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BRIEF REPORT

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Liberal vs. conservative vasopressor use to maintain mean arterial blood pressure during resuscitation of septic shock: an observational study

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Abstract *Objective:* The optimal role of vasopressor therapy in septic shock is not known. We hypothesized that the variability in the use of vasopressors to treat hypotension is associated with subsequent organ failures. *Design:* Retrospective observational single-center cohort study. *Setting:* Tertiary care hospital. *Patients and participants:* Consecutive patients with septic shock. *Measurement and results:* Ninety-five patients were enrolled. Serial blood pressure recordings and vasopressor use were collected during the first 12 h of septic shock. Median duration of hypotension that was not treated with vasopressors was 1.37 h (interquartile range [IQR] 0.62–2.66). Based on the observed variability, we evaluated liberal (duration of untreated hypotension < median) vs. conservative (duration of untreated hypotensionn > median) vasopressor therapy. Compared with patients who received conservative vasopressor therapy, patients treated liberally had similar baseline organ impairment [median Sequential Organ Failure Assessment (SOFA) score 8 vs. 8, $p = 0.438$] were more likely to be younger (median age 70 vs. 77 years, $p = 0.049$), to require ventilator support (78 vs. 49%, $p < 0.001$), and to have progression of organ failures after 24 h (59 vs. 37%, $p = 0.032$). When adjusted for age and mechanical ventilation, early therapy aimed at achieving global tissue perfusion [odds ratio (OR) 0.33, 95% confidence interval (CI) 0.11–0.88), and early adequate antibiotic therapy (OR 0.27, 95% CI 0.09–0.76), but not liberal vasopressor use (OR 2.13, 95% CI 0.80–5.84), prevented progression of organ failures. *Conclusions:* In our retrospective study, early adequate antibiotics and achieving adequate global perfusion, but not liberal vasopressor therapy, were associated with improved organ failures after septic shock. Clinical trials which compare conservative vs. liberal vasopressor therapy are warranted.

Keywords Septic shock · Resuscitation · Vasopressor

Introduction

Current guidelines recommend maintaining a mean arterial pressure (MAP) of 65 mm Hg to ensure optimal organ perfusion in septic shock [1, 2]. While some expert panels warn against the use of vasopressors prior to adequate fluid resuscitation/global tissue perfusion in most forms of shock, others recommend concurrent use of vasopressors along with treatments aimed at global tissue perfusion (fluid, inotrope, transfusion) in patients

with septic shock [1–3]. Animal studies suggested that the lower limit of autoregulation may be around a MAP of 65 mm Hg, below which organ perfusion may become linearly dependent on MAP, justifying the use of vasopressors [4]. In some animal models of septic shock, however, the use of vasopressors to maintain MAP has not been beneficial [5]. The lower limit of hypotension that may be safely tolerated in patients and the exact role of vasopressors are currently unknown. The practice is variable both with regard to the threshold for initiation of vasopressors and goals for perfusion pressure.

In this retrospective observational study, we examined the practice variability in treatment of hypotension during the first 12 h of resuscitation and its association with outcome.

Materials and methods[1]

Institutional review board approved the study. Daily screening identified consecutive patients with septic shock who were admitted to the medical intensive care unit (ICU) over a 9-month period. We excluded patients who denied research authorization, patients in whom care was withdrawn within 12 h of admission to the ICU, and those in whom septic shock had started before hospital admission. The diagnosis of septic shock was based on standard criteria: persistent hypotension (MAP < 65 mm Hg or systolic blood pressure < 90 mm Hg) after fluid resuscitation volume > 20 ml/kg crystalloid bolus and/or necessitating use of vasopressors, in patients with coexisting criteria for sepsis [3, 6].

The primary outcome variable was the progression of organ failures based on Sequential Organ Failure Assessment (SOFA) scores from the time of onset to 24 h thereafter [7, 8]. The worst levels of physiological derangement around the time points of interest (onset of septic shock – baseline and 24 h after – follow-up) were used in all SOFA calculations. Secondary outcome measures included ICU length of stay and mortality.

The following predictor variables were retrospectively collected during the first 12 h of septic shock: (a) duration and intensity of hypotension; (b) fluid administration; (c) central venous pressure (CVP) and mixed venous or central venous oxygen saturation (SvO_2 or $ScvO_2$); (d) co-interventions such as antibiotics, steroids, activated protein C, and mechanical ventilation; and (e) co-morbidities.

