Association Between Early Central Venous Pressure Measurement and Mortality in Patients With Sepsis: A Retrospective Study

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Research

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Abstract

Background: It remains controversial to abandon central venous pressure (CVP) in the monitoring of fluid resuscitation in sepsis patients. We hypothesized that early CVP measurement was associated with decreased mortality in critically ill patients with sepsis.

Methods: Critically ill patients with sepsis were identified from the Medical Information Mart for Intensive Care (MIMIC)-III database. Patients were divided into two groups based on whether or not they had a CVP measurement within the first 6 hours of ICU stay. The primary endpoint was 28-day mortality. Patients were further divided into four subgroups based on the time when the first CVP measurement was obtained: within 3 hours, between 3 and 6 hours, between 6 and 12 hours, and not measured within 12 hours. Kaplan-Meier survival analysis and Cox regression model were used for univariate and multivariate analyses of survival, respectively.

RESULTS: A total of 4733 sepsis patients were included. The 28-day mortality was significantly lower in the CVP measured group than in the control group (34.2 vs. 40.7, $p < 0.001$). A “U”-shaped relationship between initial CVP and mortality was identified. With patients without CVP measured within 12 hours serving as the reference subgroup, timely CVP measurement was associated with decreased 28-day mortality before and after adjusting for confounding variables.

CONCLUSIONS: Early CVP measurement is associated with decreased 28-day mortality in patients with sepsis. CVP should be considered as a valuable and easily accessible safety parameter during (early) fluid resuscitation.

Background

Sepsis and septic shock remain the main causes of admission to the intensive care unit (ICU) and death in critically ill patients [1]. During this first phase of treatment (“the salvage phase” [2]), one of the main therapies is fluid administration to restore blood pressure and cardiac output. Previous Surviving Sepsis Campaign (SSC) guidelines have recommended administering fluid to target central venous pressure (CVP) level [3], yet it is no longer recommended by the latest updated SSC guidelines [4]. It remains controversial to abandon CVP in the monitoring of fluid resuscitation in sepsis patients [5, 6]. CVP is often misinterpreted as an indicator of intravascular volume status. From the (patho)physiological point of view, CVP is determined by the interaction of cardiac function and venous return function, as suggested by Guyton et al. [7], and therefore does not merely reflect the intravascular volume status. Small changes in CVP along with increases in cardiac output (CO) indicate fluid responsiveness, which would thus lead to fluid administration in sepsis patients with evidence of tissue hypoperfusion. In contrast, significant increases in CVP with little changes in CO suggest poor tolerance to fluids, in which case patients are at high risk of fluid overload and may benefit little from fluids.

It is true that using CVP values to guide fluid resuscitation is far from perfect. However, CVP provides a useful indication of how well the heart interacts with venous return. To a given high CVP value, it could

attribute to either cardiac dysfunction or fluid overload, or both, if intra-thoracic hypertension caused by other factors is excluded. CVP can thus serve as a safety variable for when to stop or not to give additional fluids. This is important since sepsis patients admitted to ICU is very likely to receive a large amount of fluid before ICU admission. Low CVP, on the other hand, can be helpful for detecting inadequate fluid resuscitation but should be used with caution and together with additional monitoring. We hypothesized that early CVP measurement in the ICU was associated with decreased mortality in critically ill patients with sepsis. Data of patients with sepsis were retrospectively collected, and the association between early CVP measurement and mortality was explored.

Methods

Database

The data of the present study were collected from the Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC III) [8]. In brief, MIMIC-III database is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It contains de-identified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012. The institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) approved the establishment of the database. Therefore, consent was obtained for the original data collection and waived for the present study. Data were extracted by Dr. Shu-Rong Gong and Dr. Han Chen, who completed the online training course of the National Institutes of Health (certification number: SRG 35606844, HC 36014736).

