Early administration of norepinephrine prevents the occurrence of fluid overload in the resuscitation of septic shock patients

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Abstract

***Background*: Critically ill patients with sepsis usually receive a very large volume of fluids causing a very significant positive fluid balance in an effort to meet the needs of cardiac output, systemic blood pressure, and perfusion to the kidneys. This condition also tends to be associated with poor survival rates. The aim of this study was to determine whether early maintenance of norepinephrine can reduce fluid administration and prevent overload in the resuscitation of patients with septic shock.**

***Methods*: This study was a randomized, non-blind clinical trial, of which the subjects were adult patients with septic shock admitted to the intensive and emergency care unit from January to November 2020. There were two treatment groups of this study, the early norepinephrine group (NEP group) and the 30 ml/kgBW fluid resuscitation one (Fluid group). The test was conducted on the urinary albumin-to-creatinine ratio, increase of serum creatinine value, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2 ratio), and intra-abdominal pressure at the time of septic shock diagnosis was established, 3 hours, and 24 hours after the treatment was given. The data was processed using the SPSS device.**

***Results*: Based on the analysis, it was found that there were significant differences in all study variables of the Fluid group compared to the NEP group. The amount of fluid administration in the NEP group averaged 2198.63 ml, less than that in the Fluid group with an average of 3999.30 ml (chi square test p=0.000). By comparing the measurement results to the initial measurement values in the two groups, the fluid overload was high-risk in the Fluid group. There was a significant relationship between the urinary albumin-to-creatinine ratio (OR=48.273; 95% CI=16.708-139.472), the increase in serum creatinine value (OR=73.381; 95% CI=19.955-269.849), the low PaO2/FiO2 ratio (OR=12.225; 95% CI=5.290-28.252), and the increase in intra-abdominal pressure (OR=32.667; 95% CI=10.490-101.724) with the provision of 30 ml/kgBW fluid resuscitation, which indicated the risk of fluid overload.**

***Conclusion*: Early norepinephrine administration can reduce fluid administration and prevent overload in the resuscitation of patients with septic shock.**

Key words: Septic shock, early norepinephrine, fluid overload.

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Introduction

Sepsis is a significant global health problem. The incidence of sepsis worldwide ranges from twenty to thirty million cases/year, where the mortality rate will increase 1.5 times if the patient falls into septic shock. Critically ill patients with sepsis usually receive large volumes of fluid, resulting in a high-significant positive fluid balance to meet cardiac output requirements, systemic blood pressure, and renal perfusion. So, adequate fluid resuscitation is essential. (1,2) Another retrospective study conducted by Mitchell et al. (2015) in the United States showed that approximately 86% of septic patients who eventually experienced septic shock experienced positive fluid balance and 35% experienced fluid overload. (3) Several recent studies have shown an

association between fluid overload and outcome. Poorly, thus making the management and optimization of fluid balance a major part of the management of critically ill patients. (1,2,4-7) In addition, excess fluid is associated with increased mortality and triggers some complications, like lung edema, heart failure, slowly wound healing, tissue damage, and impaired bowel function. Administration of fluids is recommended for the initial management of patients at risk of acute kidney injury (AKI), including septic patients, but in the course of the disease it is necessary to know that in these patients there is a leak in the blood vessels so that the fluid will come out and move to the extravascular, causing edema and fluid overload. (1,2,8-11) Interstitial edema will cause blood flow to the tissues to be disrupted, impaired venous return, and lymphatic drainage, which will cause tissue hypoxia, and so on. It will trigger continued resuscitation fluids known as vicious circle fluid resuscitation, which induce tissue hypoxia (**Figure 1**). Several indicators as urinary albumin-to-creatinine ratio, change in serum creatinine value, change in ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2 ratio), and increase in intra-abdominal pressure, which can be used to assess the incidence of fluid overload. (12-18)

Resuscitation guidelines for septic patients recommend giving fluids to fill in deficient intravascular volume due to vasodilation effects and capillary leakage. In patients with sepsis, endothelial damage occurs, where the administration of excess fluid will lead to fluid overload. In addition to the damaged endothelial condition in sepsis, hypervolemia also causes damage to the glycocalyx and causes colloid/albumin to be released from intravascular to interstitial. (19-24) Early norepinephrine administration is one way to restore vascular function. With the early administration of norepinephrine, vasodilation can be restored, and the target mean arterial pressure (MAP) is achieved without having to give excessive volumes of fluids. Early administration of norepinephrine is therefore expected to prevent excessive fluid accumulation. (25,26)

