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Hemodynamic variables related to outcome in septic shock

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Abstract *Objective:* To assess the impact of hemodynamic variables on the outcome of critically ill patients in septic shock and to identify the optimal threshold values related to outcome with special reference to continuously monitored mean arterial pressure (MAP) and mixed venous oxygen saturation (SvO_2). *Design and setting:* Retrospective cohort study in a university hospital intensive care unit (ICU). *Patients:* All consecutive 111 patients with septic shock treated in our ICU between 1 Jan. 1999 and 30 Jan. 2002. *Measurements and results:* The data on the hemodynamic and respiratory monitoring and circulation-related laboratory tests over the first 48 h of treatment in the ICU were collected from the clinical data management system. Data from 6 h and 48 h were analyzed separately. The 30-day mortality rate was 33% (36 of 111). Univariate analysis and forward stepwise logistic regression analysis were performed using the 30-day mortality as the primary endpoint. Mean MAP and lactate on arrival during 6 h, while mean MAP, the area of SvO_2 under 70%, and mean CVP during 48 h were independently associated with mortality. MAP level of 65 mmHg and SvO_2 of 70% had the highest areas under receiver characteristics curves. *Conclusions:* MAP, SvO_2, CVP, and initial lactate were independently associated with mortality in septic shock, with threshold values supporting those published in recent guidelines.

Keywords Sepsis · Septic shock · Hemodynamic monitoring · Outcome

Introduction

According to the Surviving Sepsis Campaign, hemodynamic treatment in septic shock is to be guided by central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation ($ScvO_2$) [1]. Recent reviews have recommended that treatment be guided by CVP or pulmonary artery occlusion pressure (Ppao), MAP, and cardiac index or output (CI, CO) [2, 3]. However, data on the optimal level of these parameters are insufficient, and suggested goals in published guidelines vary [1, 2].

In septic shock observational studies have shown higher CI, higher SvO_2, and higher oxygen delivery and consumption in survivors. Goal-directed studies of survivors' supranormal hemodynamic pattern have failed to show clear benefit in sepsis [4, 5, 6, 7, 8]. However, those who actually did reach the targets had better outcome, indicating the crucial importance of hemodynamic response on survival. The aim of this study was to evaluate the hemodynamic response by studying common hemodynamic variables as outcome indicators during standard treatment in septic shock. Special emphasis was put on the two continuously monitored variables: arterial pressure and mixed venous oxygen saturation (SvO_2). In hypertensive patients the analysis of ambulatory blood pressure (BP) data has shown that BP load (percentage of values exceeding a certain threshold) or BP area over a certain threshold are better indicators of end-organ damage, complications, and efficacy of medical treatment

than single or mean values of BP [9]. We therefore used this approach in patients with septic shock. We evaluated whether time or area under critical MAP or SvO_2 level is a better predictor of survival than mean values of these or the other hemodynamic variables by analyzing hypotension- and hypoperfusion time (percentage of values under a certain threshold) and hypotension and hypoperfusion area (area under a certain threshold) from continuously measured MAP and SvO_2 values. In addition, we examined the most predictive threshold levels regarding mortality.

Materials and methods

Patients

This retrospective study was conducted in a nine-bed medical-surgical intensive care unit (ICU) in Helsinki University Hospital. The study protocol was approved by the local ethics committee. All 1419 consecutive patients admitted to the ICU between 1 January 1999 and 30 January 2002 were considered eligible. The 111 patients with a discharge diagnosis compatible with sepsis (sepsis, pneumonia, meningitis, or peritonitis) and a need for vasopressor support (dopamine, norepinephrine, or epinephrine) during the first 48 h constituted the final study population with septic shock. Their demographics and baseline clinical and medication data are shown in Table 1.

