Earliest Bedside Assessment of Hemodynamic Parameters and Cardiac Biomarkers: Their Role as Predictors of Adverse Outcome in Patients with Septic Shock

Benjamin Sasko, Thomas Butz, Magnus Wilhelm Prull, Jeanette Liebeton, Martin Christ, Hans-Joachim Trappe

Department of Cardiology, Ruhr University Bochum, Marien Hospital Herne, Herne, Germany

Abstract

Background: Early assessment and aggressive hemodynamic treatment have been shown to increase the survival of patients in septic shock. Current and past sepsis guidelines recommend a resuscitation protocol including central venous pressure (CVP), mean arterial blood pressure (MAP), urine output and central venous oxygen saturation (ScvO2) for resuscitation within the first six hours. Currently, the established severity score systems like APACHE II score, SOFA score or SAPS II score predict the outcome of critically ill patients on the bases of variables obtained only after the first 24 hours. The present study aims to evaluate the risk of short-term mortality for patients with septic shock by the earliest possible assessment of hemodynamic parameters and cardiac biomarkers as well as their role for the prediction of the adverse outcome.

Methods: 52 consecutive patients treated for septic shock in the intensive care unit of one centre (Marien Hospital Herne, Ruhr University Bochum, Germany) were prospectively enrolled in this study. Hemodynamic parameters (MAP, CVP, ScvO2, left ventricular ejection fraction, Hematocrit) and cardiac biomarkers (Troponin I) at the ICU admission were evaluated in regard to their influence on mortality. The primary endpoint was all-cause mortality within 28 days after the admission.

Results: A total of 52 patients (31 male, 21 female) with a mean age of 71.4±8.5 years and a mean APACHE II score of 37.0±7.6 were enrolled in the study. 28 patients reached the primary endpoint (mortality 54%). Patients presenting with hypotension (MAP <65 mmHg) at ICU admission had significantly higher rates of 28-day mortality as compared with the group of patients without hypotension (28-day mortality rate 74 % vs. 32 %, p<0.01). Furthermore, the patients in the hypotension present group had significantly higher lactate concentration (p=0.002), higher serum creatinin (p=0.04), higher NTproBNP (p=0.03) and after the first 24 hours higher APACHE II scores (p=0.04). A MAP <65 mmHg was the only hemodynamic parameter significantly predicting the primary endpoint (OR: 4.1, CI: 1.1 – 14.8, p=0.008), whereas the remaining hemodynamic variables CVP, ScvO2, Hematocrit, Troponin I and left ventricular ejection fraction (LVEF) seemed to have no influence on mortality. The primary endpoint was all-cause mortality within 28 days after the admission.

Conclusions: In our study, we identified a risk group with an exceedingly high mortality rate: the patients with an age ≥72 years and presenting with hypotension (MAP <65 mmHg). These data can be easily obtained at the time of the very first patient contact. As a result, an aggressive and a more effective treatment can be initiated within the first minutes of the primary care, possibly reducing organ failure and short-term mortality in this risk group.

Key words: sepsis, risk assessment, biomarkers, hemodynamics, shock
Introduction

Septic shock is a life-threatening condition associated with high rates of mortality and morbidity. Early recognition and source control as well as effective therapy including appropriate antimicrobial agents and hemodynamic stabilization are the most important cornerstones of sepsis therapy. In the last decade, early goal-directed therapy (EGDT) introduced by Rivers and coworkers became a widely accepted strategy in the initial hemodynamic resuscitation of patients in septic shock \(^1\) and gained a central position in previous and recent international guidelines \(^2,3\). But despite these advances in diagnostic and therapeutic strategies and the implementation of new approaches in the treatment of sepsis and septic shock, the prognosis still remains poor \(^4\).

Bedside assessment of reliable variables to predict the outcome of patients in the early course of septic shock would be desirable to help clinicians to provide an earlier optimal care. Currently, established severity score systems like APACHE II score or SAPS II score predict the outcome of critically ill patients on the bases of variables obtained only after the first 24 hours \(^5,6\), whereas the early risk assessment at the point of intensive care unit (ICU) admission might be essential for the optimization of the individual therapeutic strategy, the initial hemodynamic resuscitation approach and the prediction of short-term survival.

Thus, we established a set of predictors of adverse outcome, based on hemodynamic parameters and cardiac biomarkers which can easily be obtained during primary care at ICU admission. We hypothesized that these variables might be associated with clinically relevant adverse outcome if present at ICU admission and could reliably be used to identify patients at risk for a worse short-term survival.

Methods

Study Population and Definition of Septic Shock

Between August 2009 and December 2010, 52 patients admitted with signs and symptoms of untreated septic shock, manifested within 24 hours before admission, were prospectively enrolled in this study.

