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Hemodynamic Treatment Aimed to Reduce Catecholamine Toxicity in Patients Suffering from Septic Shock: An Observational Single Center Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author AH: data acquisition, interpretation of data drafting of the manuscript. Author BW: data acquisition, data analysis and interpretation. Authors GN and SWW: data acquisition. Author MD: data analysis and data interpretation. Author WH: conception and study design, data analysis and data interpretation, manuscript drafting and revising. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Catecholamines represent a cornerstone in the hemodynamic management of septic shock (SS). However, development of toxicity may adversely affect patient outcome. We describe the outcome of 460 consecutive SS patients who were treated with an institutional hemodynamic protocol aimed at decreasing catecholamine toxicity.
Study Design: Retrospective observational analysis.
Place and Duration of Study: Multidisciplinary intensive care unit in a 460 bed hospital between January 1, 2004 to July 31, 2010.

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Methodology: Demographic data, premorbidities, admission Simplified Acute Physiology Score (SAPS) II, most aberrant laboratory data, highest dosages of norepinephrine (NE), dobutamine, milrinone, use of ß-adrenoreceptor blocking agents, hydrocortisone and arginine vasopressin (AVP), development of new-onset tachyarrhythmia and myocardial ischemia were analyzed from an electronic database. The institutional hemodynamic treatment protocol includes early administration of hydrocortisol and arginine vasopressin in addition to norepinephrine and aggressive treatment of hyperthermia (T>38.5º). New onset tachyarrhythmia's/tachycardia were treated using amiodarone and ß-adrenoreceptor blockers to decrease heart rate below 95bpm, respectively. Observed and SAPS-predicted mortality were analyzed for all patients and SAPS-quartiles (QI-QIV) of increasing disease severity.

Results: Age, incidence of preexisting heart, renal disease, arterial hypertension, and MODS increased while body mass index significantly declined from QI to QIV. With increasing disease severity, patients received higher dosages of NE, steroids, AVP and milrinone. The incidence of tachycardic atrial fibrillation and myocardial ischemia increased from QI to QIV. Overall, there was no significant difference between the observed and SAPS II predicted mortality ($p=0.2$, Chi^2-test). However, we observed a trend (-12, 2%) towards decreased mortality in QIII ($p=0.07$) and a significant decrease in hospital mortality (-19%) in QIV ($p<0.0001$; Chi^2-test).

Conclusions: Our data suggest that a treatment protocol aimed at decreasing catecholamine toxicity including early administration of hydrocortisone, AVP, aggressive body temperature and heart rate control may decrease SS mortality, particularly in elderly, premorbid patients suffering from advanced SS.

Keywords: Septic shock; catecholamine; adrenergic stress; mortality; hydrocortisone; arginine vasopressin; temperature control; heart rate control.

1. INTRODUCTION

Septic shock (SS) represents the most serious manifestation of infection. Despite on-going scientific and wide-ranging therapeutic efforts it is still associated with an unacceptably high mortality [1,2,3]. Myocardial dysfunction and vascular hyporesponsivness to vasoactive drugs are typical components of cardiovascular failure promoting tissue hypoxia and organ failure [4,5]. Arterial hypotension, severe hypovolemia, overwhelming inflammation and systemic activation of the coagulation system may result in massive stimulation of the sympathoadrenergic system in an attempt to maintain vital organ perfusion. In critical illness, a protracted and overshooting stimulation of the SNS may exceed in time and scope the beneficial short-term effects of a normal and physiologic meaningful flight reaction. In addition, even after adequate fluid resuscitation patients with SS remain dependent on exogenously administered catecholamines. Comparable to the overwhelming immune response during systemic inflammation endogenous and exogenous adrenergic stress may get out of control in some critical ill patients. Sustained catecholamine exposure attenuates the adrenergic response to catecholamine's [4,6]. In the most severe cases of septic shock, this results in a "vicious circle" when hemodynamic deterioration leads to increases in catecholamine administration which again promotes the occurrence of adverse side effects (e.g. new onset tachyarrhythmia's, myocardial ischemia and pulmonary arterial hypertension) [7]. Therefore, it may be hypothesized that excessive endogenous catecholamine production together with exogenous administration of catecholamines contributes to myocardial dysfunction and cardiovascular collapse in SS [8].

Previous studies, have demonstrated that the addition of AVP to high vasopressor support in patients with catecholamine refractory vasodilatory shock successfully reverses hypotension, reduces catecholamine vasopressor need and significantly decreases the incidence of supraventricular tachyarrhythmia's [9,10,11]. Recently, it has been suggested that combined administration of the endogenous hormones hydrocortisone and arginine vasopressin (AVP) to catecholamine therapy reduces vasopressor requirements and mortality [12,13]. Furthermore, in a small study, the ß-blocker agent metoprolol, when given via the nasogastric route, decreased heart rate and improved myocardial performance in tachycardic SS patients [14].

Based on our own and other study results, we have established an institutional hemodynamic "treatment bundle" for SS patients aiming to decrease catecholamine load and minimize catecholamine toxicity to the cardiovascular system. In this retrospective analysis, we report the intensive care unit (ICU) and hospital outcome of 460 SS patients who were treated according this hemodynamic protocol in our institution.

