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CHEST Special Feature

Does Central Venous Pressure Predict Fluid Responsiveness?*

A Systematic Review of the Literature and the Tale of Seven Mares

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Background: **Central venous pressure (CVP) is used almost universally to guide fluid therapy in hospitalized patients. Both historical and recent data suggest that this approach may be flawed.**
Objective: **A systematic review of the literature to determine the following: (1) the relationship between CVP and blood volume, (2) the ability of CVP to predict fluid responsiveness, and (3) the ability of the change in CVP (ΔCVP) to predict fluid responsiveness.**
Data sources: **MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.**
Study selection: **Reported clinical trials that evaluated either the relationship between CVP and blood volume or reported the associated between CVP/ΔCVP and the change in stroke volume/cardiac index following a fluid challenge. From 213 articles screened, 24 studies met our inclusion criteria and were included for data extraction. The studies included human adult subjects, healthy control subjects, and ICU and operating room patients.**
Data extraction: **Data were abstracted on study design, study size, study setting, patient population, correlation coefficient between CVP and blood volume, correlation coefficient (or receive operator characteristic [ROC]) between CVP/ΔCVP and change in stroke index/cardiac index, percentage of patients who responded to a fluid challenge, and baseline CVP of the fluid responders and nonresponders. Metaanalytic techniques were used to pool data.**
Data synthesis: **The 24 studies included 803 patients; 5 studies compared CVP with measured circulating blood volume, while 19 studies determined the relationship between CVP/ΔCVP and change in cardiac performance following a fluid challenge. The pooled correlation coefficient between CVP and measured blood volume was 0.16 (95% confidence interval [CI], 0.03 to 0.28). Overall, 56 ± 16% of the patients included in this review responded to a fluid challenge. The pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index was 0.18 (95% CI, 0.08 to 0.28). The pooled area under the ROC curve was 0.56 (95% CI, 0.51 to 0.61). The pooled correlation between ΔCVP and change in stroke index/cardiac index was 0.11 (95% CI, 0.015 to 0.21). Baseline CVP was 8.7 ± 2.32 mm Hg [mean ± SD] in the responders as compared to 9.7 ± 2.2 mm Hg in nonresponders (not significant).**
Conclusions: **This systematic review demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/ΔCVP to predict the hemodynamic response to a fluid challenge. CVP should not be used to make clinical decisions regarding fluid management.**
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Key words: anesthesia; blood volume; central venous pressure; fluid responsiveness; fluid therapy; hemodynamic monitoring; ICU; preload; stroke volume

Abbreviations: AUC = area under the curve; CI = confidence interval; CVP = central venous pressure; ΔCVP = change in central venous pressure; ROC = receiver operator characteristic

Central venous pressure (CVP) is the pressure recorded from the right atrium or superior vena cava. CVP is measured (usually hourly) in almost all patients in ICUs throughout the world, in emergency department patients, well as in patients undergoing major surgery. CVP is frequently used to make decisions regarding the administration of fluids or diuretics. Indeed, internationally endorsed clinical

guidelines[1] recommend using CVP as the end point of fluid resuscitation. The basis for using CVP to guide fluid management comes from the dogma that CVP reflects intravascular volume; specifically, it is widely believed that patients with a low CVP are volume depleted while patients with a high CVP are volume overloaded. This concept is taught to medical students as well as to residents and fellows across a wide range of medical and surgical disciplines. Indeed an authoritative textbook[2] of cardiovascular physiology states as a key concept that "[the] central venous pressure gives clinically relevant information about circulatory [and volume] status." The chapter on cardiovascular monitoring in a standard anesthesiology text[3] states that "the most important application of CVP monitoring is to provide an estimate of the adequacy of circulating blood volume", and "[that] trends in CVP during anesthesia and surgery are also useful in estimating fluid or blood loss and guiding replacement therapy." Over 25 years ago, the "5–2" rule for guiding fluid therapy was popularized.[4] According to this rule, the change in CVP following a fluid challenge is used to guide subsequent fluid management decisions. This rule is still widely used today. Recently, the idea that the CVP reflects blood volume has been challenged. Since CVP plays such a central role in the fluid management strategy of hospitalized patients, the goal of this study was to systemically review the evidence that supports this practice.