Septic shock was defined according to current guidelines \(^3\) as follows: the presence of infection and the fulfillment of systemic inflammatory response syndrome. A systolic blood pressure less than 90 mmHg or a mean arterial blood pressure less than 65 mmHg respectively, persisting over a 30-minute period despite adequate fluid resuscitation (defined as 30 ml crystalloid-fluid per kg of body weight within 30 minutes) or the need of continuous administration of vasopressors. Exclusion criteria were the age <18 years and ARDS-patients ventilated mechanically in prone position.

Hemodynamic parameters and cardiac biomarkers at the point of admission were evaluated in regard to their prognostic ability concerning the short-term survival. The primary endpoint was all-cause mortality within 28 days after admission. The study complies with the Declaration of Helsinki; the local ethics committee approved the study.

Definition of Risk Factors: Hemodynamic parameters and cardiac biomarkers

Hemodynamic variables and cardiac biomarkers were evaluated at ICU admission. Potential predictors of adverse outcome were considered as being present when meeting one of the following criteria: 1) mean arterial blood pressure (MAP) <65 mmHg; 2) central venous pressure (CVP) ≤12 mmHg; 3) central venous oxygen saturation (SvO\(_2\)) <70%; 4) hematocrit (HTC) <30%; 5) troponin I (TnI) >0.015 ng/ml as an indicator of myocardial damage; 6) the presence of cardiac dysfunction, defined as a left ventricular ejection fraction (LVEF) <40%.

Hemodynamic assessment included continuous measurement of heart rate and continuous invasive measurement of arterial blood pressure. CVP and SvO\(_2\) were collected at admission and repeated every 4 hours. Laboratory methods included routine parameters (including NTproBNP) as part of the primary care at ICU admission. Blood samples were drawn from arterial blood and measured immediately after blood withdrawal by standardized methods.

Treatment of Septic Shock

All patients received the best medical treatment according to current guidelines \(^3\); empiric antibiotic treatment was initiated within the first three hours of recognition of sepsis. The selected anti-infective agents included activity against all likely pathogens. Microbiologic sampling was performed prior to the first antimicrobial dose, including blood cultures, lower respiratory tract sample, urine sample and, if indicated, cultures from pleural effusion or ascites. Hemodynamic resuscitation included the administration of crystalloid fluid to achieve a CVP of ≥8 mmHg. In case of persistent hypotension, vasopressors were applied to maintain a MAP ≥65 mmHg. Inotropic agents were used if SvO\(_2\) was <70%. If mechanical ventilation was needed, all patients were sedated with propofol or midazolam and sufentanil (Richmond Agitation-Sedation Scale -3/-4).

Data Collection

Baseline demographics, the history of cardiovascular disease, the (assumed) focus of infection,
antibiotic treatment and Horowitz quotient (PaO2/FiO2) were extracted from the patient’s medical file and the hospital’s electronic database at ICU admission. The Acute Physiology And Chronic Health Evaluation II Score (APACHE II) and Sepsis related Organ Failure Assessment Score (SOFA) were calculated 24 hours after admission to the ICU. The data collection included volume resuscitation and vasopressor or inotrope utilization during the first 24 hours.

Echocardiography Study
As part of the hemodynamic assessment, trans-thoracic echocardiography was performed in apical four and two chamber view at ICU admission (Acusson CV70, Siemens AG, Munich, Germany). LVEF was measured using the Simpson’s monoplane method. Patients were classified by their LVEF into four groups (normal, mild, moderate or severe depressed) according to the American College of Cardiology/European Society of Cardiology (ACC/ESC) guidelines.

Statistical analysis
Categorical variables were summarized as percentages. Continuous data was described by mean or median if skewed, range and standard deviation (SD). The Mann-Whitney test was used to compare continuous data among different patient groups. Significant association of binary variables with mortality was assessed by the Fisher’s exact test, followed by a calculation of odds ratio and 95% CI to compare the risk of death between the patient groups.

We constructed two logistic regression models with multivariable analysis to assess the impact of the predefined risk factors on the 28-day survival. The first model was adjusted for age, gender and history of coronary artery disease as predictor variables. Additionally we entered all defined hemodynamic risk factors with a p<0.05 in the bivariate analysis as complementing predictor variables (called Model A). The second multivariate model was adjusted for age, gender, history of coronary artery disease and all hemodynamic variables as predictor variables (called Model B). The 28-day mortality was defined as the outcome variable. For all predictor variables included in the logistic regression model, the odds ratio and 95% CI were calculated to assess the effect size of the risk factor on the outcome. P<0.05 was considered statistically significant. Analyses were carried out using IBM SPSSv.19.0 (IBM Corporation, New York, United States of America).