2. MATERIALS AND METHODS

The retrospective analysis and publication of data derived from our electronic ICU database was approved by the Ethics Committee of the Krankenhaus der Barmherzigen Schwestern, Ried im Innkreis/Austria. The analysis includes 40 patients included in a previous study [14]. In view of the retrospective study design, written informed consent was waived. From January 1, 2004 to July 31, 2010, all medical records of an eight-bed multidisciplinary ICU were reviewed for patients admitted because of SS. SS was defined in accordance with the recommendations of the American College of Chest Physicians, the American Thoracic Society, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the Surgical Infection Society [15]. Exclusion criteria were age <18 years, cardiopulmonary resuscitation before ICU admission, pregnancy, and missing electronic records during final analysis.

2.1 Definitions of Septic Shock (SS)

Presence of a definite infectious focus (lung, abdomen, blood, skin, soft tissue and bones); Systemic Inflammatory Response Syndrome (SIRS) and presence of hypotension defined as systolic blood pressure < 90mmHg or a reduction $\geq$ 40mmHg from baseline in the absence of other causes for hypotension despite aggressive fluid resuscitation necessitating vasopressor support.

SIRS – Criteria

General Signs:

- temperature > 38ºC or < 36ºC
- heart rate > 90 beats per minute or 2SD above normal value
- respiratory rate > 30 breaths per minute or need for mechanical ventilation
- altered mental status
- significant oedema formation or positive fluid balance > 20ml/kg BW within 24 hours
- hyperglycaemia without pre-existing diabetes mellitus

Laboratory Signs

- White blood cell count > 12000/µl or < 4000/µl or >10% immature band (forms)
- CRP > 2 SD above normal value
- Procalcitonin > 2 SD above normal value

2.2 Data Documentation

The following variables are routinely collected in all patients during the ICU stay and entered into the institutional electronic database: demographic data (age, gender, body mass index), premorbidities, the Simplified Acute Physiology Score II ([16]; SAPS II), perioperative data (type of surgery, estimated blood loss within the first 24 hours of surgery), a modified Goris multiple organ failure score (MODS) (calculated from worst physiologic and laboratory data during the ICU stay) ([22]; Table 1), most abnormal laboratory data during the ICU stay (PaO_2/FiO_2 gradient, serum creatinine, aspartate aminotransferase, alanine aminotransferase, arterial lactate and troponin I concentrations), development of adverse events during the ICU stay (new-onset tachyarrhythmia, acute delirium, myocardial ischemia defined as troponin I levels above normal range, use of ß-adrenergic receptor blockers, AVP and/or hydrocortisone). For the present analysis, the highest dosages of norepinephrine, dobutamine, milrinone and AVP administered during the ICU stay were retrospectively collected from electronic patient records.

2.3 Hemodynamic Management

Hemodynamic resuscitation was performed according to an institutional protocol (Fig. 1) which has been developed based on previous study results and international recommendations including the Surviving Sepsis Campaign guidelines [11,14,18,19]. The ultimate goal of all resuscitation efforts is to attain normotension without tachycardia, adequate peripheral perfusion (=warm peripheral skin) and a body temperature $\leq$38.5°C. All patients were invasively monitored with an arterial and a central venous catheter. Initially, fluid resuscitation was aggressively performed using colloids (Gelofusin®; Braun B Melsungen AG, Melsungen, Germany). In the majority of patients, resuscitation was monitored by either transesophageal echocardiography or a transpulmonary thermodilution device (PICCO®; Pulsion Medical Systems, Munich, Germany) or both. When using the PICCO® system, initial volume loading was performed until stroke volume index reached its maximum. Simultaneously, intrathoracic blood volume index was used as a surrogate of cardiac preload. In patients without pre-existent cardiovascular disease, a mean arterial pressure of 60 mmHg and in those with cardiovascular premorbidities a mean arterial pressure of 70 mmHg was targeted by continuous infusion of norepinephrine. In case of escalating norepinephrine dosages, a continuous infusion of hydrocortisone (HC; Pfizer, Berlin, Germany) was added at daily dosages of 200-300mg. If norepinephrine, despite addition of hydrocortisone had to be escalated to reach the targeted mean arterial pressure, arginine vasopressin (AVP; AOP Orphan Pharmaceuticals AG, Vienna, Austria) was added as a continuous infusion at a daily dose of 40-100 IU. In patients presenting with cold extremities and a prolonged capillary refill time or low central venous oxygen saturation despite adequate oxygenation, fluid resuscitation and hemoglobin levels, inotropic support was initiated. Depending on the heart rate and the presence of chronic cardiovascular diseases, either dobutamine (heart rate <90 bpm in patients with chronic cardiovascular diseases and heart rate <110 bpm in patients without chronic cardiovascular diseases) or milrinone (Corotrop®; Sanofi Aventis, Vienna, Austria) was chosen as the first line agent. New-onset supraventricular tachyarrhythmia and sinus tachycardia were treated following

hemodynamic resuscitation and body temperature control (target core temperature ≦38.5ºC) with the use of amiodarone (Sedacoron®; EBEWE Pharma, Uterach, Austria) according to a previously published protocol [20]. In patients with sinus tachycardia or a history of chronic atrial fibrillation, beta-adrenoreceptor blocker therapy was initiated once cardiovascular function had been stabilized targeting a heart rate <95 bpm. In these patients, a retard slow release formulation of either metoprolol 25-47.5 mg (Seloken retard®; AstraZeneca, Vienna, Austria) or atenolol 25-50 mg (Tenormin® AstraZeneca, Vienna, Austria) was administered via the enteral route. Based on the response in heart rate, stroke volume, cardiac index, and/or arterial blood pressure, beta-blocker therapy was gradually intensified or stopped if the heart rate dropped <60 bpm.