Material and methods

We recruited patients admitted to the emergency department (ED) of our hospital by the diagnosis of septic shock during the period from January - November 2020 in a disguised randomized clinical trial experimental study. Septic shock was identified as the presence of confirmed or suspected infection with a positive sequential organ failure assessment score (SOFA score) or quick SOFA (qSOFA) score (two or more of systolic blood pressure [SBP]≤100 mmHg, respiration rate [RR]≥22/min, and Glascow coma score [GCS]<15). We excluded from the study patients with morbid obese (body mass index [BMI]>35), history of kidney disease, conditions with possibly increased intra-abdominal pressure (like intra-abdominal tumors, obstructive ileus, pregnancy), and patients below 18 years old.

After initial enrollment in the ED, patients were randomized into two groups. Study group (norepinephrine group [NEP group]) patients received a titrated dose of norepinephrine (with a starting dose of 5 ug/min), which was given to the target MAP≥65 mmHg, and Ringer's lactate crystalloid fluid of 30 ml/kgBW/24 hours. The venous cannulation used an 18G intravenous cannula. Infusion line for the administration of norepinephrine using a peripheral infusion line and separated from the fluid infusion line. While the control group patients (Fluid group) were received Ringer's lactate fluid resuscitation 30 ml/kgBW/hour within 3 hours until the MAP was ≥65 mmHg. If the MAP target wais not achieved in 1 hour, then the patients immediately given a titrated dose of norepinephrine until the MAP target was reached. The primary outcome was the total volume of resuscitation fluid used in 24 hours as well as the ratio of urinary albumin to creatinine, increase in serum creatinine value based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria, change in PaO2/FiO2 ratio, and increase in intra-abdominal pressure as indicators of fluid overload.

The study protocol was approved by Konawe Hospital Research Ethics Committee. Informed consent was obtained from patients or next of kin.

Statistical analysis

Statistical analysis using SPSS software with appropriate statistical tests. Basic characteristic data were displayed according to the type of variable. Numerical variables with normal distribution were presented as mean±standard deviation and compared between the two groups using the t-test. Meanwhile, numerical variables with abnormal distribution were displayed in median form (minimum value-maximum value) and compared with the Mann-Whitney test. Categorical variables were displayed as a percentage (number) and compared with the chi-square test or alternative test. The results of the analysis would be considered statistically significant if the significance value (p value) was less than 0.05.

Result

One hudred and forty patients admitted to the ED with septic shock were initially recruited for the

study. After initial enrollment, 10 patients were excluded: 3 patients due to obstructive ileus conditions, 2 patients due to the patient's family request, and 5 patients died before the last measurement was performed. The remaining 140 patients represented the study sample (**Figure 2**).

There were no significant differences between the two treatment groups in terms of age characteristics (chi-square test, p=0.199) and gender (chi-square test, p=0.211). The mean total fluid intake in the NEP group within 24 hours was 2198.6 ml. In the Fluid group, the mean total fluid given was 3999.3 ml, higher than the NEP group (chi-square test, p=0.000) (**Table 1**).

Urinary albumin-to-creatinine ratio

In this study, the urinary albumin-to-creatinine ratio was measured three times. The first measurement was carried out at 0th hour when the diagnosis was made, the second measurement was carried out at 3 hours after treatment, and the third measurement was carried out at 24 hours after treatment. Ninety-five percent confidence interval (CI) value, p value<0.05 meant there was a difference between the results of the urinary albumin-to-creatinine ratio 3 hours after treatment and 24 hours after treatment to the initial value (0th hour) and indicated a risk of overload if the measurement value was ≥30 (**Tables 2 and 3**).

Serum creatinine measurement results

In this study, albuminuria was measured three times. The first measurement was carried out at 0th hour when the diagnosis was made, the second measurement was carried out at 3 hours after treatment, and the third measurement was carried out at 24 hours after treatment. Ninety-five percent CI value, p value<0.05 meant that there was a difference between the results of serum creatinine 3 hours after treatment and 24 hours after treatment against the initial value (0th hour) and indicated a risk of overload if there was an increase of ≥0.3 from the value at 0th hour (**Tables 4 and 5**).