Data extraction

PostgreSQL tools V.1.09 was used for data extraction. The following data were extracted by using Structured Query Language (SQL): age, gender, co-morbidities, the survival time, length of hospital stay, and length of ICU stay, sequential organ failure assessment (SOFA) score, vital signs, first-day lab results, use of vasopressors, daily fluid input, fluid balance, urine output, need for renal replacement therapy and mechanical ventilation, the present of sepsis, and the initial time and value of the first CVP measurement in the ICU.

Population and endpoint

All patients with sepsis were included. Patients younger than 18 years old were excluded. Patients were divided into two groups base on whether or not they had a CVP measurement within the first 6 hours of ICU stay (i.e., the CVP measured group and the control group). The primary endpoint was 28-day mortality.

Statistical analysis

Continuous variables were presented as mean with standard deviation or median with interquartile ranges. Student's *t*-test or Wilcoxon rank-sum test were used as appropriate. Categorical variables were presented as counts (percentages) and compared using the chi-square test. We used a locally weighted smoothing (Lowess Smoothing) technique to explore the crude relationship between initial CVP values and mortality. Patients were further divided into four subgroups based on the time when the first CVP measurement was obtained: within 3 hours, between 3 and 6 hours, between 6 and 12 hours, and not measured within 12 hours, and the Kaplan-Meier survival analysis was performed as a univariate analysis of survival, tested by the Log-Rank test. Cox regression model was used to estimate the relationships of the timeliness of CVP measurement and mortality adjusting for confounding variables (with a *p*-value < 0.05 in univariate analysis or potential confounders judged by clinical expertise).

Results

A total of 4733 sepsis patients were included, where 1673 patients had a CVP measurement within the first 6 hours of ICU stay, and another 3060 patients were allocated into the control group. Baseline patient characteristics are summarized in Table 1. It is worth mentioning that patients in the CVP measured group had higher initial lactate acid level, higher SOFA score, but a lower rate of underlying renal failure (Table 1).

Table 1
Baseline patient characteristics

	CVP not measured within 6 hr (n = 3060)	CVP measured within 6 hr (n = 1673)	p- value
Male (%)	1372 (44.8)	714 (42.7)	0.153
Age (yr)	66.9 ± 15.9	67.6 ± 15.5	0.123
Obesity (%)	190 (6.2)	111 (6.6)	0.566
Co-morbidities			
Congestive heart failure (%)	1080 (35.3)	594 (35.5)	0.885
Cardiac arrhythmia (%)	1065 (34.8)	563 (33.7)	0.425
Valvular disease (%)	302 (9.9)	160 (9.6)	0.735
Hypertension (%)	575 (18.8)	278 (16.6)	0.063
Paralysis (%)	134 (4.4)	63 (3.8)	0.312
Chronic pulmonary disease (%)	664 (21.7)	348 (20.8)	0.471
Diabetes mellitus (%)	1031 (33.7)	570 (34.1)	0.793
Renal failure (%)	787 (25.72)	350 (20.92)	< 0.001
Liver disease (%)	401 (13.1)	203 (12.1)	0.339
Tumor (%)	397 (13.0)	231 (13.8)	0.419
Admission status			
SOFA score	6.8 ± 3.8	8.2 ± 3.8	< 0.001
Initial lactate (mmol/L)	1.9 (1.3, 3.3)	2.3 (1.4, 3.7)	< 0.001
Max white blood cell count within 24 hr (K/uL)	14.4 (9.5, 20.9)	15.9 (10.7, 23.4)	< 0.001
Min hemoglobin within 24 hr (g/dL)	9.3 (8.1, 10.7)	9.3 (8.2, 10.5)	0.889
Min platelet within 24 hr (K/uL)	178 (104, 275)	171 (104, 250)	0.03

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and counts (percentages) for categorical variables.

