1811–1817
7. Tan J, Hua Q, Li J, Fan Z (2009) Prognostic value of interleukin-6 during a 3-year follow-up in patients with acute ST-segment elevation myocardial infarction. Heart Vessels 24:329–334
8. Järemo P, Nilsson O (2008) Interleukin-6 and neutrophils are associated with long-term survival after acute myocardial infarction. Eur J Intern Med 19:330–333
9. Debrunner M, Schuiki E, Minder E, Straumann E, Naegeli B, Mury R, Bertel O, Frielingsdorf J (2008) Proinflammatory cytokines in acute myocardial infarction with and without cardiogenic shock. Clin Res Cardiol 97:298–305
10. Geppert A, Steiner A, Zorn G, Delle-Karth G, Koreny M, Haumer M, Siostrzonek P, Huber K, Heinz G (2002) Multiple organ failure in patients with cardiogenic shock is associated with high plasma levels of interleukin-6. Crit Care Med 30:1987–1994
11. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS (2005) SHOCK Investigators. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. Arch Intern Med 165:1643–1650
12. Lin WC, Lin CF, Chen CL, Chen CW, Lin YS (2010) Prediction of outcome in patients with acute respiratory distress syndrome by bronchoalveolar lavage inflammatory mediators. Exp Biol Med 235:57–65
13. Prinsen JH, Baranski E, Posch H, Tober K, Gerstmeyer A (2008) Interleukin-6 as diagnostic marker for neonatal sepsis: determination of Access IL-6 cutoff for newborns. Clin Lab 54:179–183
14. Witthaut R, Busch C, Fraunberger P, Walli A, Seidel D, Pilz G, Stuttmann R, Speichermann N, Verner L, Werdan K (2003) Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. Intensive Care Med 29:1696–1702
15. Altman DA (1991) Practical statistics for medical research. Chapman & Hall, London

16. Sauerbrei W, Madjar H, Prömpeler HJ (1998) Differentiation of benign and malignant breast tumours by logistic regression and a classification tree using Doppler flow signals. Methods Inf Med 37:226–234
17. Känel R, Carney RM, Zhao S, Whooley MA (2011) Heart rate variability and biomarkers of systemic inflammation in patients with stable coronary heart disease: findings from the Heart and Soul Study. Clin Res Cardiol 100(3):241–247
18. Villar J, Maca-Meyer N, Pérez-Méndez L, Flores C (2004) Bench-to-bedside review: understanding genetic predisposition to sepsis. Crit Care 8:180–189
19. Fitting C, Cheval C, Losser MR, Carlet J, Payen D, Foster K, Cavaillon JM (1997) Presence of high levels of leukocyte-associated interleukin-8 upon cell activation and in patients with sepsis syndrome. Infect Immun 65:865–871
20. Zeerleder S, Caliezi C, van Mierlo G, Eerenberg-Belmer A, Sulzer I, Hack CE, Wuillemin WA (2003) Clin Diagn Lab Immunol 10:529–535
21. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL (2005) Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth 94:767–773
22. Weber GF, Schlautkötter S, Kaiser-Moore S, Altmayr F, Holzmann B, Weighardt H (2007) Inhibition of interleukin-22 attenuates bacterial load and organ failure during acute polymicrobial sepsis. Infect Immun 75:1690–1697
23. Torre-Amnione Kapadia S, Lee J et al (1996) Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 93:704–711
24. Werra ID (1997) Cytokines, nitrite/nitrate, soluble tumor necrosis factro receptors, and procalcitonin concentrations: comparison in patients with septic shock, cardiogenic shock, and bacterial pneumonia. Crit Care Med 25:607–613
25. Neumann FJ, Ott I, Gawaz M et al (1995) Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. Circulation 92:748–755
26. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM (2002) Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 106:562–568
27. Kohsaka S, Menon V, Iwata K, Lowe A, Sleeper LA, Hochman JS (2007) SHOCK investigators. Microbiological profile of septic complication in patients with cardiogenic shock following acute myocardial infarction (from the SHOCK study). Am J Cardiol 99:802–804
28. Kadokami T, McTiernan C, Kubota T, Frye C, Bounoutas G, Robbins P, Watkins S, Feldman A (2001) Effects of soluble TNF receptor treatment on lipopolysaccharide-induced myocardial cytokine expression. Am J Physiol Heart Circ Physiol 280:H2281–H2291
