

## Low central venous pressure is not associated with low perfusion event in the setting of septic shock: A randomized controlled trial

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### Abstract

**Background:** Guyton's concept of hemodynamic physiology shows that venous return depends on the value of central venous pressure (CVP); the lower CVP value, the higher gap between CVP and mean circulatory filling pressure (MCFP), and so the venous return and cardiac output. However, the association between CVP value and microcirculation perfusion has not been revealed. Our study was performed to investigate the association between low and high CVP values with microcirculation and perfusion in septic shock patients.

**Methods:** This randomized clinical trial was performed in an adult intensive care unit (ICU) of a referral hospital. Data collection began after the ethics certificate and location permissions were released. Included samples were patients with septic shock according to the latest definition and aged 18 to 60 years. Patients with primary heart problems, right heart failure or congenital heart disease, chronic severe obstructive pulmonary

disease, kidney stones or tumors, and chronic kidney disease were excluded. Subjects were divided into two groups: low (0-4 mmHg) and high (8-10 mmHg) CVP. CVP and perfused vessel density (PVD) in sublingual microcirculation were measured accordingly.

**Results:** There were 43 subjects: 22 subjects with low CVP and 21 with high CVP. PVD on day-0 to day-7 examination in low CVP compared to high CVP group, respectively, were 12.5 (7.0-15.4) vs 13.85 (3.4-15.6) ( $p=0.903$ ); 12.9 (7.6-17.9) vs 8.5 (1.4-17.5) ( $p=0.036$ ); 12.7 (6.5-15.5) vs 12.85 (7.6-18.2) ( $p=0.800$ ); 11.5 (3.8-32.5) vs 10.35 (1.3-14.2) ( $p=0.435$ ); 13.3 (7.1-17.5) vs 11.6 (2.7-18.6) ( $p=0.586$ ); 9.9 (1.0-14.6) vs 10.45 (4.0-15.8) ( $p=0.918$ ); 10.0 (3.5-17.1) vs 11.9 (4.1-16.3) ( $p=0.498$ ); and 10.2 (4.3-13.3) vs 13.45 (4.8-16.7) ( $p=0.074$ ).

**Conclusion:** There was no significant difference in microcirculation perfusion between the low and high CVP groups.

**Key words:** Central venous pressure, microcirculation, perfusion, septic shock.

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## Introduction

Guyton's concept of hemodynamic physiology shows that venous return depends on the value of central venous pressure (CVP); the lower the CVP value, the higher gap between CVP and mean circulatory filling pressure (MCFP), and so the venous return and cardiac output. A lower CVP value compared to MCFP is needed to ensure an optimal venous return to the right heart. (1-3) High CVP will increase back pressure and hamper venous return and so the systemic venous system (congestive organs). (4) Renal venous congestion will increase renal vein pressure, decrease gradient pressure between renal artery and vein, and decrease glomerular filtration rate (GFR). (5)

In critically ill patients, cardiovascular optimization is needed to ensure adequate oxygen delivery and tissue perfusion. In the clinical situation, the systemic hemodynamic is not a reliable surrogate to microcirculation perfusion. Microcirculation monitoring is not associated with macrohemodynamics in sepsis. (6) The persistent sublingual microcirculation changes after macrohemodynamics were known as a surrogate of poor outcomes. (7) Interventions to increase mean arterial pressure (MAP) and to improve microcirculation were known to be beneficial for some groups of patients whereas worsening the microcirculation perfusion. (8-10)

Microcirculation is considered a low-pressure compartment. Mean capillary pressure is more like venous pressure rather than arterial pressure. From this view, CVP is a major influence factor for capillary blood flow. However, the association between CVP value and microcirculation hypoperfusion has not been revealed. Our study was performed to investigate the association between CVP value and low perfusion in septic shock patients.

## Methods

This research was a randomized controlled trial that was conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia between September 2019 and October 2020. Data collection commenced by the time the ethics board issued the certificate of ethics and location permissions.

The study population was patients with septic shock admitted to the Intensive Care Unit (ICU). The sample was taken using a consecutive sampling method with a targeted population from Emergency Department (ED), ICU, and Operating Units who met the research criteria. Inclusion criteria were septic patients who met the latest criteria of Sepsis-3, patients aged between 18 and 60 years, who agreed and signed the informed consent. All patients with primary heart problems, right heart failure or con-

genital heart disease, chronic severe obstructive pulmonary disease, severe pleural effusions, stones or tumors in the kidneys detected on ultrasound, and chronic kidney disease, were rejected from the study.