Data collection

Data were recorded in the ICU clinical data management system (HP CareVue, Palo Alto, Calif., USA). The following data concerning the first 48 h were collected from the database Basic data included: age, gender, source of sepsis, Acute Physiology and Chronic Health Evaluation (APACHE) II score for the first 24 h in the ICU, Sequential Organ Failure Assessment score (SOFA) for days 1 and 2; hemodynamic data included: MAP (mmHg) was recorded in the database every 10 min (each value was considered to represent the values within the previous 10 min). Hypotension time was defined as the percentage of MAP values lower than the chosen threshold. Hypotension area was calculated as the total area of MAP values lower than chosen threshold (Fig. 1) divided by the total duration of monitoring. MAP values less than 60, 65, 70, and 75 mmHg were chosen as the threshold to be tested. Hypoperfusion time and hypoperfusion area were calculated from SvO_2 values, using SvO_2 less than 60%, 65% 70%, and more than 85% as thresholds. If the patient died within the 48-h monitoring period, the last hour's data were excluded. Ppao, CVP, CI, and SV (stroke volume) were recorded every 1–6 h. Laboratory data included: serum lactate, on arrival and on day 2. Respiratory data included: maximal and mean positive end-expiratory pressure, minimal PaO_2/FIO_2. Medication data included: maximal doses (μg/kg per minute) of norepinephrine, dopamine, dobutamine, and adrenaline. Mortality data were acquired from the hospital records and central Population Register Centre of Finland. During the 48-h study period MAP values were recorded 255±82 times and SvO_2 245±101 times per patient on average. The corresponding numbers of recorded values of CVP, Paop, CI, and SV were 19±9, 17±9, 14±7, and 14±7, respectively.

Table 1 Patients' demographic and medication data

	Survivors (n=75)	Nonsurvivors (n=36)	p[a]
Age	48.8±15.5	55.3±14.6	0.04[b]
Gender male	44 (59%)	18 (50%)	0.42
Source of sepsis			
Pneumonia	35 (47%)	12 (33%)	0.22
Meningitis	6 (8%)	2 (6)	0.39
Peritonitis	8 (11%)	7 (19%)	0.24
Blood	15 (20%)	8 (22%)	0.81
Sepsis of another or unknown origin	9 (12%)	7 (19%)	0.39
Positive blood culture	42 (56%)	19 (52%)	0.83
Pulmonary artery catheter	68 (91%)	32 (89%)	0.76
Ventilator	69 (92)	35 (97%)	0.42
Renal replacement therapy	11 (15%)	18 (50%)	<0.005
APACHE II	15±7	21±8	0.005[b]
SOFA day 1	8±3	12±3	<0.005[b]
SOFA day 2	8±2	12±3	<0.005[b]
Use of			
Norepinephrine	58 (77%)	35 (97%)	0.006
Epinephrine	12 (16%)	11 (31%)	0.09
Dopamine	40 (53%)	14 (39%)	0.07
Dobutamine	32 (43%)	18 (50%)	0.54
Maximal dose (μg/kg per minute)[c]			
Norepinephrine	0.34±0.5	1.16±2.0	0.006[b]
Epinephrine	0.43±0.8	0.13±0.1	0.44[b]
Dopamine	6.9±3.9	7.1±3.3	1.0[b]
Dobutamine	5.6±2.8	7.0±4.3	0.37[b]

[a] Fisher's exact test
[b] Mann-Whitney test
[c] Only patients with vasoactive infusion included

General policy in the management of septic shock in our ICU

The standard management of patients with septic shock in our ICU included fluid resuscitation, the use of norepinephrine as primary vasopressor and use of dobutamine as the primary inotrope. The general targets of vasoactive treatment were MAP over 65 mmHg, Ppao 12–16 mmHg, and SvO_2 over 65%. Use of pulmonary arterial catheter was considered mandatory if norepinephrine was used.

Statistical analysis

The data are presented as mean ±SD unless otherwise noted. Survivors and nonsurvivors were compared by the Mann-Whitney U test for continuous variables and by Fisher's exact test for categorical variables. The prognostic value of the variables was first determined by univariate analysis, and $p<0.1$ was the level for inclusion to the multivariate forward logistic regression analysis to test the independent effect on outcome. In addition, the area under the curve (AUC) was calculated for the MAP and SvO_2 derived variables. For mortality prediction the receiver operating characteristic curve (ROC) analysis tested the best threshold levels of the SvO_2 and MAP derived variables. Differences at the level of $p<0.05$ were considered statistically significant. Bivariate correlation was tested by Spearman's test. The analyses were performed using the SPSS 10.1.3 software (SPSS, Chicago, Ill., USA), separately for first 6 h and 48 h of treatment.