Results
All 52 patients met the inclusion criteria of septic shock with multiple organ failure and were therefore enrolled in this study. Table 1 presents the baseline characteristics for all patients, survivors and non-survivors.

Table 1. Baseline characteristics

|                        | all subjects (n = 52) | Survivors (n = 24) | non-survivors (n= 28) | p-value |
|------------------------|----------------------|-------------------|-----------------------|---------|
| Age, yr                | 71.4 ± 8.5           | 68.4 ± 6.9        | 74.1 ± 9.0            | 0.16    |
| Male, n (%)            | 31 (59.6)            | 13 (41.9)         | 18 (58.1)             | 0.64    |
| Cardiac comorbidities | Cardiac comorbidities |
|                        | Coronary artery disease | 33 (62.7)   | 15 (45.5)            | 18 (54.5) | 1.0 |
|                        | Atrial fibrillation   | 21 (39.9)        | 10 (47.6)            | 11 (52.4) | 1.0 |
|                        | Mitral valve prolapse | 10 (19.0)        | 5 (90.0)             | 5 (90.0)  | 1.0 |
|                        | Aortic valve stenosis | 6 (11.4)         | 3 (50.0)             | 3 (50.0)  | 1.0 |
|                        | Aortic valve regurgitation | 3 (5.7)   | 1 (33.3)             | 2 (66.7)  | 1.0 |
|                        | Dilatative cardiomyopathy | 3 (5.7) | 1 (33.3)             | 2 (66.7)  | 1.0 |
| Site of infection      | Pulmonary            | 36 (68.4)        | 16 (44.4)            | 20 (55.6) | 0.76 |
|                        | Intra-abdominal      | 6 (11.4)         | 2 (33.3)             | 4 (66.7)  | 0.67 |
|                        | Urosepsis            | 6 (11.4)         | 3 (50.0)             | 3 (50.0)  | 1.0 |
|                        | Neurological         | 1 (1.9)          | 0 (0.0)              | 1 (100.0) | 0.46 |
|                        | unknown              | 3 (5.7)          | 2 (66.7)             | 1 (33.3)  | 1.0 |
| APACHE II Score        | 37.0 ± 7.6           | 34.9 ± 7.3        | 38.8 ± 7.5            | 0.06    |
| SOFA Score             | 12.5 ± 2.1           | 11.8 ± 1.9        | 13.0 ± 2.3            | 0.03    |
| Hemoglobin, g/dl       | 10.5 ± 1.9           | 10.9 ± 1.9        | 10.3 ± 1.9            | 0.20    |
| Hematocrit, %          | 31.2 ± 5.5           | 32.0 ± 5.7        | 30.8 ± 5.5            | 0.36    |
| WBC count, /nl         | 17.8 ± 9.3           | 16.4 ± 6.6        | 18.9 ± 11.1           | 0.32    |
| Procalcitonin >2 ng/ml | 35 (67.3)            | 14 (40.0)        | 21 (60.0)            | 0.24    |
| Creatinine, mg/dl      | 2.4 ± 1.6            | 2.1 ± 1.3         | 2.7 ± 1.8             | 0.21    |
| Bilirubin, mg/dl       | 0.8 ± 0.8            | 0.8 ± 1.0         | 0.7 ± 0.5             | 0.71    |
| Lactat, mmol/l         | 2.6 ± 2.9            | 1.6 ± 1.1         | 3.6 ± 3.6             | 0.01    |
In accordance with the inclusion criteria of the present study, each of the enrolled patients suffered from at least one organ dysfunction: all patients suffered from circulatory failure, which is imminent in every shock. Vasopressors were used in 96% of all cases, of whom all required noradrenaline. 20 patients (38%) received dobutamine as an additional inotropic agent, and 10 patients (19%) needed adrenalin to sustain a MAP >65 mmHg. An increased Troponin I was found in 63% with a mean value of 3.3±10.2 ng/ml. 90% of the enrolled patients received mechanical ventilation. Among these, 85% had oxygenation indices (paO$_2$/FiO$_2$) of <300 mmHg, while 54% showed oxygenation indices of <200 mmHg. Furthermore, acute kidney failure occurred in 77% of all cases, of whom all required continuous hemofiltration. In the group without hypotension had a longer mean survival time than patients in the hypotension present group (23.7 vs. 13.7 days, p=0.002) (Table 4). While all of the 26 patients within the group without hypotension survived at least 72 hours, 4 of the 26 patients with hypotension died within the first 24 hours.