Materials and Methods

Identification of Trials

Our aim was to identify all relevant clinical trials that analyzed the relationship between CVP and measured blood volume as well as those studies that determined the ability of CVP to predict fluid responsiveness (*ie*, an increase in stroke index/cardiac index following a fluid challenge). Studies that compared CVP with volumetric measurements (right and left ventricular end-diastolic volumes, global left heart volume, central blood volume) but did not report the ability of CVP to predict volume responsiveness were not included. We restricted this analysis to human adults; however, there was no restriction as to the type of patient or the setting where the study was performed. We used a multimethod approach to identify relevant studies for this review. All authors independently searched the National Library of Medicine MEDLINE database for relevant studies in any language published from 1966 to June 2007 using the following medical subject headings and key words; central venous pressure (explode) AND blood volume, or fluid therapy or fluid responsiveness. In addition, we searched Embase and the Cochrane Database of Systematic Reviews. Bibliographies of all selected articles and review articles that included information on hemodynamic monitoring were reviewed for other relevant articles. In addition, the authors reviewed their personal files and contacted experts in the field. This search strategy was done iteratively until no new potential citations were found on review of the reference lists of retrieved articles. We performed this metaanalysis according to the guidelines proposed by the Quality of Reporting of Meta-analyses group.[5]

Study Selection and Data Extraction

Only studies that reported either of the following were included in this analysis: (1) the correlation coefficient between CVP and measured blood volume, or (2) the correlation coefficient or receiver operator characteristic (ROC) between CVP or change in CVP (ΔCVP) and change in stroke index/cardiac output following a fluid challenge. All authors independently abstracted data from all studies using a standardized form. Data were abstracted on study design, study size, study setting, patient population, correlation coefficients and area (including 95% confidence intervals [CIs]) under the ROC curve, the percentage of patients responding to a fluid challenge as well as the baseline CVP in the fluid responders and nonresponders. In general, an increase in the stoke index or cardiac index $>$ 10 to 15% was used as an index of fluid responsiveness.[6,7]

The random-effects models (Comprehensive Meta-analysis 2.0; Biostat; Englewood NJ) was used to determined the pooled area under the curve (AUC) and correlation coefficients.[8,9] Summary effects estimates are presented with 95% CIs. We calculated the Cochran Q statistic to test for statistical heterogeneity. Values of Q significantly > 0 ($p < 0.1$) were considered evidence of heterogeneity. When not reported in the primary paper, the correlation coefficients were calculated from the raw data (when available) [NCSS 2007; NCSS; Kaysville, UT].

Results

The initial search strategy generated 206 citations; of these, 189 were excluded due to trial design or failure to report an outcome variables of interest. An additional seven studies were identified from the bibliographies of the selected articles and review articles. Of the 24 studies included in this analysis, 5 studies compared CVP with the measured circulating blood volume while 19 studies determined the relationship between CVP and change in cardiac performance following a fluid challenge (generally defined as a $>$ 10 to 15% increase in stroke index/cardiac index). In all, 830 patients across a spectrum of medical and surgical disciplines were studied[10–33] (Tables 1, 2). In three studies,[10,15,33] the correlation coefficients were not reported in the article but were calculated from the raw data.

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Table 1—*Summary of Studies of Blood Volume

Source	Setting	Type	Patients, No.	Methodology	*r*, Blood Volume
Baek et al,[10] 1975	ICU	General surgery	69	^{125}I-albumin	0.19
Shippy et al,[11] 1984	ICU	ICU	118	^{125}I-albumin	0.27
Hoeft et al,[12] 1994	OR/ICU	CABG	11	Indocyanine green	0.12
Oohashi et al,[13] 2005	ICU	Esophagectomy	16	Indocyanine green	0.17
Kuntscher et al,[14] 2006	ICU	Burns	16	COLD system†	0.02
Pooled value					0.16

*OR = operating room; CABG = coronary artery bypass graft surgery.
†COLD Z-021 system (Pulsion Medical Systems; Munich, Germany).

The pooled correlation coefficient between the CVP and measured blood volume was 0.16 (95% CI, 0.03 to 0.28; $r^2 = 0.02$). Heterogeneity was present between studies. Figure 1 illustrates the relationship between CVP and measured blood volume from the study of Shippy et al.[11] Overall 56 ± 16% (mean ± SD) of the patients included in this review responded to a fluid challenge. The pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index (reported in 10 studies) was 0.18 (95% CI, 0.08 to 0.28). The pooled area under the ROC curve (reported in 10 studies) was 0.56 (95% CI, 0.51 to 0.61). The pooled correlation between ΔCVP and change in stroke index/cardiac index (reported in seven studies) was 0.11 (95% CI, 0.01 to 0.21). The baseline CVP (reported in 11 studies) was 8.7 ± 2.3 mm Hg in the responders, as compared to 9.7 ± 2.2 mm Hg in nonresponders (not signficant; p = 0.3). The Q statistic was not significant for the pooled correlation and area under the curve statistic.