Patients admitted to the ICU with a diagnosis of septic shock underwent an initial hemodynamic assessment. Subsequently, the patient received initial resuscitation and initial blood culture examination from peripheral access, blood lactate examination, and received broad-spectrum antibiotics. Initial resuscitation was given in the form of a mini bolus of crystalloid fluid in the amount of 300 ml followed by monitoring of MAP (target MAP 65 mmHg) to ensure organ perfusion. If MAP < 65 mmHg, the patient received noradrenaline titration drip with starting dose of 0.02 ug/kg body weight (BW)/min until a MAP > 65 mmHg. The patient was placed on a central venous catheter (after that, the patient will have a chest X-ray to make sure the central venous catheter was in the superior vena cava), which was connected to a continuous CVP device (mmHg) or a manometer tube to assess the intermittent CVP value (cmH<sub>2</sub>O/1.36) and non-invasive cardiac output monitoring using the ICON electrical cardiometry technique (data taken in the form of cardiac output index).

Patients who met the criteria for uncompensated respiratory failure received mechanical ventilation-assisted intubation, ie if they met two of the following clinical signs: respiratory rate > 25 breaths/minute, Glasgow coma score < 9, and systolic blood pressure < 90 mmHg. Patients who were intubated were given a premedication of midazolam 2 mg intravenously (IV), fentanyl 1 mcg/kg BW IV. After preoxygenation with 100% O<sub>2</sub>, anesthesia was induced with fentanyl 4 mcg/kg BW IV, propofol 1-2 mg/kg BW IV, and rocuronium 0.5 mg/kg BW IV. Endotracheal intubation with an endotracheal tube (ETT) size of 7.5 or 8.0, or the largest size as appropriate. The ETT position was confirmed by auscultation of the lungs and end-tidal carbon dioxide (EtCO<sub>2</sub>). Ventilator settings were adjusted to the patient's condition. The machine used was the Maquet I Servo. The ventilation mode was volume-control (VC) with a tidal volume of 8 ml/kg BW, respiratory rate adjusted to achieve target EtCO<sub>2</sub> of 27-30 mmHg, positive end-expiratory pressure (PEEP) 5 cmH<sub>2</sub>O, the ratio of inspiration:expiration (I:E ratio) 1:2, with a fraction of O<sub>2</sub> (FiO<sub>2</sub>) 30-50% with a mixture of O<sub>2</sub> and compressed air, peak inspiratory pressure (PIP) was limited to maximum 30 cmH<sub>2</sub>O.

Furthermore, patients who met the inclusion criteria and did not meet the exclusion criteria received an

explanation regarding the informed consent of the study to be carried out for the next 7 days. After the target MAP was achieved, the patients were randomly divided into two groups, Group I with a target CVP of 0-4 mmHg and Group II with a target CVP of 8-10 mmHg. If the patient was already on a ventilator with a PEEP setting of 5 cmH<sub>2</sub>O, then the CVP was reduced by 3 mmHg. In Group I, if CVP < 0 mmHg, the patient was given a 300 ml mini bolus crystalloid and could be repeated until CVP 0-4 mmHg was achieved. If CVP > 4 mmHg, furosemide drip would be started at 0.1 mg/kg BW/hour until CVP 0-4 mmHg was achieved. In Group II, if CVP < 8 mmHg, a 300 ml mini bolus crystalloid was administered, and this could be repeated until the CVP target of 8-10 mmHg was achieved. If CVP > 10 mmHg, furosemide drip would be started at 0.1 mg/kg BW/hour until the target CVP of 8-10 mmHg was achieved.

The target CVP of the patient was maintained, monitored periodically, and recorded during the pre-protocol (baseline) for up to 7 days. The basic data of patients before receiving treatment were documented (age, gender, hemodynamics, early acute kidney injury stage, urea, creatinine, urine production, CVP, cumulative balance, cardiac index [CI], blood gas analysis, and perfused vessel density [PVD] of microcirculation) using a Microscan device.