### Table 2. Hemodynamic variables

|                          | all subjects (n=52) | survivors (n=24) | non-survivors (n=28) | p-value |
|--------------------------|--------------------|------------------|----------------------|---------|
| MAP, mmHg                | 64.7±14.7          | 71.9±12.7        | 63.3±15.4            | 0.012   |
| ScvO$_2$, %              | 65.5±11.2          | 63.7±11.1        | 67.3±11.4            | 0.51    |
| CVP, mmHg                | 10.2±4.9           | 10.2±4.9         | 10.2±4.9             | 0.46    |
| LVEF, % (n=45)           | 43.6±13.5          | 46.1±13.1        | 41.6±13.1            | 0.45    |
| TnI, ng/ml               | 3.3±10.3           | 4.5±11.3         | 2.5±9.5              | 0.78    |
| Hct, %                   | 31.2±5.5           | 30.5±5.4         | 32.0±5.6             | 0.66    |

### Table 3. Hemodynamic function and outcome

|                          | n survivors, non-survivors, OR (95%-CI), p-value |
|--------------------------|--------------------------------------------------|
| MAP, mmHg                | [65] [≤65] [26] [17 (65.4)] [9 (34.6)] [5.1 (1.4 - 18.8)] [p = 0.012] |
| ScvO$_2$, %              | [70] [<70] [27] [26 (92.6)] [19 (73.1)] [5.1 (1.4 - 18.8)] [p = 0.012] |
| CVP, mmHg                | [12] [≤12] [31] [16 (51.6)] [15 (48.4)] [0.7 (0.2 - 2.2)] [p = 0.556] |
| HCT, %                   | [30] [<30] [29] [14 (48.3)] [15 (51.7)] [1.2 (0.4 - 3.7)] [p = 0.785] |
| TnI, ng/ml               | [0.015] [≤0.015] [15] [8 (53.3)] [7 (46.7)] [1.8 (0.5 - 6.2)] [p = 0.531] |
| LVEF, %                  | [40] [≤40] [28] [14 (50.0)] [14 (50.0)] [1.7 (0.5 - 6.0)] [p = 0.534] |

The patients in the hypotension present group had significantly higher lactate concentration (p=0.002), higher serum creatinin (p=0.04), higher NTproBNP (p=0.03) and after the first 24 hours higher APACHE II scores (p=0.04) (Table 4).
As a result of the study population’s mean age of 71.4±8.5 years, we defined 72 years as a cut-off value for the variable age. If hypotension coincided with an age ≥72 years (15 patients or 29% of the study group), the 28-day mortality rate was markedly increased up to 88% (Table 5). We therefore defined the age ≥72 years post-hoc as a predictor of adverse outcome and it was entered in the logistic regression model as we strongly expected it to influence the 28-day mortality.