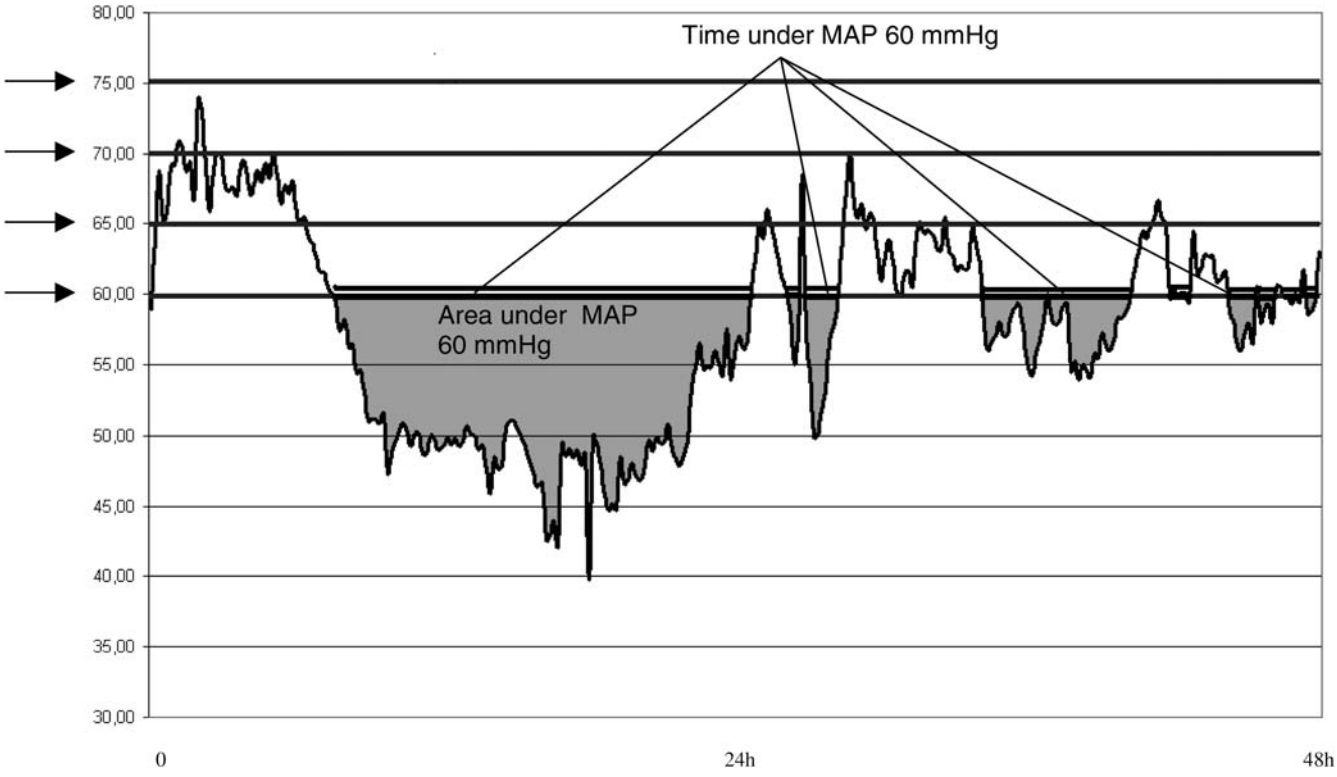

Fig. 1 An example of recording mean arterial pressure (*MAP*) during the first 48 h in the ICU. *Arrows* Threshold values used in the calculations. The hypotension area/time is calculated as the total area/time of MAP values lower than the chosen threshold divided by the duration of the monitoring of the patient. *Gray area* Hypotension area under 60 mmHg (the area of MAP under the threshold of 60 mmHg); *black line* hypotension-time under 60 mmHg (the time of MAP under the threshold of <60 mmHg). In this example the hypotension area under 60 mmHg is 12440 mmHg ×min/47.5 h=261.9 mmHg/min per hour and hypotension time under 60 mmHg is 1750 min/2850min ×100=61.4%

Results

Twelve patients (11%) died within the first 48 h. ICU and 30-day mortality rates were 30% (33 of 111) and 33% (36 of 111), respectively. Hemodynamic and laboratory data of survivors and nonsurvivors are compared in Table 2.

Univariate analysis of 6-h data showed that lactate on arrival and MAP-derived variables under every threshold limit (mean, hypotension time and area under every limit) were associated with 30-day mortality. These variables and mean CVP were included in logistic regression analysis which revealed that mean MAP (p=0.001) and lactate on arrival (p=0.02) were significantly associated with mortality with correct classification rate of 77%.

Univariate analysis of the 48-h data showed the following parameters to be significantly associated with 30-day mortality and included in the logistic regression analysis: MAP-derived variables under every counted threshold-limit (mean, hypotension time and area under every limit), SvO_2 derived variables (mean, hypoperfusion time and area under every limits), mean CVP, mean Ppao, lactate on arrival, and the maximal dose of norepinephrine. The logistic regression analysis revealed that mean MAP, mean CVP, and the hypoperfusion area (SvO_2) under 70% were independently associated with mortality with correct classification rate of 80% (Table 3). When median values were used instead of means, CVP was no longer an independent predictor of mortality.