PaO2/FiO2 ratio measurement results

In this study, the PaO2/FiO2 ratio was measured three times. The first measurement was carried out at 0th hour when the diagnosis was made, the second measurement was carried out at 3 hours after treatment, and the third measurement was carried out at 24 hours after treatment. Ninety-five percent CI value, p value≥0.05 meant there was no difference between the results of the PaO2/FiO2 ratio 3 hours after treatment and 24 hours after treatment to the initial value (0th hour) and indicated a risk of overload if the measurement value was less than 300 (**Tables 6 and 7**).

Results of intra-abdominal pressure measurement

In this study, the intra-abdominal pressure was measured three times. The first measurement was carried out at 0th hour when the diagnosis was made, the second measurement was carried out at 3 hours after treatment, and the third measurement was carried out at 24 hours after treatment. Ninety-five percent CI value, p value<0.05 meant that there was a difference between the results of intra-abdominal pressure 3 hours after treatment and 24 hours after treatment to the initial value (0th hour) and indicated a risk of overload if the measurement value >7 mmHg (**Tables 8 and 9**).

Discussion

The potential harm caused by fluid bolus therapy should be clearer featured in any therapy guide. Implementation of physiological conditions and a hemodynamically guided conservative approach to fluid therapy in patients with sepsis will very likely reduce morbidity and improve patient outcomes. In addition, it is necessary to design rigorous studies to evaluate fluid therapy techniques, in which the effects of fluid infusion on the immune system, endothelial function, and the integrity of the glycocalyx are poorly understood. (27) Degradation of glycocalyx in the luminal vascular cell membrane has been identified as an early impact in blood vessels due to septic effects on endothelial cells. Fluid therapy has the potential to further damage the glycocalyx, especially when rapid infusions are used and cause hypervolemia. (28-34)

The current discussion in the field of critical illness management is cardiovascular physiology, especially the concept of venous return. This concept has long been introduced by Guyton and allowed us to get more rational explanations, especially in the treatment of critically ill patients dominated by sepsis. According to the cardiovascular physiology approach by Guyton, there are so-called terms, the stressed volume and unstressed volume. The stressed volume is the amount of blood volume that circulates effectively and determines the volume of return blood flow, because its existence will determine the mean circulatory filling pressure (MCFP). It has been known that MCFP is very important, because it causes the pressure gradient on the central venous pressure (CVP) that will determine the acquisition of return blood flow and cardiac output in the end.

The unstressed volume is a number of blood volumes that acts as a backup whenever needed to fill the lack in the stressed volume in order to fulfill the effective circulating volume. MCFP plays an important role in hemodynamic regulation because it determines the pressure gradient against CVP to obtain normal cardiac output. As according to Guyton, cardiac output (CO) is the same as venous return (VR). This means the amount of blood that leave the heart (CO) through the left ventricle will be equal in the amount of blood received by the right heart (VR), and the pressure gradient between MCFP and CVP will determine the VR. Hence, if the pressure gradient decreases, the VR will also decrease, and so will CO. From this, we know that the gradient will decrease because of the decrease of MCFP or the increase of CVP. Administration of norepinephrine in patients with sepsis and septic shock will shift the blood volume back from unstressed volume to stressed volume. This recruitment process will increase cardiac preload as blood flow back to increase. (35,36)

Norepinephrine

Norepinephrine is the predominant endogenous sympathetic amine compound. This compound is a physiological mediator released by postganglionic adrenergic nerves. Norepinephrine is also a hormone released by the adrenal medulla. Exogenous norepinephrine is a pharmacologic agent commonly used intravenously to treat severe hypotension in shock. Norepinephrine increases arterial pressure primarily through increased arterial tone after binding to α receptors on the endothelial surface of the peripheral arterioles. (25,37)

Norepinephrine is currently the vasopressor of first choice in patients with septic shock. (37,38) Previously, norepinephrine was only the second choice after dopamine due to its vasoconstrictive effect on the regional circulation. However, this harmful effect on regional circulation has never been found in clinical studies. Norepinephrine has a stronger α-agonist effect than dopamine. Research conducted by Martin et al. (1993) demonstrated the superiority of norepinephrine over dopamine in the therapy of septic patients, both in terms of achieving targets and maintaining MAP, as well as increasing urine production and decreasing lactate levels. (38)

A study by De Baker et al. (2010), a multicenter randomized clinical trial (RCT) comparing norepinephrine and dopamine in the treatment of shock, found that although there was no difference in mortality, dopamine use was associated with the magnitude of side effects, especially the effects of arrhythmias if it compares with norepinephrine. (39)