Before data analysis, cleaning, coding, tabulation, and data entry were carried out into the computer. The first data analysis was descriptive; data with a categorical scale were presented in the distribution of frequencies and proportions, while data with a continuous scale were presented in terms of the mean and standard deviation. A normality test was conducted on research variables. After descriptive analysis, inferential analysis was conducted to test the hypothesis. The normality of numerical data was analyzed by the Shapiro-Wilk test because the research sample was less than 50, p-value > 0.05 indicating the data was normally distributed. The numerical variable relationship was done by independent t-test if the data were normally distributed, or Mann-Whitney if the data were not normally distributed. The limit of significance was p < 0.05 with a 95% confidence interval. Statistical analysis was performed with SPSS version 20.0 statistical program.

## Result

The study found a total of 44 research subjects, but there was one hemodialysis that was carried out so the subject was excluded from the study, leaving 43 subjects for analysis. As can be seen from **Figure 1**,

the subjects were then divided into two groups: low CVP (22 subjects) and high CVP (21 subjects).

It can be inferred from **Table 1** that there are no significant differences in the characteristics of MAP, PVD, CI, capillary proportion perfused vessel, norepinephrine requirements, hypertension, diabetes, and cardiovascular comorbidities in the intervention and control groups (Man-Whitney U test, p > 0.05). The absence of this difference indicated the characteristics of a homogeneous group so that it could be compared to see differences in interventions by maintaining CVP in the 0-4 mmHg range.

**Table 2** shows that there are no differences in PVD values measured at the beginning, end, and delta PVD between the intervention group (CVP 0-4 mmHg) and the control group (CVP 8-10 mmHg) (Man Whitney test, p > 0.05). From these data, it can be said that the de-resuscitation target with a CVP of 0-4 mmHg proved not better than the CVP target of 8-10 mmHg against microcirculation disorders and capillary density.

## Discussion

Adequate cellular perfusion is essential for any organ's proper functioning. The alteration, mostly negative tendency, in delivery of oxygen and tissue's oxygen consumption, are both key factors of most organic injury due to sepsis. However, they may or may not be associated with systemic circulatory disorders. Several experimental and clinical studies have revealed that even in the truancy of macro-hemodynamic instability, smaller vessel modifications can still occur during sepsis. Consequently, microcirculation alterations are thought to play a positive role in the development of organ injury. (11,12)

This study found there were no differences in hypoperfusion events between the low and high CVP groups. Significantly, different PVD values were only found on day 1: 12.9 (7.6-17.9) for CVP 0-4 mmHg versus 8.5 (1.4-17.5) for CVP 8-10 mmHg with a p-value = 0.036. In the CVP 8-10 mmHg group, it was found that the PVD value was too small (1.4 mm/m<sup>2</sup>) so the PVD value in the CVP 8-10 mmHg group on day 1 was much lower than the PVD value on days 2 to 7. This happened because first, the difficulty of performing a Microscan examination in the early situation of the COVID-19 pandemic and caution required in manipulating the patient's airway. Second, the sampling of this study was carried out by two general practitioners who have been specially trained, but the Microscan examination was still very subjective or very operator dependent. Third, conditions such as an intubated patient biting, moving due to fighting against the

ventilator require special techniques when attaching the Microscan probe to the sublingual to get optimal results. Some patients required deep sedation just to perform a Microscan examination because the Microscan probe took approximately 4 seconds to stabilize and not move to capture.

This study is consistent with the results of Vellinga et al who found no significant difference in PVD and CVP values. This is due to the upregulation mechanism of the capillaries number, to compensate for the reduction in oxygen transport. (4) PVD assessment describes the lengthening of the diffusion distance between capillaries due to interstitial edema, the smaller the PVD value, the longer distance between capillaries or interstitial edema occurs. In this study, the PVD results were found to be insignificant between low CVP (0-4 mmHg) and high CVP (8-10 mmHg). This might be due to 1) the process of interstitial edema in the CVP 8-10 mmHg was not very significant due to the lack of aggressive fluid resuscitation carried out in the control group or the determination of the CVP 8-10 mmHg value was too low. This can be confirmed by cumulative balance data, i.e., statistically, the cumulative balance between CVP 0-4 mmHg was not significantly different from the CVP 8-10 mmHg, so the formation of edema that caused a decrease in the PVD value in the CVP 8-10 mmHg did not occur. There is a need for further studies with more extreme CVP settings in the control group, that is >12 mmHg; 2) the distance was too far where the capillary density assessment was carried out, namely on the sublingual to the kidney organ. Embryologically, sublingual is part of the gastrointestinal tract, not the kidney, so the sublingual microcirculation cannot directly represent the microcirculation of the kidney.