Receiver operation curves regarding 30-day mortality were plotted for all the MAP and SvO_2 derived variables. The highest AUC values were found for hypotension area under 65 mmHg (AUC 0.853, 95% CI 0.772–0.934) and for hypoperfusion time under 70% (AUC 0.747, 95% CI 0.618–0.876; Table 3).

Discussion

Our results suggest that during standard treatment the most important hemodynamic variables predicting 30-day outcome in septic shock are MAP and lactate for the first 6 h and MAP, SvO_2, and CVP for the first 48 h. The best predictive threshold level for mortality was 65 mmHg for MAP and 70% for SvO_2. Averaged values of cardiac performance (SV, CI) or oxygenation (PaO_2/FIO_2) had no

Table 2 Basic median hemodynamic, laboratory and respiratory data of the study patients, stratified by 30-day survival (*parentheses* interquartile range, *MAP* mean arterial pressure, SvO_2 mixed venous oxygen saturation, *Paop* pulmonary artery occlusion pressure, *CI* cardiac index, *SV* stroke volume, *CVP* central venous pressure, PaO_2/FIO_2 ratio of arterial partial oxygen to fraction of inspired oxygen, *PEEP* positive end expiratory pressure)

	Survivors (n=75)	Nonsurvivors (n=36)	p[a]
6 h data			
MAP mean (mmHg)	76 (72–84)	67 (63–72)	<0.005
SvO_2 mean (%)	73 (68–77)	70 (62–73)	0.01
Paop mean (mmHg)	16 (13–18)	17 (15–20)	0.19
CI mean (l/min per m^2)	3.7 (3.0–4.8)	3.8 (3.0–4.6)	0.94
SV mean (ml)	70 (58–88)	73 (50–85)	0.62
CVP mean (mmHg)	14 (11–16)	16 (14–19)	0.008
48 h data			
MAP mean (mmHg)	78 (74–84)	67 (60–74)	<0.005
SvO_2 mean (%)	73 (71–77)	67 (63–74)	0.002
Paop mean (mmHg)	15 (13–17)	16 (15–19)	0.038
CI mean (l/min per m^2)	4.0 (3.1–4.7)	3.8 (3.1–4.9)	0.81
SV mean (ml)	75 (63–92)	71 (55–92)	0.26
CVP mean (mmHg)	13 (11–15)	16 (13–18)	<0.005
MAP time <65 mmHg (%)	6 (3–15)	40 (14–74)	<0.005
MAP time <70 mmHg (%)	17 (9–35)	64 (33–90)	<0.005
MAP area <65 mmHg (mmHg/min per hour)	14 (9–31)	123 (45–420)	<0.005
MAP area <70 mmHg (mmHg/min per hour)	48 (27–110)	271 (109–662)	<0.005
SvO_2 time <65% (%)	5 (1–11)	35 (3–54)	0.001
SvO_2 time <70% (%)	28 (5–42)	64 (22–96)	0.004
SvO_2 area <65% (mmHg/min per hour)	11 (1–21)	88 (8–245)	0.004
SvO_2 area <70% (mmHg/min per hour)	57 (9–82)	252 (50–429)	0.001
S-lactate on arrival (mmol/l)	2.1 (1.1–2.7)	3.4 (1.6–7.3)	<0.005
S-lactate 48 h (mmol/l)	1.4 (0.9–1.8)	5.1 (1.3–7.4)	0.003
PaO2/FIO_2 lowest (mmHg)	141 (90–220)	103 (54–164)	0.01
PaO2/FIO_2 mean (mmHg)	211 (167–310)	161 (95–227)	0.004
PEEP maximal (H_2Ocm)	12 (10–14)	12 (10–15)	0.53
PEEP mean (H_2Ocm)	10 (9–12)	11 (9–13)	0.64

[a] Mann-Whitney test

Table 3 The variables independently related to mortality by multiple logistic regression model and the corresponding area under the curve (*AUC*) in receiver operating characteristics curve analysis (*ROC*)

	Logistic regression		ROC analysis	
	p	Exp (B)	AUC	95% CI
MAP, mean	0.013	1.156	0.841	0.761–0.921
SvO_2 area under 70%	0.024	0.993	0.737	0.601–0.873
CVP, mean	0.044	0.738	0.712	0.599–0.825

independent effect on mortality, but these affected patient treatment.