| Table 4. Organ function and survival time of survivors and non-survivors from hypotension group |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Variable                           | Survivors           | Non-survivors       | p-value *            |
| all subjects                       | MAP < 65 mmHg (n=26) | MAP ≥ 65 mmHg (n = 26) |                      |
| Age, yr                            | 73.3 ± 9.3          | 67.4 ± 7.1          | 75.0 ± 9.3          | 69.6 ± 7.4          | 0.12 |
| Male, n (%)                        | 18 (69.2)           | 4 (15.3)            | 14 (53.8)           | 13 (50.0)           | 0.39 |
| Cardiac comorbidities †, n (%)     |                     |                     |                     |                     |      |
| Coronary artery disease            | 17 (65.3)           | 4 (15.3)            | 13 (50.0)           | 16 (61.5)           | 1.0  |
| Atrial fibrillation                | 11 (42.3)           | 3 (11.5)            | 8 (30.7)            | 10 (38.5)           | 1.0  |
| Mitral valve prolapse              | 5 (19.2)            | 1 (10.0)            | 4 (15.3)            | 5 (19.2)            | 1.0  |
| Aortic valve stenosis              | 3 (11.5)            | 0                   | 3 (11.5)            | 3 (11.5)            | 1.0  |
| Aortic valve regurgitation         | 2 (7.7)             | 1 (3.8)             | 1 (3.8)             | 1 (3.8)             | 1.0  |
| Dilatative cardiomyopathy          | 2 (7.7)             | 0                   | 2 (7.7)             | 1 (3.8)             | 1.0  |
| Site of infection †, n (%)         |                     |                     |                     |                     |      |
| Pulmonary                          | 19 (73.0)           | 8 (30.7)            | 11 (42.3)           | 17 (65.3)           | 1.0  |
| Intra-abdominal                    | 3 (11.5)            | 0                   | 3 (11.5)            | 3 (11.5)            | 1.0  |
| Urosepsis                          | 3 (11.5)            | 1 (3.8)             | 2 (7.7)             | 3 (11.5)            | 1.0  |
| Neurological                       | 1 (3.8)             | 0                   | 1 (3.8)             | 0                   | 0.46 |
| unknown                            | 1 (3.8)             | 0                   | 1 (3.8)             | 2 (7.7)             | 1.0  |
| APACHE II Score                    | 39.0 ± 8.2          | 36.6 ± 10.0         | 40.0 ± 7.6          | 34.7 ± 6.3          | 0.04 |
| SOFA Score                         | 12.8 ± 2.2          | 12.7 ± 1.6          | 12.8 ± 2.4          | 12.2 ± 2.1          | 0.31 |
| Hemoglobin, g/dl                   | 9.8 ± 1.4           | 10.5 ± 1.5          | 9.6 ± 1.4           | 11.4 ± 1.9          | <0.01|
| Hematocrit, %                      | 29.4 ± 4.3          | 30.9 ± 4.3          | 28.9 ± 4.4          | 33.1 ± 6.1          | 0.01 |
| WBC count, /nl                     | 19.5 ± 10.4         | 17.7 ± 3.9          | 20.1 ± 11.9         | 15.9 ± 7.8          | 0.17 |
| Procalcitonin ≥2 ng/ml, n (%)      | 21 (60.0)           | 6 (17.1)            | 15 (42.9)           | 14 (40.0)           | 0.14 |
| Creatinine, mg/dl                  | 2.8 ± 1.8           | 2.5 ± 1.8           | 2.9 ± 1.9           | 1.9 ± 1.1           | 0.04 |
| Bilirubin, mg/dl                   | 0.8 ± 1.0           | 0.6 ± 0.3           | 0.8 ± 0.5           | 0.7 ± 0.5           | 0.71 |
| Lactate, mmol/l                    | 3.7 ± 3.7           | 2.1 ± 1.2           | 4.2 ± 4.1           | 1.5 ± 0.9           | <0.01|
| NTproBNP, pg/ml                    | 4136 ± 33619        | 9634 ± 41906        | 1086 ± 2783         | 1341 ± 4966         | 0.03 |
| PaO2, mmHg                          | 76.5 ± 25.5         | 88.3 ± 31           | 72.7 ± 22.4         | 86.2 ± 25.6         | 0.17 |
| PCO2, mmHg                          | 40.8 ± 10.3         | 45.2 ± 13.3         | 37.9 ± 7.7          | 39.8 ± 9.7          | 0.70 |
| Oxygenation index (PaO2/FiO2) mmHg | 202.6 ± 111.7       | 207.6 ± 147.0       | 200.8 ± 101.1       | 203.3 ± 85          | 0.97 |
| PaO2/FiO2 < 300 mmHg, n (%)         | 24 (92.3)           | 8 (30.7)            | 16 (61.5)           | 20 (76.9)           | 0.45 |
| PaO2/FiO2 < 200 mmHg, n (%)         | 14 (53.8)           | 5 (19.2)            | 9 (34.6)            | 14 (53.8)           | 0.78 |
| Mean volume resuscitation, ml      | 6929 ± 3086         | 6396 ± 3510         | 7116 ± 3000         | 5543 ± 2518         | 0.08 |
| Dosage of Norepinephrine, µg/kg/min| 0.5 ± 0.9           | 0.3 ± 0.3           | 0.6 ± 1.0           | 0.6 ± 1.4           | 0.90 |
| Mean survival, days                | 13.7 ± 10.4         | 28.0 ± 0            | 9.2 ± 6.7           | 23.7 ± 8.9          | 0.002|
| 28-day-mortality, %                | 73                  |                      |                      | 27                  | 0.001|

* p-value for comparison of variables between patients with MAP < 65 mmHg and MAP ≥ 65 mmHg

In the first multivariate regression analysis (Model A, Table 6), the variables age ≥72 years (p=0.01) and MAP < 65 mmHg (p=0.008) were significantly associated with an increased mortality rate. The odds of mortality was 4.1 (95% CI, 1.1 – 14.8) higher for the hypotension present group compared to the group without hypotension. The impact of an age ≥72 years significantly increases the odds of dying to 4.0 (95% CI, 1.0 – 15.0). These results indicate a four-fold increase in the risk of death for both factors. The logistic regression model is therefore consistent with the results of the bivariate analysis performed earlier. Finally, the results of the second logistic regression (Model B, Table 6) are in line with the bivariate and multivariate analysis presented above.

Vasopressors and inotropic agents

96% of the patients needed vasopressor and/or inotrope agents during the first 24 hours to sustain a MAP >65 mmHg despite crystalloid fluid challenge. In the univariate analysis, there was no significant difference in the volume application or the vasopres-
sor/inotropic dosage between the survivors and non-survivors within the first 24 hours, all p<0.05.