The effect of norepinephrine on the venous compartment of the cardiovascular circuit has been explored more widely than its effect on the arterial and microcirculation compartments. It is known that peripheral veins are thin-walled vessels that cover 2/3 of the circulating blood in normal humans. This is a reservoir of blood that can be physiologically drawn/recruited to increase venous return and cardiac output. Venous return has two determinants, namely the pressure gradient between the mean systemic pressure/MCFP/mean systemic pressure (Pms) and the right atrial pressure on one side, and resistance to venous return on the other. The backward pressure of the back blood itself depends on the capacity of the veins. The overall effect of a vasoactive drug on venous return depends on the balance between its action on the pressure gradient and resistance to venous return. Evidence suggests that the venous effect of norepinephrine has crucial clinical consequences. (25)

In some animal studies, it has shown an increase in venous return induced by norepinephrine. Studies conducted by Datta and Magder (1999) showed that norepinephrine administration increased MCFP (Pms) which was important in determining venous return and cardiac output. From this study, it was concluded that norepinephrine administration did not cause an increase in venous return resistance, which was initially thought to be due to norepinephrine-induced venoconstriction. (40)

An animal study conducted by Imai et al. (1978) proved a reduction in resistance to venous return to norepinephrine administration. The stimulatory effect of β-adrenergic was believed to be the hypothesis in this study. Norepinephrine exerts α- and β-adrenergic stimulatory effects. Stimulation of α-adrenergic in the veins will cause increasing in Pms, which in turn increases venous return. Meanwhile, β-adrenergic stimulation will increase cardiac contractility. The effect of both causes an increase in cardiac output, but it is accompanied by only a minor increase in right atrial pressure. (25)

In the early phase of septic shock there was an assumption that a decrease in MCFP/Pms was the main cause of the stressed volume transfer to the unstressed one caused by the increased venous capacitance of active dilation of the veins (**Figure 3**). (35) Administration of norepinephrine to patients with vasoplegia such as in sepsis and septic shock will increase the stressed volume as a result of mobilization/recruitment of blood volume from unstressed volume. So, it is not like the administration of intravenous fluids that having a temporary effect as a

volume expander, which actually contributes to the formation of tissue edema (**Figure 4**). (35) Research conducted by Hamzaoui et al. (2010) demonstrated the effect of early maintenance of norepinephrine in maintaining the desired MAP in septic patients associated with a significant increase in cardiac index (CI) and stroke volume index (SVI). (41) Martin et al. (1993) also reported improved right ventricular function in septic patients treated with norepinephrine as a beneficial effect of β-agonist effects or as a result of their ability to increase coronary perfusion pressure through correction of hypotension or both. (38)

In this study, it was proven that early norepinephrine administration had the ability to reduce fluid administration and prevented overload in the resuscitation of patients with septic shock. It was found that early use of norepinephrine reduced fluid administration by only using maintenance fluids of 30 ml/kgBW/24 hours without giving significant adverse effects on organs as seen from the comparison of the effects on the variables studied, in this regard the ratio of urinary albumin to creatinine, serum creatinine, PaO2/FiO2 ratio, and intra-abdominal pressure. This study only observed septic shock patients by observing the urinary albumin-to-creatinine ratio, elevated serum creatinine, PaO2/FiO2 ratio, and intra-abdominal pressure. As an indicator of overload without assessing the outcome of treatment and the interaction of each component of septic shock therapy, so that further research is needed to determine a better and comprehensive therapy in the management of sepsis and septic shock. Likewise, the type of diagnosis should be homogeneous, and the time of observation should be maximized, so that the phases of the course of sepsis and septic shock can be observed as a whole.

Table 1. Characteristics of research subjects based on output (n=130)