Discussion

The results of this systematic review are clear: (1) there is no association between CVP and circulating blood volume, and (2) CVP does not predict fluid responsiveness across a wide spectrum of clinical

Table 2—*Summary of Studies of Volume Challenge

Source	Setting	Type	Patients, No.	Methodology	AUC†	*r*, CVP/SI	*r*, ΔCVP/SI	CVP-R	CVP-NR
Calvin et al,[15] 1981	ICU	Mixed ICU	28	PAC/Scint		0.16	0.26	4.7	4.8
Reuse et al,[16] 1990	ICU	ICU	41	PAC		0.21		8.5	8.4
Godje et al,[17] 1998	ICU	CABG	30	PAC, COLD system‡			0.09		
Wagner and Leatherman,[18] 1998	ICU	ICU	25	PAC		0.44		7.4	10.1
Wiesenack et al,[19] 2001	OR	CABG	18	PAC, TPT			0.09		
Berkenstad et al,[20] 2001	OR	Neurosurgery	15	TPT	0.49	0.05	0.08	9.3	9.3
Michard et al,[21] 2000	ICU	ICU	40	PAC	0.51				
Reuter et al,[22] 2002	ICU	CABG	20	TPT	0.42				
Reuter et al,[23] 2003	ICU	CABG	26	PAC, TEE	0.71				
Barbier et al,[24] 2004	ICU	Sepsis	20	TEE	0.57			10	9
Kramer et al,[25] 2004	ICU	CABG	21	PAC	0.49	0.13		13.5	13.3
Marx et al,[24] 2004	ICU	Sepsis	10	PAC, TPT		0.41	0.28		
Preisman et al,[27] 2005	OR	CABG	18	TPT, TEE	0.61			8.7	10
Perel et al,[28] 2005	ICU	Vascular surgery	14	TEE		0.27		9.6	12.2
Hofer et al,[29] 2005	OR	CABG	40	PAC, TEE	0.54	0.02	0.2		
De Backer et al,[30] 2005	ICU	ICU	60	PAC	0.54			10	12
Kumar et al,[31] 2004	ICU	Healthy volunteers	12	PAC/Scint		0.32	0.22		
Osman et al,[32] 2007	ICU	Septic	96	PAC	0.58			8	9
Magder and Bafaqeeh,[33] 2007	ICU	CABG	66	PAC		0.36		5.9	8.7
Pooled					0.56	0.18	0.11	8.7	9.7

*PAC = pulmonary artery catheter; TEE = transesophageal echocardiography; Scint = radionuclide scintography; TPT = transpulmonary thermodilution; CVP-R = baseline CVP of responders; CVP-NR = baseline CVP of nonresponders; SI = fluid responsiveness; see Table 1 for expansion of abbreviations.
†Area under ROC curve of CVP and fluid responsiveness.
‡COLD Z-021 system (Pulsion Medical Systems; Munich, Germany).