29. Miettinen JA, Ylitalo K, Hedberg P, Kervinen K, Niemelä M, Säily M, Koistinen P, Savolainen ER, Ukkonen H, Pietilä M, Airaksinen KE, Knuuti J, Vuolteenaho O, Mäkikallio TH, Huikuri HV (2011) Effects of intracoronary injection of autologous bone marrow-derived stem cells on natriuretic peptides and inflammatory markers in patients with acute ST-elevation myocardial infarction. Clin Res Cardiol 100(4):317–325
30. Prondzinsky R, Müller-Werdan U, Pilz G, Witthaut R, Stabenow I, Werdan K, Zerkowski HR (1997) Systemic inflammatory reactions to extracorporeal therapy measures (II): cardiopulmonary bypass. Wien Klin Wochenschr 109:346–353
31. Prondzinsky R, Knüpfer A, Loppnow H, Redling F, Lehmann DW, Stabenow I, Witthaut R, Unverzagt S, Radke J, Zerkowski HR, Werdan K (2005) Surgical trauma affects the proinflammatory status after cardiac surgery to a higher degree than cardiopulmonary bypass. J Thorac Cardiovasc Surg 129:760–766
32. Kilger E, Heyn J, Beiras-Fernandez A, Luchting B, Weis F (2011) Stress doses of hydrocortisone reduce systemic inflammatory response in patients undergoing cardiac surgery without cardiopulmonary bypass. Minerva Anestesiol 77:268–274
33. Steinvil A, Berliner S, Shapira I, Rogowski O, Justo D, George J, Halkin A, Keren G, Finkelstein A, Banai S, Arbel Y (2010) Time to rheology in acute myocardial infarction: inflammation and erythrocyte aggregation as a consequence and not necessarily as precursors of the disease. Clin Res Cardiol 99(10):651–656
34. Jung C, Rödiger C, Fritzenwanger M, Schumm J, Lauten A, Figulla HR, Ferrari M (2009) Acute microflow changes after stop and restart of intra-aortic balloon pump in cardiogenic shock. Clin Res Cardiol 98(8):469–475
35. Munsterman LD, Elbers PW, Ozdemir A, van Dongen EP, van Iterson M, Ince C (2010) Withdrawing intra-aortic balloon pump support paradoxically improves microvascular flow. Crit Care 14(4):R161
36. Osuchowski MF, Welch K, Siddiqui J, Remick DG (2006) Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. J Immunol 177:1967–1974
37. Schröder J, Kahlke V, Staubach KH, Zabel P, Stüber F (1998) Gender differences in human sepsis. Arch Surg 133:1200–1205
38. Arranz L, Lord JM, De la Fuente M (2010) Preserved ex vivo inflammatory status and cytokine responses in naturally long-lived mice. Age (Dordr) 32:451–466
39. Agarwal S, Busse PJ (2010) Innate and adaptive immunosenescence. Ann Allergy Asthma Immunol 104:183–190
40. Wong CP, Magnusson KR, Ho E (2010) Aging is associated with altered dendritic cells subset distribution and impaired proinflammatory cytokine production. Exp Gerontol 45:163–169
41. Schmidt C, Höcherl K, Kurt B, Moritz S, Kurtz A, Bucher M (2010) Blockade of multiple but not single cytokines abrogates downregulation of angiotensin II type-I receptors and anticipates septic shock. Cytokine 49:30–38
42. Cha J, Wang Z, Ao L et al (2008) Cytokines link Toll-like receptor 4 signaling to cardiac dysfunction after global myocardial ischemia. Ann Thorac Surg 85:1678–1685
43. Katz JN, Stebbins AL, Alexander JH, Reynolds HR, Pieper KS, Ruzyllo W, Werdan K, Geppert A, Dzavik V, Van de Werf F, Hochman JS (2009) TRIUMPH investigators. Predictors of 30-day mortality in patients with refractory cardiogenic shock following acute myocardial infarction despite a patent infarct artery. Am Heart J 158:680–687
44. Youssef AA, Chang LT, Hang CL, Wu CJ, Cheng CI, Yang CH, Sheu JJ, Chai HT, Chua S, Yeh KH, Yip HK (2007) Level and value of interleukin-18 in patients with acute myocardial infarction undergoing primary coronary angioplasty. Circ J 71:703–708
45. Yamamoto T, Terajima K, Kato K, Iwasaki YK, Miyagi Y, Sato N, Takeda S, Tanaka K, Takano T (2006) Transient leukocytopenia associated with a steep surge of pro-inflammatory cytokines in a patient with severe cardiogenic pulmonary edema. Intern Med 45:1153–1155
46. Buerke M, Murohara T, Skurk C et al (1995) Cardioprotective effect of insulin-like growth factor I in myocardial ischemia followed by reperfusion. Proc Natl Acad Sci 92:8031–8035
47. Rupprecht HJ, vom Dahl J, Terres W et al (2000) Cardioprotective effects of the Na^+/H^+ exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. Circulation 101:2902–2908
48. Werdan K, Pilz G, Bujdoso O et al (2007) Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. Crit Care Med 35:2693–2701