Characteristics	Treatment groups	
	NEP group (n=60)	Fluid group (n=70)
Age (years), n (%)		
- ≥65	11 (18.33)	21 (30.00)
- <65	49 (81.67)	49 (70.00)
Gender, n (%)		
- Male	36 (60.00)	36 (51.43)
- Female	24 (40.00)	34 (48.57)
Diagnosis, n (%)		
- Ovary cancer	0 (0.00)	1 (1.43)
- HIV	1 (1.67)	0 (0.00)
- DHF	1 (1.67)	2 (2.86)
- DM	19 (31.67)	18 (25.71)
- COPD	5 (8.33)	2 (2.86)
- DM+COPD	0 (0.00)	1 (1.43)
- UTI	0 (0.00)	1 (1.43)
- Nasopharyngeal cancer	1 (1.67)	0 (0.00)
- Uterine cancer	0 (0.00)	1 (1.43)
- Intraabdomen	10 (16.67)	14 (20.00)
- Meningitis	4 (6.67)	0 (0.00)
- Pneumonia	17 (28.33)	27 (38.57)
- Pneumonia+DM	1 (1.67)	2 (2.86)
- Pneumonia+mammary cancer	1 (1.67)	0 (0.00)
- Pneumonia+pulmonary TB	0 (0.00)	1 (1.43)
Urinary albumin-to-creatinine ratio (mg/g), mean (SD)		
- 0th hour	26.33 (4.10)	25.93 (4.11)
- 3rd hour	27.33 (4.33)	37.14 (7.15)
- 24th hour	26.92 (4.42)	43.07 (10.19)
Serum creatinine (mg/dl), mean (SD)		
- 0th hour	0.71 (0.35)	0.66 (0.32)
- 3rd hour	0.86 (0.41)	1.00 (0.39)
- 24th hour	0.98 (0.49)	1.58 (0.69)
PaO2/FiO2 ratio, mean (SD)		
- 0th hour	257.83 (21.30)	263.21 (22.23)
- 3rd hour	295.10 (36.44)	264.84 (28.04)
- 24th hour	315.92 (59.88)	267.31 (45.76)
Intra-abdominal pressure (mmHg), mean (SD)		
- 0th hour	5.10 (1.52)	4.87 (1.44)
- 3rd hour	5.55 (1.54)	7.05 (1.69)
- 24th hour	5.58 (1.52)	7.90 (1.37)
Total amount of fluid input (ml), mean (SD)	2198.6 (222.35)	3999.3 (503.60)
Risk of overload based on observational variables, n (%)		
- Urinary albumin-to-creatinine ratio		
Yes	6 (10.00)	59 (84.29)
No	54 (90.00)	11 (15.71)
- Serum creatinine		
Yes	14 (23.33)	67 (95.71)
No	46 (76.67)	3 (4.29)
- PaO2/FiO2 ratio		
Yes	17 (28.33)	58 (82.86)
No	43 (71.67)	12 (17.14)

- Intra-abdominal pressure Yes No	 4 (6.67) 56 (93.33)	 49 (70.00) 21 (30.00)
Fluid overload - 3rd hour - 24th hour	 No No	 Yes Yes

Legend: NEP group=norepinephrine group; HIV=human immunodeficiency virus; DHF=dengue hemorrhagic fever; DM=diabetes mellitus; COPD=chronic obstructive pulmonary disease; UTI=urinary tract infection; TB=tuberculosis; SD=standard deviation; PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen.

Table 2. Comparison of urinary albumin-to-creatinine ratio in the two groups after treatment

Urinary albumin-to-creatinine ratio	0th hour Mean (SD)	3rd hour Mean (SD)	24th hour Mean (SD)	p*
NEP group	26.33 (4.10)	27.33 (4.36)		0.22
			26.92 (4.42)	0.301
Fluid group	25.93 (4.11)	37.14 (7.15)		0.000
			43.07 (10.19)	0.000

Legend: NEP group=norepinephrine group; SD=standard deviation. *t-test.

Table 3. Relationship between treatment groups and overload risk based on the incidence of albuminuria

Group	No risk of overload ACR<30	Risk for overload ACR≥30	OR (95% CI)	p
NEP group	54	6	48.27 (16.70-139.47)	0.000
Fluid group	11	59		

Legend: ACR=urinary albumin-to-creatinine ratio; OR=odds ratio; CI=confidence interval; NEP group=norepinephrine group. Chi-square test, p=0.05.

Table 4. Comparison of serum creatinine in the two groups after treatment

Serum creatinine	0th hour Mean (SD)	3rd hour Mean (SD)	24th hour Mean (SD)	p*
NEP group	0.71 (0.35)	0.86 (0.41)		0.000
			0.98 (0.49)	0.000
Fluid group	0.66 (0.32)	1.00 (0.39)		0.000
			1.58 (0.69)	0.000

Legend: SD=standard deviation; NEP group=norepinephrine group. *t-test

Table 5. Relationship between treatment groups and overload risk based on an increase in serum creatinine

Group	No risk of overload (increase in serum creatinine <0.3)	Risk for overload (increase in serum creatinine ≥0,3)	OR (95% CI)	p
NEP group	46	14	73.38 (19.95-269.84)	0.000
Fluid group	3	67		

Legend: OR=odds ratio; CI=confidence interval; NEP group=norepinephrine group. Chi-square test, p=0.05.