Though 31 patients (65%) were presented with ScvO2 levels <70%, only 20 patients (39%) were treated with dobutamine. Furthermore, 6 patients (12%) who received dobutamine showed ScvO2 values of >70%. Table 7 illustrates the hemodynamic of patients treated with dobutamine versus patients who did not receive dobutamine.

**Transthoracic echocardiography**

Transthoracic echocardiography could be obtained in 45 cases (86%). The quantitative evaluation of LVEF was classified according to the ACC/ESC guidelines 7, results are shown in Table 8.

**Missing data**

Among all included patients, there was an incomplete data set in 10 cases (19%). As indicated in Table 8, echocardiography could not be performed in 7 cases (14%). Furthermore, we had missing data in connection to 3 other patients (6%), which affected CVP and ScvO2 due to a missing central catheter at the time of examination. TnI was not obtained in 4 cases (8%).

**Discussion**

Well established tools for risk stratification and prediction of death of critically ill patients are the APACHE II and SOFA score. Both of them can technically be only evaluated after 24 hours and not obtained at ICU admission. It has been previously documented that the improvement of hemodynamic function leads to the highest benefit of survival and a delayed treatment of cardiovascular organ failure is associated with an increased mortality 8. Therefore, our idea was the earliest possible risk assessment in patients with septic shock – which in the present study is at ICU admission – using hemodynamic parameters and cardiac biomarkers.

**Table 7. Hemodynamic function of patients with dobutamine vs. without dobutamine**

| Variable          | With dobutamine (n=20) | Without dobutamine (n=32) | p-value |
|-------------------|------------------------|--------------------------|---------|
| MAP, mmHg         | 63.0 ± 14.9            | 69.9 ± 9.0               | 0.10    |
| NTproBNP, pg/ml   | 17285 ± 40808          | 4133 ± 6848              | 0.10    |
| Lactate, mmol/l   | 3.9 ± 3.7              | 1.8 ± 2.0                | 0.01    |
| TnI, ng/ml        | 6.0 ± 15.0             | 1.5 ± 3.1                | 0.13    |
| ScvO2, %          | 64.1 ± 14.3            | 66.6 ± 14.9              | 0.45    |
| LVEF, %           | 38.5 ± 15.2            | 47.4 ± 10.9              | 0.02    |
| Mean norepinephrine dosage, µg/kg/min | 1.0 ± 1.7 | 0.2 ± 0.2 | 0.01 |

The key findings of the present study are as follows: a mean arterial blood pressure of <65 mmHg at the time of ICU admission was the only hemodynamic factor associated with an increased rate of the 28-day mortality. A decreased CVP was of no prognostic value regarding the 28-day survival in this study, nor was a decreased ScvO2 or hematocrit, an increased troponin I or altered LVEF.

Our results support the findings of previous studies in which hypotension is clearly associated with adverse outcome in critically ill patients 9-12. A MAP <65 mmHg might therefore be suitable as a prognostic factor at ICU admission for patients presented in septic shock. This is particularly the case with regard to elderly patients with an age ≥72 years. Here we demonstrated a 28-day mortality rate of 88%.

The patients in the group with hypotension had an increased risk of death in all three performed statistical analyses – the bivariate analysis and both logistic regression models. As a result of missing data described in the results section, 10 patients could not be included into the second multivariate regression model (Model B), which therefore only consisted of 42 patients. Due to this smaller sample size, statistics from this particular analysis seem to be more inaccurate, indicated by an OR (95% CI) of 18.8 (2.4 – 148.2) for the variable MAP <65 mmHg. Still, in particular the bivariate analysis and the first logistic regression model (Model A: variables age, gender, known CAD and MAP <65 mmHg) indicated a four-fold increased risk of death if hypotension is present. Not surpris-
ingly, patients with hypotension had significantly higher
degrees of organ dysfunction.

The interpretation of hemodynamic variables is a
well-established tool to guide intensive care therapy.
Therefore, the recommended resuscitation approach
for patients with septic shock suggests the use of
MAP, CVP, ScvO₂ and HTC. As the present study
was unable to show an association between the im-
paired hemodynamic variables (other than MAP) and
mortality, one has to ask for the reasons why there
was no difference regarding the outcome.

Our hypothesis is that the present results differ
due to the heterogeneous characteristics of our study
setting as well as of our study population when
compared with other studies investigating the he-
modynamic resuscitation in septic shock.