Earlier studies often report hemodynamic variables as single measurements or as a mean of several values [5, 10, 11]. In septic shock this approach may be misleading since rapid changes in hemodynamics occur due to the disease and treatment. In the present study we studied parameters derived from continuous monitoring of MAP and SvO_2, allowing better exploration of these parameters cumulatively over time. We took into account both the duration and severity of hypotension and hypoperfusion. Bakker and colleagues [12] used a similar approach in their study of hyperlactatemia, in which AUC for lactate above 2.0 mmol/l and duration of lactate above 2.0 mmol/l were more significant predictors of survival than the initial value. We did not find hypotension time or area more informative than mean MAP over 6 h or 48 h. Hyperperfusion area of SvO_2 under 70% was more predictive than the mean value of continuous SvO_2-measurements over 48 h.

The most powerful predictor of mortality in our study was MAP, which is commonly used as an indicator of global perfusion pressure. In recent reviews and guidelines on septic shock the target value of MAP varies from 60 to 75 mmHg [1, 2, 13, 14, 15]. MAP of 60–65 mmHg is a threshold at which the autoregulation of blood flow to vital organs ceases, resulting in pressure-dependent regional blood flow [16]. Increasing MAP over this limit does not necessary improve organ perfusion [17]. However, the optimal level of MAP may vary depending on the previous BP and vessel status. In this study we could not identify one threshold significantly better than another although the limit 65 mmHg was the most predicative in ROC analysis.

SvO_2, which can be considered an indicator of the adequacy of whole-body tissue perfusion, was another significant variable in this study but only after 48 h. The trial by Rivers and colleagues [18] found that the early goal-directed therapy targeting central venous hemoglobin saturation ($ScvO_2$) over 70% during the first 6 h in the emergency department resulted in significant reduction in mortality in septic patients. In our study SvO_2 was not an independent predictor of mortality during first 6 h in ICU although mean SvO_2 was lower in nonsurvivors. How-

ever, we treated patients in somewhat later phase and fluid resuscitation was continuing.

In shock SvO_2 is usually lower than $ScvO_2$, which should indicate a lower target for SvO_2. In the Rivers et al. study the achieved mean $ScvO_2$ after 6 h was actually 77% in the therapy group, in which fewer than one-half needed any vasopressor therapy. Thus we cannot assume that the target goal for SvO_2 should be lower than for $ScvO_2$, but this needs further investigation. In cardiac surgical patients the goal-oriented treatment of SvO_2 of higher than 70% and lactate higher than 2.0 mmol/l resulted in shorter hospital stay and less organ dysfunction than in control group [19] while no benefit was seen when a SvO_2 goal of 65% was used in vascular surgery patients [20]. A large prospective trial by Gattinoni and colleagues [5] reported that goal-directed therapy targeting to SvO_2 higher than 70% over 5 days did not result in lower mortality than in the control group (63.8% vs. 62.3%). However, in their study only 66.7% of patients reached the target goal, and mortality of these was much lower, 39.0%, supporting our results.

Mean CVP during the first 48 h of ICU treatment was the third variable independently associated with mortality, being lower in survivors than in nonsurvivors. No detrimental effect of high CVP was seen during the first 6 h, and early, adequate fluid resuscitation is regarded as a necessity in septic shock. The significance of CVP disappeared when medians were used instead of means, which emphasizes the effect of extreme values. High CVP probably reflects the aggressive fluid resuscitation in most severe shock patients.

Lactate on arrival and after 48 h was significantly higher in nonsurvivors than survivors, and lactate on arrival was also predictive to mortality by logistic regression analysis after first 6 h. Initial lactate level, peak lactate, duration of lactatemia, and lactate clearance during first 6 h have been shown to predict survival [12, 21].

The retrospective nature of this study is a limitation. Although the data were collected online with the data management system, we cannot exclude the possibility of some false recordings related to patient care or movement or signal artifacts. We checked all data before analysis, and outliers were eliminated. Bias seems unlikely because of the substantial number of recorded values. We did not record fluid balance, which could have been informative concerning CVP. As in all cohort studies in the critical care setting the widely recommended use of standardized treatment protocols and goals affects the results regarding predictive factors of outcome. Therefore our results should be assessed in the light of the included treatment goals of ours.

In our study nonsurvivors received higher doses of norepinephrine and dobutamine and more renal replacement therapy than survivors. They were older and presented with higher APACHEII and SOFA scores, indicating more severe shock. Based on our data it is not possible to assess whether more aggressive treatment improves survival, or whether our results only reflect sepsis severity. We conclude that during standard treatment routinely monitored variables MAP, SvO_2, CVP, and lactate on arrival are independently associated with 30-day mortality in septic shock. In addition, our results, including area under curve analysis, support the recent guidelines aiming at MAP over 65 mmHg and SvO_2 over 70%.

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