Table 6. Comparison of the PaO2/FiO2 ratio in the two groups after treatment

PaO2/FiO2 ratio	0th hour Mean (SD)	3rd hour Mean (SD)	24th hour Mean (SD)	p*
NEP group	257.83 (21.30)	295.10 (36.44)		0.000
			315.92 (59.88)	0.000
Fluid group	263.21 (22.23)	264.84 (28.04)		0.525
			267.31 (45.76)	0.441

Legend: PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen; SD=standard deviation; NEP group=norepinephrine group. *t-test.

Table 7. Relationship between treatment groups and overload risk based on the PaO2/FiO2 ratio

Group	No risk of overload (PaO2/FiO2≥300)	Risk for overload (PaO2/FiO2<300)	OR (95% CI)	p
NEP group	43	17	12.225 (5.29-28.25)	0.000
Fluid group	12	58		

Legend: PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen; OR=odds ratio; CI=confidence interval; NEP group=norepinephrine group. Chi-square test, p=0.05.

Table 8. Comparison of the intra-abdominal pressure in both groups after treatment

Intrabdomenal pressure	0th hour Mean (SD)	3rd hour Mean (SD)	24th hour Mean (SD)	p*
NEP group	5.10 (1.52)	5.55 (1.54)		0.023
			5.58 (1.52)	0.019
Fluid group	4.87 (1.44)	7.05 (1.69)		0.000
			7.90 (1.37)	0.000

Legend: SD=standard deviation; NEP group=norepinephrine group. *t-test.

Table 9. Relationship between treatment groups and overload risk based on the increase in intra-abdominal pressure

Group	No risk of overload (increase in intra-abdominal pressure ≤7 mmHg)	Risk for overload (increase in intra-abdominal pressure >7 mmHg)	OR (95% CI)	p
NEP group	56	4	32.667 (10.490-101.724)	0.000
Fluid group	21	49		

Legend: OR=odds ratio; CI=confidence interval; NEP group=norepinephrine group. Chi-square test, p=0.05.