We found several limitations in our study. This study was a single-center study and had a small sample size; hence it might have low statistical power and could not be generalized. Further wide-scale research is needed to better estimate the effects of CVP on the incidence and severity of microcirculation hypoperfusion. There is a need for further research to carry out direct PVD assessment of the

kidneys to directly see renal interstitial edema through laparotomy research samples. Another possible cause is that the sublingual PVD value was not different from the CVP because CVP describes the value of central venous pressure while PVD was to see capillary blood vessel density or to see interstitial edema conditions. Therefore, further research is needed to assess the effect of CVP changes on renal venous pressure directly by intrarenal non-invasive doppler. The PVD value is seen as the cumulative balance or the type of fluid given between crystalloids and colloids.

### **Conclusion**

There was no significant difference in microcirculation perfusion between the low and high CVP groups. However, the results may support that a low CVP value is not associated with microcirculation hypoperfusion.

### **Ethics approval and consent to participate**

Faculty of Medicine Universitas Indonesia Ethics Committee issued the certificate of ethics and location permissions under reference number 1199/UN2.F1/ETIK/2018 and ClinicalGov NCT04156451.

### **Availability of data and materials**

Data are available on request to the corresponding authors.

### **Competing interest**

The authors declare that they have no competing interests.

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### **Authors' contributions**

The paper was conceived by YG, ASM, AL, IT, IA, SB, MS, HT, and DA. All authors commented on initial drafts of the article and approved the final version.

**Table 1.** Subjects' characteristic

Variable	CVP		p
	Low ( 0-4 mmHg)	High (8-10 mmHg)	
Age (year), median (min-max)	47.00 (18-60)	46.00 (20-60)	0.961*
Sex, n (%)			
Male	10 (45.5%)	12 (57.1%)	0.443*
Female	12 (54.5%)	9 (42.9%)	
Body weight (kg), mean±SD	54.50±11.02	62.95±15.17	0.65**
Height (cm), mean±SD	159.77±8.06	165.00±7.91	0.404**
BMI (kg/m <sup>2</sup> ), mean±SD	21.35±2.99	24.19±5.35	0.074**
MAP (mmHg), median (min-max)	88 (67-116)	79 (65-122)	0.056*
Norepinephrine (mcg/kg BW/min), median (min-max)	0.025 (0.00-0.30)	0.005 (0.00-0.80)	0.082*
SOFA score, median (min-max)	6 (2-12)	10 (4-16)	0.136*
Lactate (mmol/l), median (min-max)	1.5 (0.6-2.6)	2.0 (0.5-10.4)	0.214*
CVP (mmHg), median (min-max)	2.8 (-0.05-5.00)	5.80 (0.30-10.90)	<0.001*
Creatinine (U/l), median (min-max)	0.5 (0.3-1.7)	0.9 (0.2-7.9)	0.002*
Urea (mg/dl), median (min-max)	33 (23.7-88.2)	85.2 (7.2-242.7)	0.009*

Legend: SD=standard deviation; BMI=body mass index; MAP=mean arterial pressure; SOFA=sequential organ failure assessment; CVP=central venous pressure.

\*Mann-Whitney U test; \*\*independent t-test.

**Table 2.** Association between CVP value and PVD

PVD	CVP		p*
	Low ( 0-4 mmHg)	High (8-10 mmHg)	
PVD day-0	n=22	n=21	0.903
Median (min-max)	12.5(7.0-15.4)	13.85 (3.4-15.6)	
PVD day-1	n=22	n=19	0.036
Median (min-max)	12.9 (7.6-17.9)	8.5 (1.4-17.5)	
PVD day-2	n=20	n=17	0.800
Median (min-max)	12.7 (6.5-15.5)	12.85 (7.6-18.2)	
PVD day-3	n=20	n=15	0.435
Median (min-max)	11.5 (3.8-32.5)	10.35 (1.3-14.2)	
PVD day-4	n=18	n=15	0.586
Median (min-max)	13.3 (7.1-17.5)	11.6 (2.7-18.6)	
PVD day-5	n=18	n=14	0.918
Median (min-max)	9.9 (1.0-14.6)	10.45 (4.0-15.8)	
PVD day-6	n=18	n=14	0.498
Median (min-max)	10.0 (3.5-17.1)	11.9 (4.1-16.3)	
PVD day-7	n=18	n=14	0.074
Median (min-max)	10.2 (4.3-13.3)	13.45 (4.8-16.7)	

Legend: CVP=central venous pressure; PVD=perfused vessel density.