Table 1. Multiple organ failure score (modified after goris)
(Organ dysfunction has to be present at least for a period of 24 hours to be counted)

Function	0	1	2
Lung	$PaO_2/FIO_2 \geq 300$	PaO_2/FIO_2 >250	$PaO_2/FIO_2 \leq 250$
Kidney	S-Cr ≤ 2 mg%	S-Cr > 2 mg% or S-Cr increment ≥ 2-times above initial value	Renal replacement therapy
Liver	AST/ ALT not elevated bilirubin < 2 mg%	AST/ ALT elevated ≤ 3x of normal value bilirubin 2-5 mg%	AST/ ALT elevated > 3x of normal value bilirubin > 5 mg%
Blood	thrombocytes and coagulation parameters within normal range	decline of thrombocytes ≥ 25%, abnormal PT or PTT with or without active bleeding	consumption coagulopathy, massive transfusion (>5 PRBC within one hour or >10 PRBC within 24 hours)
Cardiovascular-System	normal fluid requirements, no catecholamines	fluid requirement > 50% of normal fluid intake and/ or norepinephrine ≤ 300 µg/h and/or vasopressin ≤ 1,6 IU/h	norepinephrine > 300 µg/h and/or vasopressin > 1,6 IU/h and/ or any combination with inotropes IABP
Gastrointestinal-Tract	gastric reflux < 500cc per day, tender abdomen, no active GI bleeding	gastric reflux ≥ 500cc per day, bloated abdomen, no defecation > 5 days, diarrhea negative for Clostridium difficile	peritonitis, active gastrointestinal bleeding, acute necrotizing pancreatitis, enterocolitis caused by Clostridium difficile
Central Nervous-System	GCS ≥ 12	GCS 11-9	GCS ≤ 8

S-Cr = Serum Creatinine, AST = Aspartate Transaminase, ALT = Alanine Transaminase, PT = Prothrombin Time, PTT = Partial Thromboplastin Time, PRBC = Packed Red Blood Cells, IABP = Intraaortic Balloon Pump, GCS = Glasgow Coma Scale

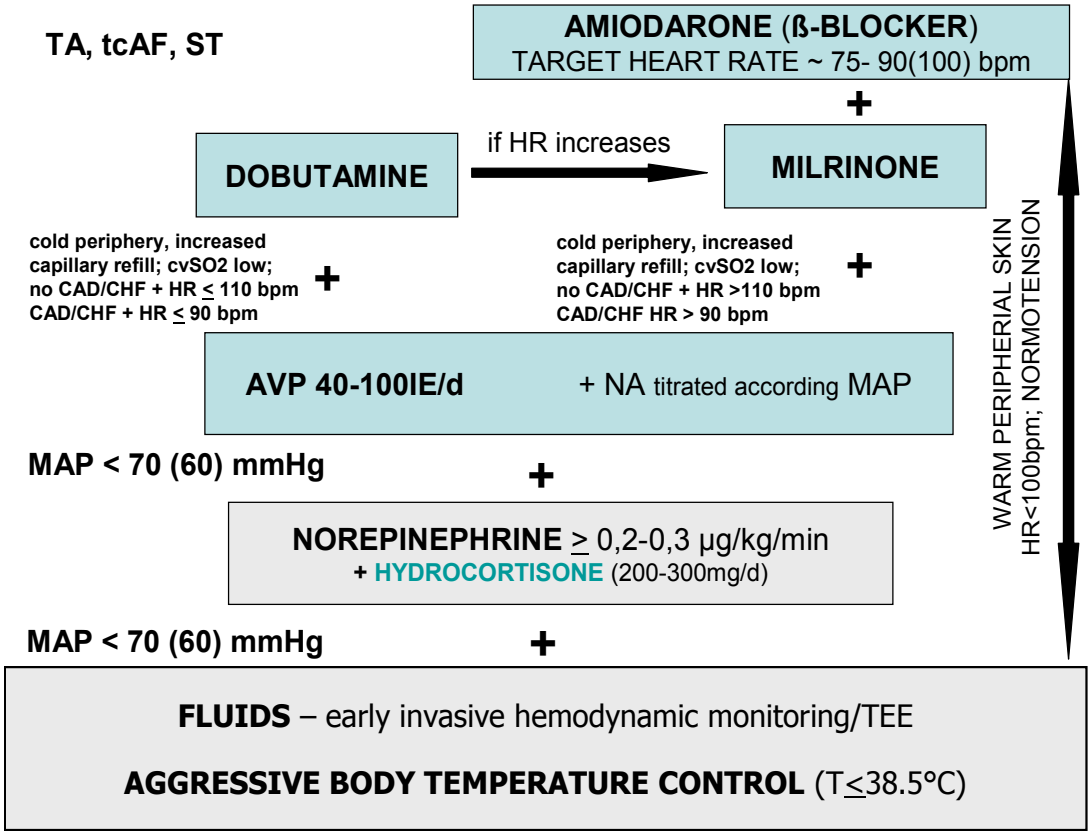

Fig. 1. Treatment algorithm in septic shock

TEE – Transesophageal echocardiography; MAP – Mean arterial pressure; AVP – Arginine vasopressin; NA – Norepinephrine; CAD/CHF – Coronary artery disease/congestive heart failure; HR – Heart rate; cvSO2 – Central venous oxygen saturation; TA – Tachyarrythmia; tcAF – Tachycardic atrial fibrillation; ST – Sinus tachycardia