For each patient, an expert assessment was made with regard to achievement of adequate global tissue perfusion [1, 6], based on perfusion indices independent of absolute levels of MAP. Adequate global perfusion was defined as achievement of $SvO_2 > 65\%$ or $ScvO_2 > 70\%$ within 6 h of septic shock [1, 6]. If SvO_2 or $ScvO_2$ were not measured, timely restoration of adequate global perfusion was defined based on serial determination of serum lactate, base deficit, urine output (≥ 0.5 ml/kg h^{-1}), mental state, skin perfusion, and evidence of adequate fluid resuscitation (CVP > 8 mm Hg or 6 l of crystalloid or equivalent amount of colloid administration) [1, 9]. We defined adequate antibiotic therapy as appropriate antibiotic initiation within 1 h of ICU admission or 3 h of emergency department (ED) admission [10].

Serial blood pressure recordings from arterial lines (or non-invasive cuff readings before the arterial line was placed) starting from the time of onset of septic shock were obtained from the electronic information system and scanned ED records. In order to accurately determine the total duration of vasopressor-untreated hypotension in the first 12 h, we collected individual start and stop times for each vasopressor and subsequently calculated the time intervals devoid of vasopressor therapy coincident with hypotension. The severity of hypotension was defined in terms of an area under the curve (AUC), calculated as follows: AUC = $\sum$ (65-MAP) $\times$ duration of measurement [11]. Patients with gaps in blood pressure recordings were excluded from analyses.

The variability of practice with regard to liberal vs. conservative vasopressor therapy was determined from the median duration and intensity of untreated hypotension and by calculating coefficient of variation (mean/standard deviation). Duration of untreated hypotension < median value was considered liberal and if > median value was deemed conservative. The effect of starting vasopressor therapy before, as opposed to after, achieving adequate global perfusion was evaluated in a post-hoc analysis. Acute Physiology and Chronic Health Evaluation (APACHE III) predicted mortality was calculated based on the worst values obtained from the institutional APACHE III database during the first 24 h after ICU admission. Continuous and categorical variables were compared using Mann–Whitney and chi-square tests or Fisher's exact test. Stepwise multivariate regression models were examined to assess the effect of liberal vs. conservative vasopressor therapy on development of organ failures and hospital mortality. JMP statistical software (version 6.0, SAS, Cary, N.C.) was used for all data analysis.

Results[2]

Ninety-five patients met the inclusion criteria. We observed substantial variability in both the duration [median 1.37, interquartile range (IQR) 0.62–2.66 h] and the AUC (median 11.39, IQR 3.87–29.18 mm Hg $\times$ h) of vasopressor-untreated hypotension. The coefficient of variation was 1.15 for the duration and 0.97 for the AUC.

[1] See online data supplement.

[2] See online data supplement.

Table 1 Baseline clinical characteristics of patients with septic shock categorized according to aggressive vs. conservative vasopressor use. *CHF*, congestive heart failure; *APACHE*, Acute Physiology and Chronic Health Evaluation; *IQR*, interquartile range

	Conservative vasopressor therapy ($n = 49$)	Liberal vasopressor therapy ($n = 46$)	Significance (p)
Age (years, median IQR)	77 (64–85)	70 (51–80)	0.04
Female gender, *n* (%)	20 (40)	16 (34)	0.54
CHF, *n* (%)	12 (24)	12 (26)	0.85
Diabetes, *n* (%)	16 (32)	16 (34)	0.82
Renal failure, *n* (%)	34 (69)	24 (52)	0.08
Liver disease, *n* (%)	3 (6)	3 (6)	1.0
Coronary artery disease, *n* (%)	16 (32)	13 (28)	0.64
Baseline SOFA	8 (6–9)	8 (6–11)	0.43
Baseline SOFA, non-cardiovascular[a]	6 (4–8)	6 (5–8)	0.70
APACHE III predicted hospital mortality, median (IQR)[b]	0.41 (0.18–0.56)	0.42 (0.28–0.66)	0.23
Source of sepsis			
Lung, *n* (%)	24 (48)	24 (52)	
Urinary, *n* (%)	8 (16)	6 (13)	
Other, *n* (%)	17 (34)	15 (32)	

[a]SOFA score excluding cardiovascular component; [b]Calculated from the worst values obtained during the first 24 h

Table 2 Treatment characteristics of patients with septic shock categorized according to liberal vs. conservative vasopressor use