Figure 1. Illustration vicious circles in capillary leak syndrome

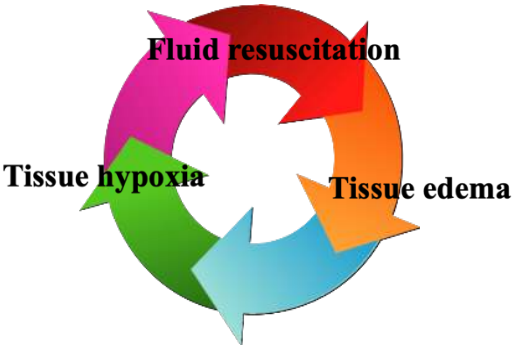


Figure 2. Inclusion and exclusion flow chart

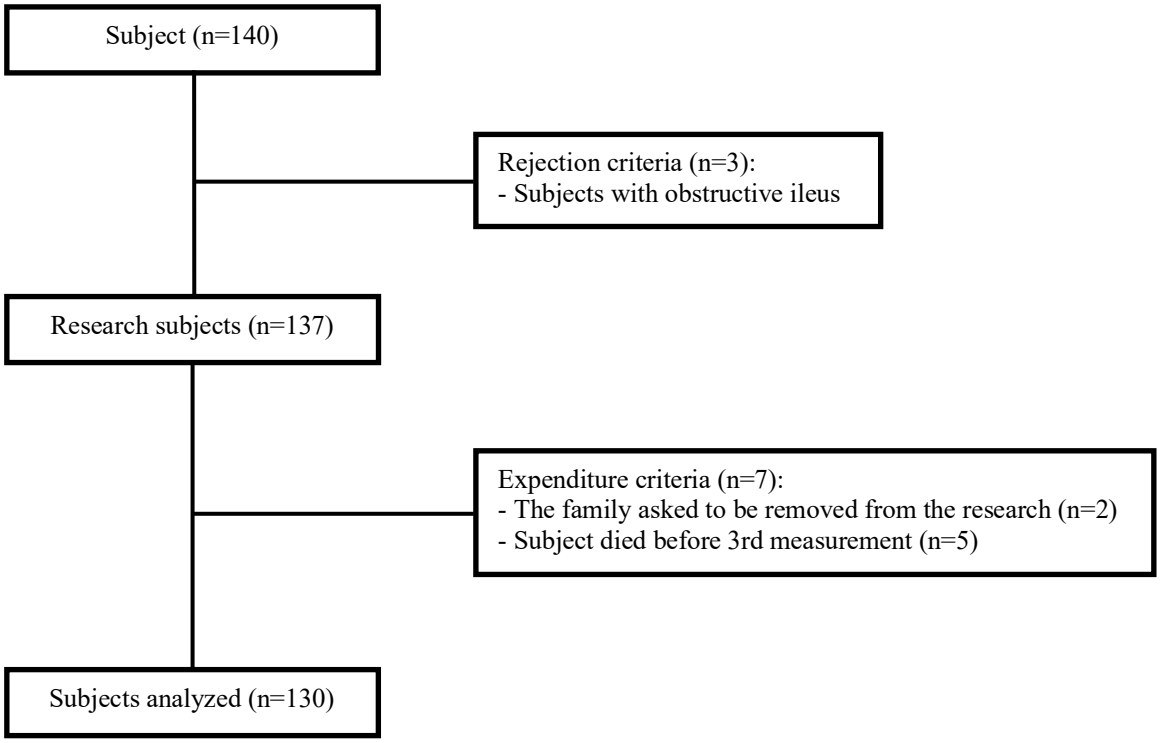
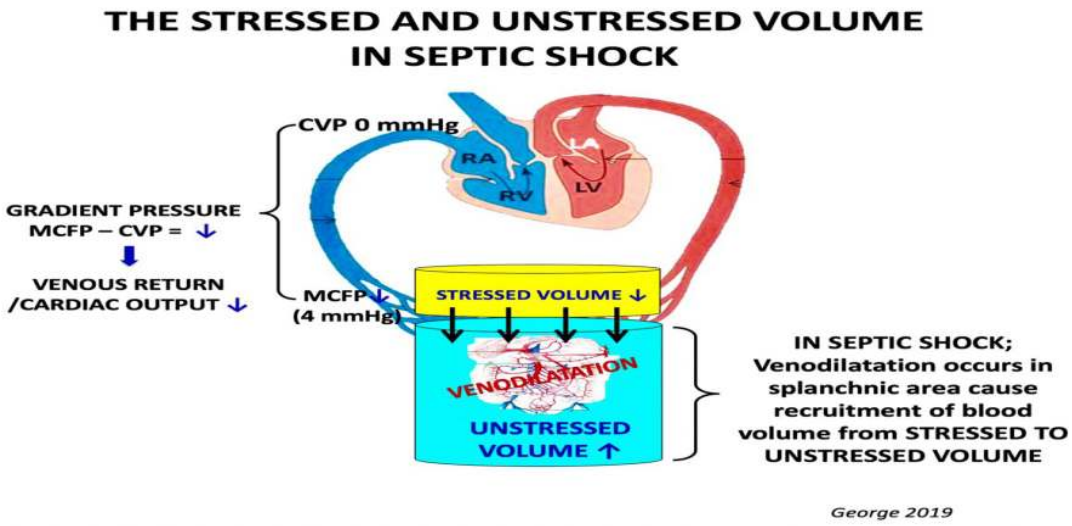
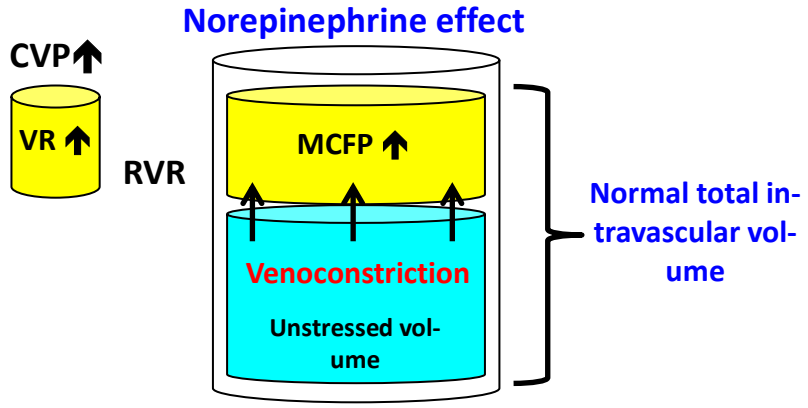


Figure 3. Illustration of stressed and unstressed volume in septic shock



Legend: CVP=central venous pressure; MCFP=mean circulatory filling pressure.

Figure 4. Illustration of blood volume mobilization from unstressed volume to stressed volume after norepinephrine administration



Legend: CVP=central venous pressure; VR=venous return; RVR=resistance to venous return; MCFP=mean cisculatory filling pressure.