CVP central venous pressure, *SOFA* sequential organ failure assessment

	CVP not measured within 6 hr (n = 3060)	CVP measured within 6 hr (n = 1673)	<i>p</i> - value
Min albumin within 24 hr (g/dL)	2.7 (2.3, 3.1)	2.6 (2.2, 3.0)	< 0.001
Max creatine within 24 hr (mg/dL)	2.2 ± 1.9	2.2 ± 1.8	0.544
Max blood glucose within 24 hr (mg/dL)	152 (120, 205)	167 (132, 219)	< 0.001
Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and counts (percentages) for categorical variables.			
<i>CVP</i> central venous pressure, <i>SOFA</i> sequential organ failure assessment			

The 28-day mortality was significantly lower in the CVP measured group than in the control group (34.2 vs. 40.7, $p < 0.001$, Table 2). Compare to the control group, the hospital length of stay was significantly shorter in the CVP measured group, but the ICU length of stay was significantly longer. More patients needed mechanical ventilation in the CVP measured group, but there was no difference in the duration of mechanical ventilation. Similarly, more patients needed vasopressors in the CVP measured group, but no difference in the duration of vasopressor use was observed. No difference in the occurrence of acute kidney injury (AKI), need for renal replacement therapy, or urine output was observed (Table 2).

Table 2
Unadjusted outcomes in patients with or without CVP measured within 6 hours

	CVP not measured within 6 hr (n = 3060)	CVP measured within 6 hr (n = 1673)	p- value
28-day mortality (%)	1246 (40.7)	572 (34.2)	< 0.001
Length of ICU stay (day)	4.0 (1.9, 9.5)	4.6 (2.2, 10.4)	< 0.001
Length of hospital stay (day)	12.4 (6.0, 24.6)	11.5 (6.0, 22.4)	0.019
Occurrence of acute renal injury (%)	2469 (80.69)	1384 (82.73)	0.085
Need for mechanical ventilation (%)	1671 (54.61)	1119 (66.89)	< 0.001
Need for renal replacement therapy (%)	292 (9.5)	180 (10.8)	0.182
Need for vasopressors (%)	1810 (59.2)	1403 (83.9)	< 0.001
Mechanical ventilation duration (hour)	118 (37, 260)	110 (38, 250)	0.389
Vasopressor duration (hour)	31 (12, 68)	31 (13, 63)	0.513
Urine output on day 1 (mL)	1188 (590, 2010)	1168 (560, 2110)	0.912
Data are presented as median (interquartile range) for continuous variables, and counts (percentages) for categorical variables.			
<i>CVP</i> central venous pressure, <i>ICU</i> intensive care unit			

A “U”-shaped relationship between initial CVP and mortality was found (Fig. 2). The 28-day survival was significantly different among patients with CVP measured at different time points (Fig. 3). Compare to patients without CVP measured within 12 hours, patients with CVP measured within 3 hours had significantly lower mortality, but no significant difference was observed in the other subgroups (adjusted $p < 0.001$, = 0.053, and > 0.999 , respectively; Fig. 3).

With patients without CVP measured within 12 hours serving as the reference group, timely CVP measurement was associated with decreased 28-day mortality before adjusting for confounding variables. After adjusting age, gender, SOFA score, initial lactate, renal failure, and the first-day lab results, including max blood glucose, minimum platelet and max white blood cell count, the association between timely CVP measurement and decreased 28-day mortality was still observed (Table 3).

Table 3
Adjusted hazard ratio using timepoint of CVP measurement as the design variable