		Conservative vasopressor therapy ($n = 49$)	Liberal vasopressor therapy ($n = 46$)	Significance (p)
Fluid resuscitation and tissue perfusion	Fluid received in 6 h (l)	3.31 (1.6–4.8)	5.5 (4.1–8.6)	< 0.01
	CVP at 6 h, mm Hg, $n = 69$	6 (2–9)	8 (6–12)	< 0.01
	$ScvO_2$ at 6 h, %, $n = 45$	65 (56–74)	67 (58–77)	0.45
	Adequate global perfusion, *n* (%) perfusion, *n* (%)	28 (57)	35 (76)	0.04
	Serum lactate (mmol/l)	2.2 (1.2–3.5)	3.4 (1.8–4.9)	0.02
Vasopressor use	AUC of untreated hypotension (< 65) mm Hg×h, median (IQR)	26.96 (39.51–14.33)	3.812 (8.88–0.55)	< 0.01
	Duration of untreated hypotension, minutes, median (IQR)	153 (106–244)	38 (23–60)	< 0.01
	Type of pressor			
	Dopamine	4	7	0.28
	Phenylephrine	7	7	0.89
	Norepinephrine	22	33	< 0.01
	Vasopressin	13	28	< 0.01
Other interventions	Adequate antibiotic therapy, *n* (%)	36 (73)	32 (69)	0.17
	Dobutamine, *n* (%)	4 (8)	8 (17)	0.17
	RBC transfusion, *n* (%)	14 (29)	14 (30)	0.84
	Mechanical ventilation at the onset of septic shock, *n* (%)	9 (18)	27 (59)	< 0.01
	Mechanical ventilation any, *n* (%)	24 (48)	36 (78)	< 0.01
	Steroids for relative adrenal insufficiency, *n* (%)	8 (16)	18 (39)	0.03
	Activated protein C, *n* (%)	11 (23)	16 (35)	0.18

Table 3 Summary of outcome data of patients with septic shock categorized according to liberal vs. conservative vasopressor use. *AUC*, area under the curve; *RBC*, red blood cells; *LOS*, length of stay; *CVP*, central venous pressure

	Conservative vasopressor therapy ($n = 49$)	Liberal vasopressor therapy ($n = 46$)	Significance (p)
SOFA at 24 h, median (IQR)	8 (4–11)	10 (6–13)	0.04
Non-cardiovascular SOFA at 24 h, median (IQR)[a]	6 (4–8)	7 (4–10)	0.06
Change in SOFA at 24 h, median (IQR)	−1 (−2 to 2)	+1 (−1.3 to 3)	0.05
Progression of organ failures (SOFA worsening at 24 h), *n* (%)	18 (37)	27 (59)	0.03
Change in non-cardiovascular SOFA at 24 h, median (IQR)[a]	0 (−3 to 0)	0 (0–2)	< 0.01
Progression of organ failures (non-cardiovascular SOFA worsening at 24 h), *n* (%)[a]	10 (20)	21 (46)	< 0.01
Change in creatinine (mg/dl), median (IQR)	−0.1(0 to −0.4)	−0.2 (0.02 to −0.4)	0.59
Hospital mortality, *n* (%)	15 (30)	16 (34)	0.66
ICU LOS, days, median (IQR)	2.73 (5.23–1.56)	4.14 (6.67–2.08)	0.09

[a]SOFA score excluding cardiovascular component; [b]Calculated from the worst values obtained during the first 24 h

The baseline characteristics, treatments, and outcome of patients who underwent liberal vs. conservative vasopressor treatment during the first 12 h of septic shock resuscitation are presented in Tables 1–3. Twelve of 49 patients in the conservative group did not receive any vasopressor treatment at the discretion of the treating physician despite the total duration of hypotension (MABP< 65 mm Hg) ranging from 1.5 to 6 h. When stratified by the adequacy of global perfusion (Fig. 1), liberal use of vasopressors without adequate global perfusion resulted in maximal worsening of SOFA scores, whereas adequate global perfusion with conservative use of vasopressors was most likely to result in improvement of SOFA scores (Fig. 1). In a post-hoc analysis, patients who were started on vasopressor therapy before achieving adequate global perfusion had significantly worse outcome (see online data supplement).