2.4 General Treatment

During shock, the majority of patients was mechanically ventilated and sedated using a combined midazolam/fentanyl infusion. After hemodynamic stabilization, analgosedation was rapidly reduced to stimulate spontaneous respiration. Complete weaning from mechanical support and extubation was performed after shock resolution in the awake, responsive patient with a PaO_2/FiO_2 gradient >200 mmHg and forceful exhalation upon request.

In patients admitted to the ICU with suspected or diagnosed systemic infection microbiological specimens including sets of blood cultures were obtained and broad-spectrum antibiotic therapy was started whenever possible within the first hour. In SS patients requiring surgical drainage of the infectious focus swabs from the infected tissue were routinely performed and broad-spectrum antibiotic therapy already started in the operation room.

Continuous veno-venous hemofiltration with a filtration rate between 30-35 mL/minute was commenced in patients with oliguria/anuria despite hemodynamic stabilization and in

patients suffering from high degree fever unresponsive to physical/pharmacologic interventions. Nutrition was initiated in all patients via the parenteral route on ICU day 2 and gradually substituted with enteral nutrition starting in most patients on ICU day 3. All patients receive 200 mg of N2-L-Alanyl-glutamine (Dipeptiven®; Fresenius Kabi Austria GmbH; Graz; Austria) intravenously starting on ICU day 2. Nutritional goals are a total caloric intake of 25 kcal/kg lean body weight with targeted blood glucose levels between 80-180 mg/dl.

2.5 Statistical Analysis

The SPSS® 12.0.1 software package was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods were applied to present demographic and clinical data. Observed and SAPS-predicted mortality was compared using the Fisher's Exact test. Based on their disease severity at ICU admission, assessed by the SAPS II, patients were classified into quartiles. Within each SAPS quartile, the observed and SAPS-predicted mortality was compared with the Fisher's Exact test applying Bonferroni corrections for multiple comparisons. Absolute Risk Reduction (ARR) for mortality was calculated by subtracting observed mortality from SAPS-predicted mortality. The Chi² (categorical data) and analysis of variance (continuous data) were used to compare variables between SAPS quartiles as well as between survivors and non-survivors within SAPS quartiles III and IV. Data are presented as median values with interquartile range, if not otherwise indicated. P-values <0.05 were considered to indicate statistical significance.

3. RESULTS AND DISCUSSION

During the observation period, 3,488 patients were admitted to the study ICU. Four hundred-eighty-seven patients (14%) were admitted because of SS. Of these, 27 patients had to be excluded from the final analysis because of cardiopulmonary resuscitation before ICU admission (*n*=10), age <18 years (*n*=7), and missing electronic records (*n*=10).

Table 2 presents data on demographics, admission SAPS II, premorbidities, and source of infection, ICU-, hospital mortality and SAPS-predicted mortality. Overall, there was no significant difference between the observed and SAPS-predicted hospital mortality (p=0.2; Fisher´s Exact Test).

Table 3 presents patients categorized into SAPS quartiles consistent with increasing disease severity. With increasing SAPS quartiles, age, incidence of preexisting heart disease, chronic arterial hypertension and preexisting renal disease increased while body mass index declined. At the same time, MODS, in particular the severity of lung, liver and renal failure, increased. This was accompanied by an increased need for mechanical ventilation and veno-venous hemofiltration. Maximum plasma lactate concentration rose with increasing disease severity. The incidence of new-onset tachycardic atrial fibrillation more than doubled from QI to QIV. Plasma troponin I concentrations rose with increasing SAPS quartiles. Patients received higher maximal dosages of norepinephrine, AVP and milrinone and more patients received hydrocortisone with increasing disease severity. There was a trend towards an increased use of ß-adrenoreceptor blocking agents in patients with higher SAPS quartiles.

Table 2. Demographics, admission–SAPS II, premorbidities, source of infection, mortality

		All patients
		Median (IQR)
Demographics		
Age-yr		72 (60.3-79)
Gender-no. (%)		
	female	198 (43)
	male	262 (57)
BMI (kgxm^{-2})		25.7 (22.8-30.4)
SAPS II		42 (34-52)
Premorbidity - no (%)		
COPD		92 (20)
CAD/CHF		240 (52)
Hypertension		237 (52)
RF		184 (40)
DM		97 (21)
CLD		25 (5)
Neurologic disease		134 (29)
Immunosuppression		39 (8)
Neoplasma		118 (26)
Source of Infection - NO (%)		
Abdomen		267 (58)
Thorax		17 (4)
Soft Tissue/Bones		88 (19)
Pneumonia		55 (12)
CRBSI		17 (4)
Urosepsis		16 (3)
Mortality (%)		
ICU-Mortality		19
Hospital-Mortality		24.5
Predicted Mortality (SAPS II)		28.5

BMI – Body Mass Index; SAPS – Simplified Acute Physiologic Score; COPD – Chronic Obstructive Pulmonary Disease; CAD/CHF – Coronary Artery Disease/ Congestive Heart Failure; RF – Renal Failure; DM – Diabetes Mellitus; CLD – Chronic Liver Disease; CRBSI, catheter-related bloodstream infection.