\*Mann-Whitney U test.

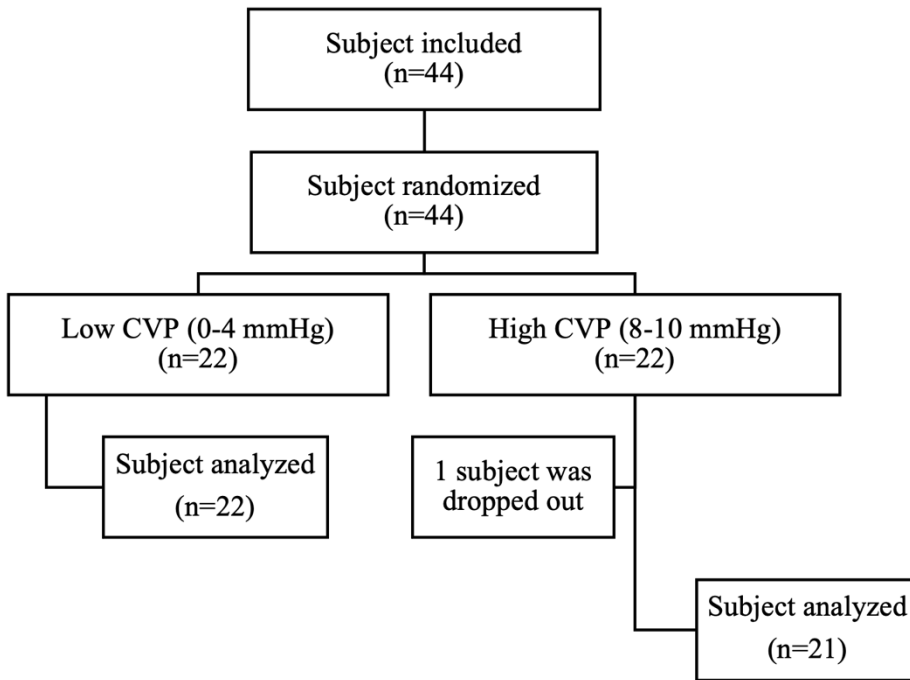
**Table 3.** Association between CVP value and delta PVD

Delta PVD	CVP		p*
	Low ( 0-4 mmHg)	High (8-10 mmHg)	
Delta PVD 0-1	n=22	n=21	0.082
Median (min-max)	2.2(-6.70-11.5)	-1.4 (-14.2-8.1)	
Delta PVD 1-2	n=22	n=19	0.019
Median (min-max)	-1.1 (-5.6-7.6)	2.5 (-2.5-11.6)	
Delta PVD 2-3	n=20	n=17	0.322
Median (min-max)	-1.0 (-8.6-24.6)	-1.8 (-14.0-5.5)	
Delta PVD 3-4	n=20	n=15	0.773
Median (min-max)	0.4 (-18.2-9.6)	0.1 (-8.0-15.1)	
Delta PVD 4-5	n=18	n=15	0.309
Median (min-max)	-3.0 (-8.2-4.3)	-2.0 (-13.3-9.1)	
Delta PVD 5-6	n=18	n=14	0.430
Median (min-max)	0.0 (-4.0-2.9)	1.95 (-9.6-10.7)	
Delta PVD 6-7	n=18	n=14	0.458
Median (min-max)	0.3 (-5.9-9.8)	1.1 (-5.6-9.2)	
Delta PVD initial-end	-1.0 (-8.3-2.5)	1.4 (-8.0-11.10)	0.104
Median (min-max)			

Legend: CVP=central venous pressure; PVD=perfused vessel density.

\*Mann-Whitney U test.

**Figure 1.** Study subjects



Legend: CVP=central venous pressure.

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