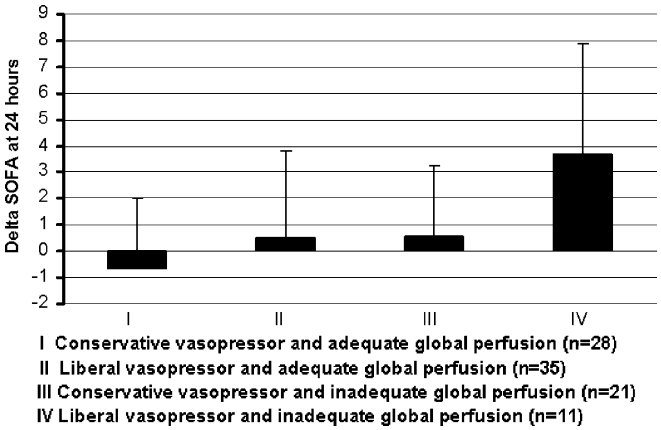

Fig. 1 Change in SOFA at 24 h stratified by fluid resuscitation and vasopressor use ($p = 0.019$): *I* Conservative vasopressor and adequate global perfusion ($n = 28$); *II* liberal vasopressor and adequate global perfusion ($n = 35$); *III* conservative vasopressor and inadequate global perfusion ($n = 21$); *IV* liberal vasopressor and inadequate global perfusion ($n = 11$). *Error bars* represent standard deviations

When adjusted for age and mechanical ventilation in a multiple logistic regression analysis, adequate global perfusion (OR 0.33, 95% CI 0.11–0.88) and adequate antibiotic therapy (OR 0.27, 95% CI 0.09–0.76), but not liberal vasopressor therapy (OR 2.13, 95% CI 0.80–5.84) were associated with less progression of organ failures after 24 h. When adjusted for predicted mortality, admission source, gender, and adequate fluid resuscitation, liberal vasopressor use did not significantly influence hospital mortality (OR 1.40, 95% CI 0.46–4.38). When adjusted for predicted ICU length of stay, liberal vasopressor use did not significantly influence ICU length of stay (adjusted mean difference 0.42, 95% CI –1.4 to 2.24 days).

Discussion

The results of our study suggest significant practice variability in the use of vasopressors to treat hypotension during resuscitation of septic shock. Liberal use of vasopressors did not result in improvement of organ failures 24 h later. In fact, our results raise the hypothesis that titrating care with vasopressors to predefined numerical end points of mean arterial pressure early in the course of septic shock may neither be required nor

beneficial, as suggested by the worsening of SOFA scores in patients who were treated with liberal vasopressors without adequate global perfusion (Fig. 1) or were started on vasopressors prior to achievement of adequate global perfusion (see online data supplement).

In our study, restoration of adequate global perfusion appeared to have the most significant impact on outcomes, in line with the results of the landmark clinical trial [6]. The basic premise of early goal-directed resuscitation in shock is to correct the mismatch between global oxygen delivery and consumption before the occurrence of irreversible cellular damage and, at the organ level, multiple organ failure [1, 6]. The markers of global tissue perfusion used in this study included central venous oxygen saturation, base deficit, and serum lactate. The clinical value of these markers has been emphasized in the recent consensus conference on hemodynamic monitoring in shock [1]. Previous animal experiments suggested that maldistribution of blood flow may be accentuated by liberal use of vasopressors in the setting of septic shock [5]. In patients with septic shock sequential increases in norepinephrine failed to produce any significant changes in lactate levels, urinary output, microcirculatory blood flow, splanchnic perfusion or oxygen metabolism [12]. A recent study of 28 patients with septic shock randomized to goal MAP of 65 vs. 85 mm Hg after initial stabilization showed no significant difference between the two groups in oxygen variables and renal function [13]. Data from animal models and from one case series suggesting that early vasopressor treatment may be beneficial have not been reproduced in controlled human studies [14, 15]. In fact, reversing the vasodilatory state in sepsis may be detrimental as suggested by the recent trial of nitric oxide synthase inhibitor 546C88 in patients with septic shock [16].

Using a methodology similar to ours (AUC for MAP < 65), Varpula et al. reported on the association between the degree of hypotension and worse outcome in septic shock [11]. The main difference between this study and that of Varpula et al. is the collection of data on vasopressor-untreated hypotension (representing the variability in vasopressor use) rather than *all* hypotension (reflecting the severity of vasodilatation/hemodynamic compromise) in the former study. While the study by Varpula et al. suggests that patients who have lower blood pressure are more severely ill, no inference can be made about the efficacy of vasopressor therapy [11]. In a recent animal study, early use of norepinephrine (concurrent with fluid resuscitation) improved tissue perfusion [15]. In contrast, the increase in vasoconstriction and mean arterial blood pressure using the inhibitor of nitric oxide synthetase was associated with worse outcome in a multicenter clinical trial [16]. Conflicting results in previous animal and human studies may be explained partly by dose-dependent differences in vasoconstrictor vs. inotropic activity of specific vasoactive drugs. There may be a level of hypotension that is life-threatening where vasopressor support may be beneficial. This threshold, however, may be lower than the currently accepted norm of 65 mm Hg, in particular, before adequate fluid resuscitation/tissue perfusion.