Unadjusted outcomes by CVP measurement categories				Adjusted outcomes with confounding variables included in the model			
Variable	HR	95% CI	p-value	Variable	HR	95% CI	p-value
CVP measured within 3 hr	0.79	(0.70, 0.89)	< 0.001	CVP measured within 3 hr	0.65	(0.55, 0.77)	< 0.001
CVP measured between 3 and 6 hr	0.84	(0.73, 0.97)	0.021	CVP measured between 3 and 6 hr	0.72	(0.6, 0.87)	0.001
CVP measured between 6 and 12 hr	0.98	(0.84, 1.14)	0.757	CVP measured between 6 and 12 hr	0.8	(0.66, 0.98)	0.032
CVP not measured within 12 hr	Ref.			CVP not measured within 12 hr	Ref.		
				Gender	1.02	(0.89, 1.16)	0.820
				Age	1.02	(1.01, 1.02)	< 0.001
				SOFA	1.13	(1.1, 1.15)	< 0.001
				Initial lactate	1.12	(1.1, 1.14)	< 0.001
				Max blood glucose within 24 hr	1	(1, 1)	0.139
				Min platelet within 24 hr	1	(1, 1)	0.770
				Max WBC within 24 hr	1	(1, 1)	0.900
				Renal failure	0.94	(0.81, 1.09)	0.419
Patients were divided into four subgroups base on the time when the first CVP measurement was obtained: within 3 hours, between 3 and 6 hours, between 6 and 12 hours, and not measured within 12 hours. Two COX proportional hazards models were built with the CVP not measured within 12 hours subgroup as the reference group.							
CVP central venous pressure, CI confidence interval, HR hazard ratio, SOFA sequential organ failure assessment, WBC white blood cell count							

Discussion

The main findings of the present study were: 1) the 28-day mortality was significantly lower in patients with CVP measured within 6 hours than in those who did not; 2) the improvement of 28-day mortality was associated with the time when the CVP measurement was established.

The results of three recent multi-center randomized controlled trials (ProCESS, ARISE and ProMiSe) have led to the abandonment of the “early goal-directed therapy” (EGDT) strategy [9, 10]. CVP is no longer recommended to guide fluid resuscitation by the most recent SSC guidelines [4]. Instead, dynamic measures of assessing fluid responsiveness, encompass passive leg raises, fluid challenges against stroke volume measurements, or the variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation, are recommended. However, new concerns regarding the concept of fluid responsiveness have been raised: “volume responsive, but does the patient need volume?” [11]

What is the significance of CVP measurement in this context? CVP is determined by the complex interplay of the preload, afterload, compliance, and contractility of the right ventricle, venous tone, volume status, abdominal and intrathoracic pressure, and many other factors [12]. For simplicity, it can be interpreted as that measured CVP is determined by the interaction of the cardiac and venous return functions [13]. Indeed, a single static measurement of CVP does not predict blood volume or fluid responsiveness. However, this statement misses the value of CVP as a readily available indicator that mirrors the complex interaction between the heart and the blood returning from circulation. In other words, CVP is more likely a “dependent variable” in this interplay rather than an “independent variable.” The “independent variables,” on the other hand, are intravascular volume and cardiac function, which are manipulated in daily clinical practice (for instance, fluid administration for intravascular volume and inotropic agents for cardiac function). In this point of view, CVP does not indicate volume status, and in isolation, it is not a strong predictor of fluid responsiveness. But an abnormal CVP value must attribute to either abnormal intravascular volume or abnormal cardiac function, or both, and the choice of further (advanced) assessments can be made by the measurement of CVP (e.g., echocardiography, inferior vena cava diameter, CO measurement via thermal dilution, etc.). Together with the further evaluations, the decision whether to continue or stop fluid administration or even to achieve a negative fluid balance (i.e., “reverse fluid resuscitation”), can be made.

In the present study, our data suggested a “U” shape relationship between initial CVP and 28-day mortality. As discussed above, an extremely low CVP value may due to hypovolemia or a hyperdynamic heart in the setting of sepsis. Patients are at higher risk of mortality if hypovolemia is inadequately resuscitated [4]. The association between elevated CVP and increased mortality has been found by numerous studies [14–19]. Besides, since CVP serves as the backpressure of venous return, upstream capillary pressures must be even higher in the setting of increased CVP to maintain an intact venous return. Therefore, clinicians should not only further look into cardiac function or intravascular volume, but also the possible impact of venous congestion on upstream organs. The association between elevated CVP and kidney dysfunction has also been found in critically ill patients [18, 20, 21]. In the perspective of venous return function, under the premise of maintaining adequate tissue perfusion, CVP should be

maintained as low as possible to allow an adequate venous return, and thus to increase CO (in a steady condition, CO must equal venous return) and reduce tissue edema.