Table 3. Septic shock and outcome study – ICU data

SAPS II – Quartiles (Median; IQR)	**QI 28 (24-32)**	**QII 37 (35-39)**	**QIII 46 (43-49)**	**QIV 61 (56-72)**	**p-value**
n	**113**	**113**	**117**	**117**	
Age	59 (44-72)	72 (64-81)	74 (67-79)	75 (67-82)	0.0001
BMI (kg x m^{-2})	27,6 (23-33)	26,1 (23-30)	25,5 (23-29)	24,5 (22-28)	0.0001
Mechanical ventilation n (%)	87 (77)	105 (93)	108 (92)	116 (99)	0.0001
vv-Hemofiltration n (%)	31 (27)	31 (27)	63 (54)	87 (74)	0.0001
ICU-days	6 (3-11)	8 (5-13)	9 (6-13)	8 (3-15)	0.2
Premorbidity - no (%)					
COPD	25 (22)	21 (19)	30 (26)	16 (14)	0.13
CAD/CHF	29 (26)	63 (56)	67 (57)	81 (69)	0.0001
Hypertension	34 (30)	69 (61)	67 (57)	67 (57)	0.0001
RF	29 (26)	30 (27)	60 (51)	65 (56)	0.0001
DM	18 (16)	20 (18)	28 (24)	31 (27)	0.16
CLD	4 (4)	5 (4)	8 (7)	8 (7)	0.6
Neurologic disease	23 (20)	39 (35)	36 (31)	36 (31)	0.11
Immunosuppression	4 (4)	8 (7)	12 (10)	15 (13)	0.07
Neoplasma	31 (27)	33 (29)	30 (26)	24 (21)	0.47
Organ dysfunction (Median;IQR)					
MODS (mod. GORIS)	6 (3-8)	6 (4-8)	7 (6-9)	9 (8-11)	0.0001
PaO2/FIO2	276 (175-320)	236 (160-300)	200 (120-270)	140 (100-218)	0.0001
S-Cr (0.6-1.1 mg%)	1.4 (1-2)	1.6 (1.3-2.4)	2.1 (1.5-3.2)	2.8 (1.9-3.7)	0.0001
SGOT (3-35 U/l)	45 (27-113)	43 (27-91)	73 (37-145)	127 (47-439)	0.0001
SGPT (<45 U/l)	34 (16-85)	28 (16-73)	50 (25-109)	66 (24-258)	0.0001
Bilirubin (0.1-1.2 mg%)	1.3 (0.8-2)	1.4 (0.8-2.6)	1.4 (0.8-2.4)	1.7 (0.9-3.6)	0.02
Trop I (0-0.15 ng/ml)	0.05 (0.02-0.21)	0.1 (0.04-0.28)	0.19 (0.07-0.58)	0.39 (0.11-2)	0.009
TcAF (n; %)	20 (18)	32 (28)	42 (36)	52 (44)	0,0001
Lactate (0.4-2 mmol/l)	1.6 (1.1-2.8)	1.9 (1.3-3.2)	2.4 (1.7-4.1)	3.3 (2.1-7.2)	0.0001
Hemodynamic treatment					
ß-Adrenoreceptor blockers n (%)	66 (58)	66 (58)	84 (72)	78 (67)	0.06
Steroids n (%)	64 (57)	69 (61)	99 (85)	102 (87)	0.0001
NE µgxkg^{-1}xmin^{-1}	0.11 (0.07-0.17)	0.13 (0.08-0.19)	0.19 (0.13-0.23)	0.25 (0.14-0.41)	0.0001

Median; (IQR); n/%	113/100	113/100	117/100	117/100	
Dob μgxkg^{-1}xmin^{-1}	1.9 (1.7-2.1)	3 (2.1-3.7)	2.4 (1.8-3.0)	3.9 (2.8-5.6)	0.05
Median; (IQR); n/%	3/3	4/4	5/4	7/6	
AVP U/h	1.6 (1.6-2.7)	1.6 (1.6-2.4)	2.4 (1.6-3.2)	2.4 (1.6-4)	0.0001
Median; (IQR); n/%	47/42	55/49	73/62	102/87	
Mil μgxkg^{-1}xmin^{-1} Median; (IQR);	3.2 (2.5-4.4)	3.6 (2.8-4.6)	3.4 (2.5-4.0)	4.0 (3.3-4.6)	0.03
n/%	24/21	36/32	81/51	81/69	

BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; CAD/CHF – Coronary Artery Disease/ Congestive Heart Failure; RF – Chronic Renal Insufficiency; DM – Diabetes Mellitus; CLD – Chronic Liver Disease; MODS – Multiple Organ Dysfunction Score (modified GORIS); S-Cr – Serum Creatinin; SGOT – Serum Glutamic Oxaloacetic Transaminase; SGPT – Serum Glutamic Pyruvic Transaminase; Trop I – Troponin I; NE – Norepinephrine; Dob – Dobutamine; AVP – Arginine Vasopressin; Mil - Milrinone

Fig. 2 compares observed and SAPS II-predicted hospital mortality within each SAPS II quartile. There were no significant differences between the observed and SAPS II-predicted mortality in QI and QII (p = 0.63 and p = 0.14; Fisher´s exact test). We observed a trend (-12, 2%) towards decreased mortality in QIII (p=0.07). There was a significant decrease in hospital mortality (-19%) in QIV when compared to the SAPS-predicted mortality (p<0.0001). The Chi² (categorical data) and analysis of variance (continuous data) were used to compare variables between SAPS quartiles.