**ScvO₂**

One distinct example underlining our assump-
tion is the following interpretation of ScvO₂ and its
impact on mortality, if viewed in the light of other
studies:

It is known that four factors negatively influence
the ScvO₂ level: anemia, decreased arterial oxygen
saturation, increased oxygen demand and impaired
cardiac output. Mechanical ventilation on the other
hand achieves an improvement of ScvO₂ through
an increased oxygen balance through increased oxygen
delivery (DO₂) and decreased oxygen demand (VO₂).
Therefore, low pre-intubation levels of ScvO₂ may rise
as an effect of mechanical ventilation itself. Rivers
and colleagues described a mean ScvO₂ of 49.2% at
baseline for the standard therapy group and a mean
ScvO₂ of 48.6% for the EGDT group. The rate for me-
chanical ventilation was 53% within the study popu-
lation. In contrast, the mean ScvO₂ level of the pre-
sent study at ICU admission was mounting 65.5%
with simultaneously exceedingly high mechanical
ventilation rate of 90%. Therefore, according to our
observations an improved ScvO₂ depends heavily on
study setting and applied therapies.

This is in line with findings from other studies in
which hemodynamic resuscitation using ScvO₂ as a
marker of hemodynamic function and systemic oxy-
genation resulted in contrary data regarding the out-
come. As a consequence, there has been rising
concern assuming that it was premature to recom-
end a general applicability of resuscitation strate-
gies in current guidelines using ScvO₂ with such
emphasis as a hemodynamic goal based only on data
from one single-centre study.

As our data show, despite trying to follow the
current guidelines in this matter, our clinical expe-
rience suggests a certain inconsistent usage of dobuta-
mime if guided by ScvO₂ levels. Only two thirds of all
patients with a ScvO₂ <70% received dobutamine
while as a contrast, 6 patients were treated with ino-
tropic agents although showing ScvO₂ levels of 70%
or more. As Table 7 indicates, patients who received
dobutamine showed to have increased lactate levels,
increased LVEF and a higher mean value of norepi-
nephrine. All three might indicate a clinically more
severe septic shock. As a conclusion, ScvO₂ levels did
not always reflect the severity of disease adequately
and therapeutic concepts in these cases resulted from
decisions based rather on practical experience than on
guidelines. The seemingly inconsistent handling of
dobutamine may raise the question whether this is
partly due to the above mentioned controversy in the
literature concerning a ScvO₂ guided resuscitation
approach.

**CVP**

The same holds true for CVP. Its measurement in
critically ill patients is widely debated in literature,
and reports of its reliability in reflecting adequate
fluid status have been inconclusive. Though CVP
is traditionally considered to be a measure of cardiac
preload, our belief was that accuracy of CVP is limited
due to the different daily clinical setting of an ICU.
Physicians are confronted with unselected patient
groups, faced with such influences on CVP as positive
pressure ventilation, elevated abdominal pressure or
valve diseases combined with the patients’ critical
conditions.

**TnI and LVEF**

Beyond the common resuscitation approach us-
ing MAP, CVP, ScvO₂ and HTC, the current study
investigated additional variables in the management
of hemodynamic resuscitation: TnI and LVEF. TnI
was measured as an indicator of myocardial damage.
Several authors reported a relationship between ele-
vated TnI levels and a worse prognosis of survival,
higher severity of disease, higher incidence of organ
dysfunction and a longer ICU stay. Our included
patients had elevated TnI levels in 65% of all cases and
a CAD occurrence of 64% as a known comorbidity.
Data from other studies differ, with an elevated TnI
ranging from 15% to 85% and rates of around 20% for
a known CAD.

We were not able to show a higher risk for death
in patients with septic shock if TnI was increased. We
hypothesize, that elevated TnI levels are more fre-
quent in our study population due to a higher extend
of preexisting CAD, leading to a higher incidence of
troponin release (73% with CAD vs. 47% without
CAD).

As a second additional variable, LVEF was
measured to assess the presence of a cardiac dysfunc-
tion. The results from our study show that a reduced LVEF <40% is a common condition in patients with septic shock, without having an impact on survival (p=0.06). Indeed, these findings are in line with numerous studies, but interestingly with ambiguous findings regarding their impact on survival 25–28. The reasons for that might lie in physiological preconditions, as LVEF is influenced not only by contractility, but also by pre- and afterload. According to the Frank-Starling law of the heart, preload is a major determinant of cardiac output and depends on intravascular volume and venous return. If a reduced LVEF is present at the time of ICU admission, it cannot be definitely said, whether LVEF is depressed as a result of hypovolemia in the early course of septic shock or as a result of the septic cardiomyopathy itself.