The principal limitations of our study lie in its single-center retrospective observational design. Liberal vasopressor use was associated with overall more aggressive care, in particular with regard to mechanical ventilation and fluid resuscitation. Our study design did not allow us to distinguish between the (a) provider characteristics (aggressive intensivists having a low threshold for vasopressors and positive pressure ventilation with subsequent larger fluid requirements to compensate for decreased venous return) vs. (b) patient characteristics (patients who were treated liberally with vasopressors were simply sicker, as evidenced by poor response to initial treatment and quick deterioration despite similar baseline severity of illness scores).

Although statistical modeling can adjust for measured confounding variables, there may be other important determinants of vasopressor preference that have not been recorded. Classification according to median duration of vasopressor-untreated hypotension, although arbitrary, was a reasonable attempt to define "liberal" vs. "conservative" approach. Also, the median duration of untreated hypotension appears to be longer than reported in other studies which limit the external validity of our results [14]. The absence of cardiac output measurements further limits the interpretations of our study, as it is possible that low cardiac output states may have remained undiagnosed in some of our patients who were treated with vasopressors.

Post-hoc analysis comparing the use of vasopressors before, as opposed to after, achieving adequate global perfusion revealed stronger association between liberal use of vasopressors and worse outcome (see online data supplement). Our choice of surrogate outcome, the difference in SOFA between 0 and 24 h, is supported by the literature [8] and correlated with hospital mortality. Since the use of vasopressors influences cardiovascular SOFA calculation, we reported additional analysis excluding the cardiovascular SOFA component. Additional data with respect to organ-specific SOFA scores is reported in the ESM that accompanies this article.

Conclusion

In conclusion, early adequate antibiotics and adequate global perfusion, but not liberal vasopressor use, were associated with less progression of organ failures in septic shock. Clinical trials are required to determine the effects of different thresholds for vasopressor therapy on outcomes of patients with septic shock.

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References

1. Antonelli M, Levy M, Andrews PJD, Hudson LD, Manthous C, Meduri UG, Moreno IP, Putensen C, Stewart T, Torres A (2007) Hemodynamic monitoring in shock and implications for management. Intensive Care Medicine 33:575–590
2. Beale RJ, Hollenberg SM, Vincent JL, Parrillo JE (2004) Vasopressor and inotropic support in septic shock: an evidence-based review. Crit Care Med 32:455–465
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM (2004) Surviving sepsis campaign guidelines. Crit Care Med 32:858–873
4. Kirchheim HR, Ehmke H, Hackenthal E, Lowe W, Persson P (1987) Autoregulation of renal blood flow, glomerular filtration and renin release in conscious dogs. Pflugers Arch 410:441–449
5. Tang W, Pakula JL, Weil MH, Noc M, Fukui M, Bisera J (1996) Adrenergic vasopressor agents and mechanical ventilation for the treatment of experimental septic shock. Crit Care Med 24:125–130
6. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
7. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) The use of SOFA score to assess the incidence of organ failure in intensive care units: results of a multicenter prospective study. Crit Care Med 26:1793–1800
8. Levy MM, Macias WL, Vincent JL, Russell JA, Silva E, Trzaskoma B, Williams MD (2005) Early changes in organ function predict eventual survival in severe sepsis. Crit Care Med 33:2194–2201
9. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP (2006) A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 26:551–557
10. Institute for Healthcare Improvement "Sepsis Bundle": Available online at http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis. Accessed 10 September 2006. http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis/
11. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettila V (2005) Hemodynamic variables related to outcome in septic shock. Intensive Care Med 31:1066–1071
12. Ledoux D, Astiz ME, Carpati CM, Rackow EC (2000) Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 28:2729–2732
13. Bourgoin A, Leone M, Delmas A, Garnier F, Albanese J, Martin C (2005) Incr easing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. Crit Care Med 33:780–786
14. Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G (2004) Early and exclusive use of Norepinephrine in septic shock. Resuscitation 62:249–254
15. Sennoun N, Montemont C, Gibot S, Lacolley P, Levy B (2007) Comparative effects of early versus delayed use of norepinephrine in resuscitated endotoxic shock. Crit Care Med 35:1–5
16. Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, Silverman MS, Takala J, Donaldson J, Arneson C, Grove G, Grossman S, Grover R (2004) Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 32:21–30