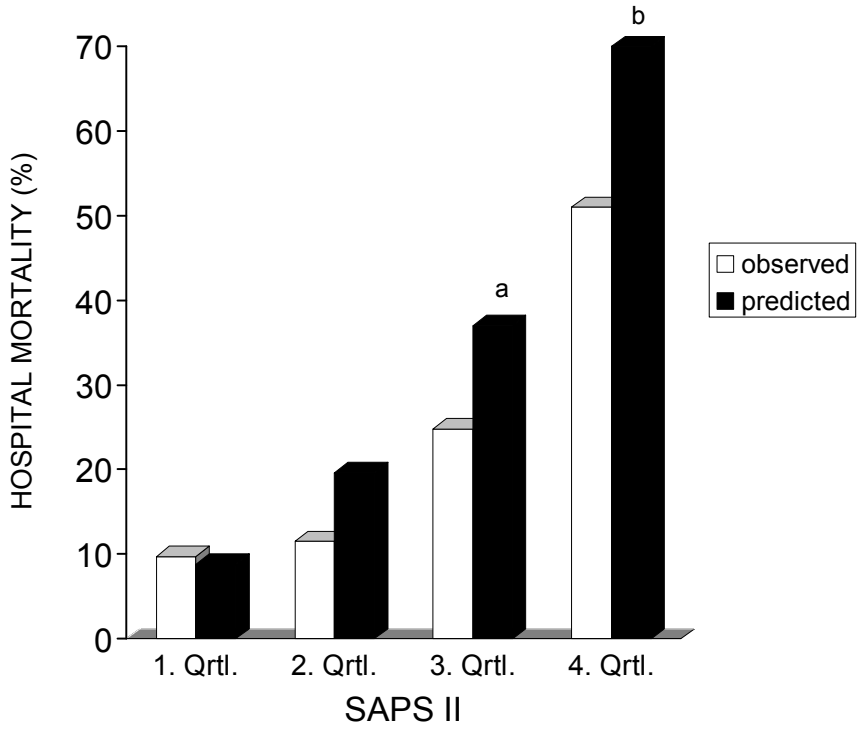

Fig. 2. Mortality observed versus SAPS II predicted

Statistics: Chi-Quadrat Test; OneWay ANOVA

[a] p = 0.065 Fisher`s Exact Test

[b] p = 0.0001 Fisher`s Exact Test

In this observational study including 460 SS patients, existing hemodynamic treatment guidelines have been extended in an institutional algorithm to optimize fluid resuscitation and decrease catecholamine toxicity to the cardiovascular system (Fig. 1). Although, we observed no difference between the observed and SAPSII-predicted hospital mortality in the overall study population, subgroup analysis demonstrated: 1) a trend towards reduced hospital mortality in the third highest SAPS II – quartile in comparison to SAPS II predicted mortality (Table 3; ARR=12%) and 2) a significantly decreased hospital mortality in patients with the highest disease severity (Table 3; ARR= 19%).

In our institution, SS affects a predominantly elderly population with an exceptional high incidence of cardiovascular premorbidities. Overall, more than 50% of SS patients suffered from coronary artery disease and/or congestive heart failure and arterial hypertension before developing SS. In addition, 40% of all patients demonstrated some degree of renal dysfunction before ICU admittance which is also suggestive of an extremely high prevalence

of arteriosclerotic disease. A recent National Centre of Health Statistics (NCHS) data brief reports not only a doubling of hospital admissions because of sepsis in US hospitals but also, similar to our experience, a sharp increase in the incidence of sepsis particularly in patients aged > 65 years [20]. In our population, age, incidence of chronic heart disease, arterial hypertension and preexisting renal failure increased and body mass index decreased with incremental admission SAPSII supporting reports that in high-income countries SS mainly affects a growingly elderly and premorbid patient population.

During the past, animal and clinical studies have demonstrated the involvement of multiple pathophysiologic mechanisms in the development of irreversible multiple organ failure and death [4,5,21,22,23]. However, when looking at the clinical evolution of severe infection the transition between a low to a high mortality disease usually coincidences with the development of hemodynamic failure leading to tissue hypoxia and typical clinical signs of organ malperfusion [24,25]. Therefore, aggressive initial hemodynamic resuscitation constitutes one mainstay of SS management despite on-going discussions of exact hemodynamic targets [26]. Current guidelines provide basal consensus information on possible rational endpoints regarding fluid resuscitation and arterial blood pressure targets and have repeatedly been proven to decrease mortality [27,28]. The SSC guidelines recommend fluid administration according to CVP measurements despite well-known severe physiologic limitations of the method [29,30,31]. Therefore, we perform TEE examinations and/or invasive systemic blood flow monitoring early on during resuscitation from septic shock. In addition, these measurements are combined with close subjective observation of skin temperature and capillary refill which have been shown to be reliable predictors of subsequent morbidity and mortality [24,32]. Suggestions concerning for example the maximum tolerable heart rate or adequacy of systemic blood flow are much less clear [33]. The latter considerations may be specifically important in the presence of limited cardiovascular reserve, e.g in the elderly, premorbid patient population.