We therefore assume that the LVEF alone does not sufficiently characterize the hemodynamic function in the early phase of sepsis treatment. A risk stratification regarding the outcome by using LVEF as an indicator of cardiac dysfunction does not seem feasible at this early point of assessment.

Therefore, taking all these parameter into account, another important result of our study is the observation that there are probably many factors that influence the evaluation of hemodynamic function and its impact on mortality.

**Baseline data of the study population**

In our study, we furthermore analyzed the baseline data of our study population and observed yield two important findings: firstly, a rather elderly study population (mean age 71.4±8.5 years), with 80% being older than 65 years, and secondly, a relatively high APACHE II score, with a mean of 37.0±7.6 points.

Both findings can be explained by the study setting: as a result of studying a population treated in a tertiary centre focusing on internal medicine in a well-developed country, we assume that the study collective is likely to be affected by multimorbidity and advanced age. Moreover, we would like to emphasize that without exception all of our enrolled patients suffered from septic shock with multi-organ failure. In contrast, many studies of the past included patients with sepsis as well as severe sepsis or septic shock 4,29. Therefore, our inclusion criteria led to a study population with more severe diseases, reflected in a higher APACHE II score in comparison to other studies.

Additionally, socioeconomic aspects may also have contributed to a different age distribution. By comparison, as shown in the PROGRESS registry, the mean age of the patients included from Malaysia was 50.1 years. Similar age numbers can be found for other so-called newly industrialized countries such as Brazil or India 30,31. In contrast, German patients showed to have a mean age of 64.2 years 31.

In conclusion, the results of the current and of the past studies suggest ambiguous results regarding the outcome which are heavily depending on study settings and study populations as much as applied therapies and surrounding conditions. These respective surrounding conditions must be taken into consideration when it comes to the interpretation of results.

**Limitations of the present study**

We acknowledge some limitations of our study. Firstly and most importantly, due to the small number of patients enrolled and the strict focus on hemodynamic function there might also be other unconsidered factors influencing the observed mortality rate.

Finally, as a single-centre observational trial with clinical orientation, its non-experimental study design was not intended to prove causality of observed findings and their impact on the outcome. Furthermore, the results from one single-centre might not be equivalent to experiences of other medical centers.

**Conclusions**

The aim of the present study was the identification of risk patients at the time of ICU arrival by bedside assessment of hemodynamic function and cardiac biomarkers in septic shock. We hypothesized that once a person is being identified as a critically ill patient with a greater risk of death, it would allow the medical team to initiate a more aggressive and a more effective treatment within the first minutes of the primary care. The goal would be to achieve a quicker decision process during intensive medical care, e.g. the earlier administration of fluids, antibiotic or vasactive agents, which can be done in any medical environment (emergency room, ICU or ward).

We demonstrated convincingly that a decreased MAP <65 mmHg was the only hemodynamic risk factor associated with an increased 28-day mortality rate. Although the use of echocardiography and measurement of TnI as variables predicting a short-term outcome showed no significant impact on survival in this trial, we assume that both parameters are a useful additional tool to assess cardiac performance during the course of septic shock if measured regularly. Multiple studies proved the benefit of an advanced hemodynamic assessment and it is evident that MAP alone cannot reflect the patient’s hemodynamic function during shock in total.

The authors would like to point out that our study shows very interesting results regarding the bedside assessment in the first few hours of septic
shock. This study was able to identify a risk group with an exceedingly high mortality rate: the patients with an age of 72 years or older, admitted to an ICU with yet untreated septic shock and presented with hypotension (MAP <65 mmHg). This patient group had a 28-day mortality rate of 88%.

The importance of this finding lies in its simplicity. Organ failure and the outcome are likely to be favorably influenced by the immediate therapy and management of the case if rapidly initiated after recognition of primary objectives in the treatment. Optimal therapeutic approaches therefore include a MAP >65 mmHg as a target goal in the hemodynamic resuscitation. This can be assessed easily in every medical center and it is one of the first parameters which can be obtained at the time of the very first patient contact independent from medical environment.

Abbreviations

MAP: mean arterial blood pressure; CVP: central venous pressure; ScvO₂: central venous oxygen saturation; LVEF: left ventricular ejection fraction; HTC: Hematocrit; TnI: Troponin I; NTproBNP: N-terminal pro-brain natriuretic peptide; EGDT: early goal-directed therapy; APACHE II score: Acute Physiology And Chronic Health Evaluation II score; SAPS II score: Simplified Acute Physiology II score; SOFA score: Sepsis Related Organ Failure Assessment score; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; DO₂: oxygen delivery; VO₂: oxygen demand; FiO₂: fraction of inspired oxygen; pao₂: arterial oxygen partial pressure

Competing Interests

The authors have declared that no competing interest exists.

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