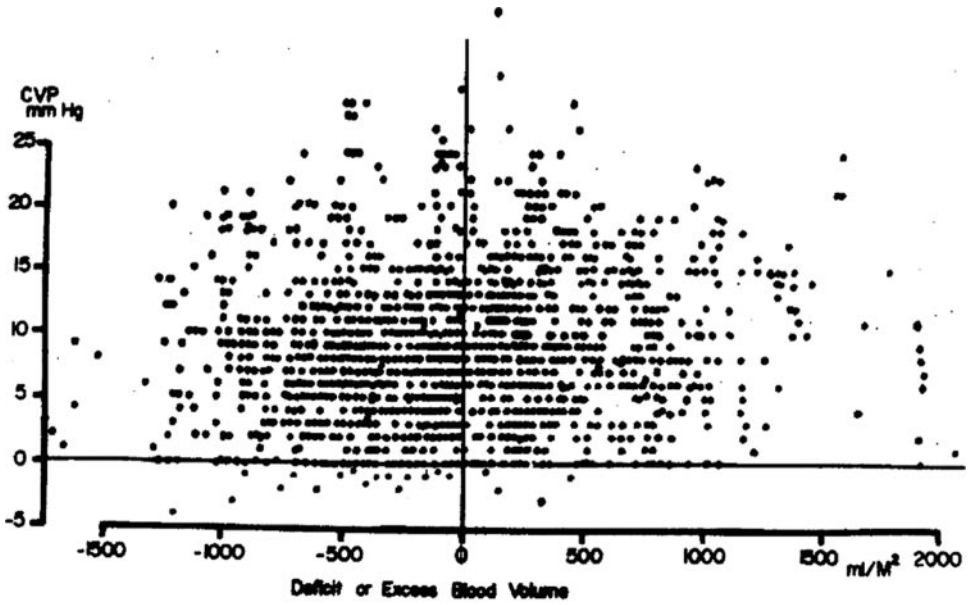

FIGURE 1. Fifteen hundred simultaneous measurements of blood volume and CVP in a heterogenous cohort of 188 ICU patients demonstrating no association between these two variables ($r = 0.27$). The correlation between ΔCVP and change in blood volume was 0.1 ($r^2 = 0.01$). This study demonstrates that patients with a low CVP may have volume overload and likewise patients with a high CVP may be volume depleted. Reproduced with permission from Shippy et al.[11]

conditions. In none of the studies included in this analysis was CVP able to predict either of these variables. Indeed, the pooled area under the ROC curve was 0.56. The ROC curve is a statistical tool that helps assess the likelihood of a result being a true positive vs a false positive. As can be seen from Figure 2, an ROC of 0.5 depicts the true-positive rate equal to the false-positive rate; graphically, this is represented by the straight line in Figure 1. The higher the AUC, the greater the diagnostic accuracy of a test. Ideally, the AUC should be between 0.9 to 1 (0.8 to 0.9 indicates adequate accuracy with 0.7 to 0.8 being fair, 0.6 to 0.7 being poor, and 0.5 to 0.6 indicating failure). In other words, our results suggest that at any CVP the likelihood that CVP can accurately predict fluid responsiveness is only 56% (no better than flipping a coin). Furthermore, an AUC of 0.56 suggests that there is no clear cutoff point that helps the physician to determine if the patient is "wet" or "dry." It is important to emphasize that a patient is equally likely to be fluid responsive with a low or a high CVP (Fig 1). The results from this study therefore confirm that neither a high CVP, a normal CVP, a low CVP, nor the response of the CVP to fluid loading should be used in the fluid management strategy of any patient.

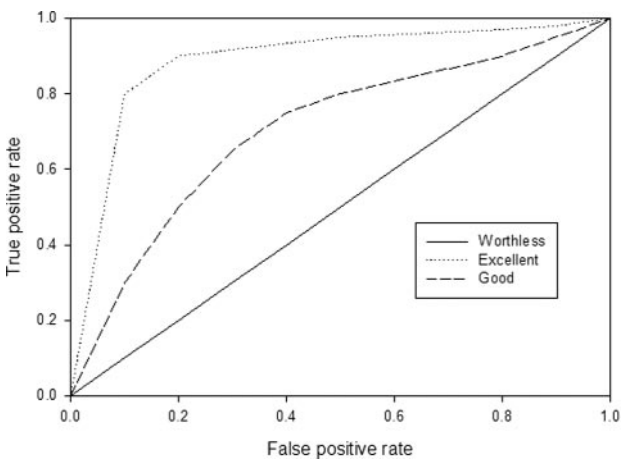

FIGURE 2. Comparison of ROC curves showing tests with different diagnostic accuracies.

The strength of our review includes the rigorous selection criteria used to identify relevant studies as well as the use of quantitative end points.[8,9,34] Furthermore, the studies are notable for the consistency (both in magnitude and direction) of their findings. This suggests that the findings are likely to be true.[8,9,34] The results of our study are most disturbing considering that 93% of intensivists report using CVP to guide fluid management.[35] It is likely that a similar percentage (or more) of anesthesiologists, nephrologists, cardiologists, and surgeons likewise use CVP to guide fluid therapy. It is important to note that none of the studies included in our analysis took the positive end-expiatory pressure levels or changes in intrathoracic pressure into account when

recording CVP. This is important because right ventricular filling is dependent on the transmural right atrial pressure gradient rather than the CVP alone.[36] However, in the real world, transmural filling pressures are rarely if ever calculated.