Cumulative evidence suggests an important influence of catecholamine excess promoting development of tachycardia/tachyarrhythmia and cardiovascular failure thus worsening final prognosis of SS patients [7,34,35,36,37]. In a previous study investigating risk factors for death of critically ill patients in the intensive care unit the severity of cardiovascular failure defined by increasing catecholamine support was a major independent predictor of death [35]. Likewise, in a recent retrospective analysis of two PRCT including 290 septic shock patients in whom a mean MAP ≥ 70 mmHg was maintained during shock, the mean vasopressor load was an independent predictor of mortality, the occurrence of acute circulatory failure, metabolic acidosis and renal failure [34]. Another new prospective observational study investigated seven predefined adverse cardiac events in 112 critically ill patients and reported that extend and duration of catecholamine vasopressor therapy were independently associated with and may have contributed to the pathogenesis of cardiac morbidity [37]. The two most frequently observed adverse cardiac events were new-onset tachyarrythmias and prolonged elevated heart rate, both of which were correlated with significant morbidity and mortality. It is well known that excessive stimulation of ß1-adrenoreceptors induces myocardial inflammation, myocardial apoptosis and necrosis in animal experiments which can be blocked by administration of ß1-adrenoreceptor blocking agents [38,39,40]. Moreover, blood flow to the left ventricle not only depends on the difference between aortic- and left ventricular pressures but is also critically dependent on diastolic time which of course suffers most when tachycardia develops [41]. Under physiologic conditions e.g. dynamic exercise cardiac output linearly increases with heart rate, while the associated increase in stroke volume only accounts for approximately 25% of the increase in systemic blood flow [42]. It is interesting to note that under resting conditions

an increase in heart rate by 50 bpm induced by atrial pacing does not increase cardiac output in healthy men because of a significant reduction in stroke volume due to a striking decrease in venous return [43]. However, activation of the “skeletal muscle pump” results in a significant increase in venous return and thus systemic blood flow which is a hallmark of the physiologic response to dynamic exercise. One may speculate that, in contrast to common clinical believe, tachycardia often represents a maladaptive process in bedridden critically ill patients already adequately volume resuscitated and free of pain and fear.

In this study, incidence of new-onset tachyarrhythmia’s and highest troponin I plasma concentrations increased together with maximum dosages of norepinephrine applied to patients in each SAPS quartile. In a previous study on the effects of rescue use of AVP on hemodynamic performance in vasodilatory shock, we observed a striking increase in overall ICU mortality if norepinephrine administration exceeded 0.6 µg/kg/min before AVP had been started [11]. Furthermore, in vasodilatory shock, addition of AVP to conventional catecholamine treatment did not only result in a significant decrease of norepinephrine requirements but also in a spontaneous and persistent conversion of new-onset tachyarrhythmia’s into sinus rhythm [10]. Interestingly, in contrast to our previous studies, dosages of NE applied in this study population, even in patients with most advanced MODS, have been low to modest [9,10,11]. We speculate that, in contrast to our previous studies, early co-administration of hydrocortisone and AVP to conventional catecholamine therapy prevented excessive catecholamine dosing favouring early stabilization of systemic hemodynamics, particularly in patients suffering from most advanced disease [8,13]. Likewise, in a post hoc analysis of a multicentre randomized controlled trial, Russell et al reported that the concomitant use of low-dose AVP and corticosteroids in addition to conventional vasopressor therapy was associated with a reduced 28 day-mortality when compared with AVP and catecholamine therapy alone [12].

Prolonged elevated heart rate has been identified as a significant risk factor not only for the occurrence of cardiovascular failure but also for increased mortality in the ICU [44,45,46]. In cardiovascular high-risk patients, a heart rate of 95 bpm was shown to be the critical threshold when myocardial oxygen demand outstripped coronary supply and myocardial ischemia was likely to occur [45]. In a previous study we have demonstrated a significant decrease in heart rate together with an unchanged or even slightly increasing CI and cardiac power index in tachycardic septic shock patients treated with a slow release formulation of metoprolol given via the nasogastric route in order to decrease heart rate to normal values [14]. All together this finding can be interpreted as an economization of cardiac work and oxygen consumption. Reduction of heart rate lowers the risk of myocardial ischemia [47,48], particularly in patients with obstructive coronary artery disease. Instead of beta-agonists, a phosphodiesterase III inhibitor was applied as an inotropic agent in patients with clinical signs of low peripheral perfusion and/or low central venous oxygen saturation. Although this does not correspond to current recommendations [18], milrinone has been used in patients with septic shock at our institution throughout the last decade. Positive inotropic effects of milrinone are mediated through inhibition of the breakdown of cyclic adenosine monophosphate (cAMP) by phosphodiesterase activity in the myocardium [49] and act independently of the beta-1 adrenoreceptor. Milrinone has been successfully used in the treatment of septic shock paediatric patients with normal or low cardiac output [50]. In patients with low cardiac output after cardiotomy, milrinone was equally effective in increasing systemic blood flow when compared to dobutamine and in patients with severe heart failure and low cardiac output [51] a recent small study reported no exacerbation of myocardial injury as assessed by measurements of biomarkers of myocardial injury and inflammation [52]. However, the use of milrinone has been associated with new onset

arrhythmias e.g. atrial fibrillation in particular after cardiac surgery [53]. Experimental evidence suggests that inhibition of phosphodiesterase III and IV may potentiate catecholaminergic Ca++ dependent automatism induced by ß1-adrenoreceptor stimulation [54].