References

1. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol 2016;17:109.
2. Butcher BW, Liu KD. Fluid Overload in AKI – Epiphenomenon or Putative Effect on Mortality? Curr Opin Crit Care 2012;18:593-8.
3. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. Ann Am Thorac Soc 2015;12:1837-44.
4. Wiedermann CJ, Dunzendorfer S. Fluid resuscitation targeting sepsis-induced cardiovascular dysfunction: severity of disease as effect modifier. J Thorac Dis 2017;9:3541-4.
5. Byrne L, Van Haren F. Fluid rescucitation in human sepsis: Time to rewrite history? Ann Intensive Care 2017;7:4.
6. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 2017;43:625-32.
7. Cecconi M, Hofer C, Teboul J-L, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med 2015; 41:1529-37.
8. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. Ann Intensive Care 2012;2:S1.
9. Brandt S, Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. Crit Care 2009;13:R186.
10. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12:R74.
11. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370: 1683-93.
12. O'Connor ME, Prowle JR. Fluid Overload. Crit Care Clin 2015;31:803-21.
13. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care 2014;18:696.
14. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76:422-7.
15. Drumheller BC, McGrath M, Matsuura AC, Gaieski DF. Point-of-care urine albumin: Creatinine ratio is associated with outcome in emergency department patients with sepsis: A pilot study. Acad Emerg Med 2012;19:259-64.
16. Stein A, de Souza LV, Belettini CR, Menegazzo WR, Viegas JR, Pereira EMC, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. Crit Care 2012;16:R99.
17. De Laet I, De Waele JJ, Malbrain ML. Fluid Rescucitation and Intra-abdominal Hypertension. In: Vincent J-L, editor. Intensive Care Med. New York: Springer-Verlag; 2008.
18. Szakmany T, Heigl P, Molnar Z. Correlation between extravascular lung water and oxygenation in ALI/ARDS patients in septic shock: possible role in the development of atelectasis? Anaesth Intensive Care 2004;32:196-201.
19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
20. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med 2010;38:367-74.
21. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med 2015;43:3-12.
22. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018;44:925-8.
23. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017;45:486-552.
24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.

Crit Care Med 2013;41:580-637.
25. Monnet X, Teboul J-L. Cardiovascular Effects of Norepinephrine in Septic Shock. In: Vincent J-L, editor. Annual Update in Intensive Care and Emergency Medicine 2012. Berlin, Germany: Springer-Verlag Berlin Heidelberg; 2012.
26. Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care 2014;18:532.
27. van Haren F. Personalised fluid rescucitation in the ICU: still a fluid concept? Crit Care 2017; 21:313.
28. Henrich M, Gruss M, Weigand MA. Sepsis-induced degradation of endothelial glycocalix. ScientificWorldJournal 2010;10:917-23.
29. Berg S, Golster M, Lisander B. Albumin extravasation and tissue washout of hyaluronan after plasma volume expansion with crystalloid or hypooncotic colloid solutions. Acta Anaesthesiol Scand 2002;46:166-72.
30. Berg S, Engman A, Hesselvik JF, Laurent TC. Crystalloid infusion increases plasma hyaluronan. Crit Care Med 1994;22:1563-7.
31. Chappell D, Bruegger D, Potzel J, Jacob M, Brettner F, Vogeser M, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. Crit Care 2014;18:538.
32. Opal SM, van der Poll T. Endothelial barrier dysfunction in septic shock. J Intern Med 2015;277:277-93.
33. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascón GA, et al. The endothelium in sepsis. Shock 2016;45:259-70.
34. Ishihara H, Matsui A, Muraoka M, Tanabe T, Tsubo T, Matsuki A. Detection of capillary protein leakage by indocyanine green and glucose dilutions in septic patients. Crit Care Med 2000; 28:620-6.
35. Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock-part I: physiology. Crit Care Med 2013;41:255-62.
36. Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock: part II-shock and mechanical ventilation. Crit Care Med 2013;41:573-9.
37. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. Am J Respir Crit Care Med 2019;199:1097-105.
38. Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest 1993;103:1826-31.
39. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
40. Datta P, Magder S. Hemodynamic response to norepinephrine with and without inhibition of nitric oxide synthase in porcine endotoxemia. Am J Respir Crit Care Med 1999;160:1987-93.
41. Hamzaoui O, Georger J-F, Monnet X, Ksouri H, Maizel J, Richard C, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care 2010;14:R142.