As demonstrated by this study, only about a half of patients administered a fluid bolus will demonstrate a positive hemodynamic response to the intervention. With an ROC of 0.56, the play of chance (or a dice) will be as helpful as CVP in predicting which patients will respond to a fluid challenge. If fluid resuscitation is guided by CVP, it is likely that patients will have volume overload and pulmonary edema. Indeed the practice parameters for hemodynamic support of sepsis in adult patients concludes that "fluid infusion should be titrated to a filling pressure" and that "pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation."[37] Should volume overload and pulmonary edema be the end point of fluid resuscitation?[38] This is clinically important because a positive fluid balance in both ICU patients and those undergoing surgery has been associated with increased complications and a higher mortality.[39–41] It is however equally likely that resuscitation guided by CVP will results in inadequate volume replacement. Furthermore, the use of diuretics based on CVP may result in intravascular volume depletion leading to poor organ perfusion and ultimately renal failure and multiorgan failure because a "high" CVP does not necessarily reflect volume overload.

Fundamentally the only reason to give a patient a fluid challenge is to increase the stroke volume.[6] This assumes that the patient is on the ascending portion of the Frank-Starling curve and has "recruitable" cardiac output. Once the left ventricle is functioning near the "flat" part of the Frank-Starling curve, fluid loading has little effect on cardiac output and only serves to increase tissue edema and to promote tissue dysoxia. It is therefore crucial during the resuscitation phase of all critically ill patients to determine whether the patient is fluid responsive or not; this determines the optimal strategy of increasing cardiac output and oxygen delivery.[42] The results from this article clearly demonstrate that CVP should not be used for this purpose.

The notion that CVP does not reflect intravascular volume and is a misleading tool for guiding fluid therapy is not new. In an article published in 1971, Forrester and colleagues,[43] the pioneers of hemodynamic monitoring, concluded that "CVP monitoring in acute myocardial infarction is at best of limited value and at worst seriously misleading." In their landmark article that was published in 1975, Baek and colleagues[10] convincingly established that "there was no correlation of blood volume with central venous pressure" and suggest that "inaccurate physiologic evaluation of critically ill patients is likely to jeopardize survival by inviting inappropriate and ineffectual therapy." In 1977, Dr. Burch,[44] a well-respected cardiologist, noted that "to accept noncritically the level of central venous pressure as a quantitative index of blood volume can only lead to physiologic and/or therapeutic errors." The observations of Forrester et al,[43] Baek and colleagues,[10] and Burch[44] have now been confirmed by 23 more recent studies. Indeed, limited data support using CVP to guide fluid therapy. The only study[45] we could find demonstrating the utility of CVP in predicting volume status was performed in seven standing, awake mares undergoing controlled hemorrhage! In addition, Magder and colleagues[46] reported that the respiratory variation in CVP in spontaneously breathing patients was predictive of fluid responsiveness. Additional studies are required to support using the respiratory variation in CVP to guide fluid management. In addition, it should be noted that in the ARDSnet fluid management trial,[47] those patients randomized to the "CVP conservative-strategy" group had significantly more ventilator-free days and a shorter length of ICU stay. It is unclear from this study whether CVP or the conservative fluid strategy was the important intervention because there was no "no-CVP" study arm. It should also be recognized that CVP was a component of early goal-directed therapy in the landmark article by Rivers and colleagues.[48] However, both the control and intervention groups had CVP targeted to 8 to 12 mm Hg. Based largely on the results of the early goal-directed therapy study, the Surviving Sepsis Campaign guidelines[1] for management of severe sepsis and septic shock recommend a CVP of 8 to 12 mm Hg as the "goal of the initial resuscitation of sepsis-induced hypoperfusion" and "a higher targeted central venous pressure of 12–15 mm Hg" in patients receiving mechanical ventilation. The results of our study suggest that these recommendations should be revisited.

The origins of CVP monitoring can be traced back to Hughes and Magovern,[49] who in 1959 described a complicated technique for right atrial monitoring as a guide to blood volume replacement in post-thoracotomy patents. These authors described a fall in CVP with blood loss and a relationship between the CVP and blood transfusion. The technique of CVP monitoring was further popularized by Wilson and Grow[50] and soon became routine in patients undergoing thoracic surgery. Based on scarce data, CVP became the standard tool for guiding fluid therapy, initially in the operating room and then in the ICU. However, what was not generally appreciated is that the CVP is a

measure of right atrial pressure alone; and not a measure of blood volume or ventricular preload. Based on the results of our systematic review, we believe that CVP should no longer be routinely measured in the ICU, operating room, or emergency department. However, measurement of the CVP may be useful in select circumstances, such as in patients who have undergone heart transplant, or in those who have suffered a right ventricular infarction or acute pulmonary embolism. In these cases, CVP may be used as a marker of right ventricular function rather than an indicator of volume status.

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