In view of differences in cAMP-independent actions and compartimentation of cAMP-mediated signaling [49], the combined application of milrinone and metoprolol may bear potential benefits on myocardial function [8,14,49,55]. To date, combination therapy of ß-blocker and phosphodiesterase inhibitor has been used either as a bridge to ß-blocker therapy in patients with severe heart failure or as a twitch instead of dobutamine for the cardiac patient dependent on inotropic support and started on ß-blocker therapy [56].In the latter patients, chronic ß-adrenergic stress causes adrenergic desensitization thereby blunting the inotropic response in particular to dobutamine but also to milrinone [57]. In this situation beta-blocker therapy has been reported to restore the blunted inotropic response to milrinone, independent of ß-adrenoreceptors [57]. In a recent study including 20 patients with acute decompensated heart failure and tachycardia low dose ß-blocker therapy in conjunction with milrinone significantly improved cardiac function by decreasing heart rate and improving left ventricular ejection fraction [58]. These findings are in accordance with our previous results on combined milrinone and enteral slow release metoprolol in patients with septic myocardial depression [14].

Fever is a very common symptom of infection. However, the value of fever control during severe infections is a matter of controversy [59,60]. Previous studies suggested possible harmful effects of temperature control using antipyretics in patients suffering from different infections and experimental models of SS [59]. From a physiologic stand-point temperature control would be a logical approach to decrease the sympathoadrenergic stress to the cardiovascular system [61]. Hyperthermia induced by passive heating decreases blood flow in all major organ systems in which flow has been measured, e.g. splanchnic region, kidneys, and skeletal muscle despite significant increased cardiac output [62,63,64]. Therefore a critical decrease in blood flow in particular to the kidneys and the splanchnic region may be expected to occur early in patients with limited cardiac reserve. External cooling should be expected to attenuate side effects of excessive catecholamine stress thereby supporting the stabilisation of the cardiovascular system. In our institution, fever control is aggressively performed by external cooling if body temperature exceeds 38.5°C. Recently, a multicentre randomized controlled trial in febrile patients suffering from SS reported a significant decrease in vasopressor administration (-50%) within 12 hours of body temperature control by external cooling Schortgen et al. [65]. In addition, shock reversal was significantly more common and 14-day mortality significantly less (-16%) in the cooling group.

The major drawback of our study is its purely observational character. In addition, hospital mortality is not directly compared with a control group but is contrasted with calculated SAPS II - predicted mortality. We are aware of the fact, that the SAPS II - score was originally validated for a case mix of intensive care patients and not specifically for patients suffering from SS. However, this argument is in part offset by the fact that SS patients in particular represent a population with one of the highest mortality rates in the ICU. Thus, reduced actual compared with SAPS II -predicted mortality in the most severely premorbid and diseased study patients (SAPSII QIV) are unlikely to result from coincidental changes in case mix.

Another limitation of the study is that the influence of other treatments e.g. early antibiotics, type of mechanical ventilation, blood sugar management have not been explicitly considered. However, in our institution, early administration of antibiotics, and an individualized blood sugar management strategy have been key elements of sepsis therapy since many years. With regard to mechanical ventilation no changes have been introduced during the study period.

In our opinion, the major strength of this study is that the hemodynamic treatment algorithm described consists of a bundle of interventions which are applied in a stepwise fashion according to increasing severity of hemodynamic failure. In addition, the resuscitation goals are not restricted to pressures and laboratory measurements but are complemented by heart rate control, temperature control and regular clinical evaluation of peripheral circulation. A major goal of our treatment algorithm is limitation and attenuation of sympathoadrenergic stress to the cardiovascular system.

We feel that such an approach is more likely to account for the complexity of the actual disease since treatment does not follow an on/off protocol but is rather adjusted according to increasing cardiovascular derangement.

4. CONCLUSION

In conclusion, our data suggest that a hemodynamic treatment protocol aimed at decreasing catecholamine toxicity including early administration of hydrocortisone, AVP, aggressive body temperature and heart rate control may significantly decrease mortality in particular in the elderly, premorbid patient suffering from advanced SS. Prospective studies will be necessary to confirm the beneficial effects of this hemodynamic treatment algorithm.

DECLARATION OF COMPETING INTERESTS

All authors declare that they have no competing interests concerning the publication of this study or the interpretation of study results. The authors have neither received any reimbursement, funding or salary from an organisation or company. In addition, the authors declare that they hold no stocks or shares from a pharmaceutical company mentioned in the material and method section of this manuscript and that they do not gain or lose financially in any way by publishing this manuscript. The authors declare that their interests are solely scientific in nature.

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