Criticisms have been raised since the current SSC guidelines recommend intravenous infusing at least 30 mL/kg of crystalloids within the first three hours of resuscitation [5]. A fixed, large volume of fluid infusion could result in fluid overload. As previously discussed, a high CVP indicates either fluid overload or the current cardiac function is incapable of matching the increased venous return. Either way, the fluid infusion should be discontinued. Early CVP monitoring may be helpful in reducing the risk of fluid overload. In this setting, CVP can serve as a safe limit rather than a target of fluid resuscitation [22]. Our data suggested that early CVP measurement was associated with decreased 28-day mortality, which can be partially explained in this way.

Higher baseline SOFA score and initial lactate were observed in patients who received CVP measurement within 6 hours, suggested a more severe illness of the patients. Interestingly, these sicker patients had better survival than the controls. After adjusting the confounding variables in multivariate analysis, we found that early CVP measurement was the independent factor associated with decreased mortality. However, it should be emphasized that it is not the monitoring, but the adjustment of interventions given by the caregivers based on the results of the monitoring improves patients' outcomes. Although a cause-effect relationship cannot be established in this retrospective study, given the nature of cheap, easily obtainable, and repeatable, early CVP measurement is still a valuable aid for diagnosis and hemodynamic management when properly understood, especially in preventing fluid over-resuscitation.

This study has several limitations. First, the study was limited by the nature of retrospective design and the source of data used. For this reason, no cause-effect relationships could be established. Second, although some confounding variables were adjusted in multivariate analysis, confirming that early CVP measurement was associated with poor outcomes, the results may be affected by other confounding variables related to organ damage or mortality. Additional prospective studies are needed to investigate the association between CVP monitoring and treatment adjustments and the related outcomes to these adjustments.

Conclusions

Early CVP measurement is associated with decreased 28-day mortality in patients with sepsis. CVP should be considered as a valuable and easily accessible safety parameter during (early) fluid resuscitation.

Abbreviations

AKI

acute kidney injury; CO = cardiac output; CVP = central venous pressure; EGDT = early goal-directed therapy; HR = hazard ratio; ICU = intensive care unit; MIMIC = Medical Information Mart for Intensive Care;

SOFA = sequential organ failure assessment; SQL = Structured Query Language; SSC = Surviving Sepsis Campaign; WBC = white blood cell count

Declarations

Ethics approval and consent to participate

The institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) approved the establishment of the database. Therefore, consent was obtained for the original data collection and waived for the present study.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author Contributions:

Conception and design: HC, XLS, RGY; *Data collection and analysis:* HC, SRG; *Drafting the manuscript:* HC, SRG, SLS, RGY. All authors have read and approved the manuscript.

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Figures

Figure 1

Flowchart showing a step-by-step selection of patients included in the study CVP central venous pressure, ICU intensive care unit.

Figure 2

Mortality rate in patients with different Initial central venous pressure The bar plot demonstrates the raw mortality rate in each patient subgroup with different Initial central venous pressure. Locally weighted smoothing (Lowess Smoothing) showed a “U”-shaped relationship between initial central venous pressure and mortality.

Figure 3

Kaplan-Meier survival analysis of patients with central venous pressure measured at different time points. The 28-day survival was significantly different among patients with central venous pressure (CVP) measured at the different time points (CVP measured within 3 hours, between 3 and 6 hours, between 6 and 12 hours, and not measured within 12 hours, $p < 0.001$). Pairwise comparison showed a significant difference between patients with CVP measured within 3 hours and patients without CVP measured within 12 hours (adjusted $p < 0.001$). A statistical trend was observed between patients with CVP measured between 3 and 6 hours and patients without CVP measured within 12 hours (adjusted $p = 0.053$). No difference was observed between patients with CVP measured between 6 and 12 hours and those who without CVP measured within 12 hours (adjusted $p > 0.999$).