Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge*

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Objective: **Values of central venous pressure of 8–12 mm Hg and of pulmonary artery occlusion pressure of 12–15 mm Hg have been proposed as volume resuscitation targets in recent international guidelines on management of severe sepsis. By analyzing a large number of volume challenges, our aim was to test the significance of the recommended target values in terms of prediction of volume responsiveness.**

Design: **Retrospective study.**

Setting: **A 24-bed medical intensive care unit.**

Patients: **All consecutive septic patients monitored with a pulmonary artery catheter who underwent a volume challenge between 2001 and 2004.**

Intervention: **None.**

Measurements and Main Results: **A total of 150 volume challenges in 96 patients were reviewed. In 65 instances, the volume challenge resulted in an increase in cardiac index of ≥15% (responders). The pre-infusion central venous pressure was similar in responders and nonresponders (8 ± 4 vs. 9 ± 4 mm Hg). The pre-infusion pulmonary artery occlusion pressure was slightly lower in responders (10 ± 4 vs. 11 ± 4 mm Hg, $p < .05$). However, the significance of pulmonary artery occlusion pressure to predict fluid responsiveness was poor and similar to that of central venous pressure, as indicated by low values of areas under the receiver operating characteristic curves (0.58 and 0.63, respectively). A central venous pressure of <8 mm Hg and a pulmonary artery occlusion pressure of <12 mm Hg predicted volume responsiveness with a positive predictive value of only 47% and 54%, respectively. With the knowledge of a low stroke volume index (<30 mL·m^{-2}), their positive predictive values were still unsatisfactory: 61% and 69%, respectively. When the combination of central venous pressure and pulmonary artery occlusion pressure was considered instead of either pressure alone, the degree of prediction of volume responsiveness was not improved.**

Conclusion: **Our study demonstrates that cardiac filling pressures are poor predictors of fluid responsiveness in septic patients. Therefore, their use as targets for volume resuscitation must be discouraged, at least after the early phase of sepsis has concluded. (Crit Care Med 2007; 35:64–68)**

KEY WORDS: central venous pressure; pulmonary artery occlusion pressure; volume challenge; volume responsiveness; septic shock

Recent guidelines for the hemodynamic management of severe sepsis have emphasized the importance of aggressive volume resuscitation in the initial phase (1, 2). These recommendations have been partly based on the results of a randomized study (3) that demonstrated the positive effect on outcome of early goal-directed therapy—targeting a central venous oxygen saturation of >70%—vs. standard therapy. The patients in the early goal-directed treatment group received more fluids in the first 6 hrs than those of the standard treatment group. However, the end point of volume resuscitation was a central venous pressure of ≥8–12 mm Hg in both groups. Moreover, the mean central venous pressure value after 6 hrs was similar in both groups. Despite these latter observations, levels of central venous pressure of 8–12 mm Hg have been established as fluid resuscitation targets in the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock, not only in the initial phase, but even in later periods (1). The updated guidelines for hemodynamic support of adult patients with sepsis of the American College of Critical Care Medicine have emphasized the use of levels of pulmonary artery occlusion pressure (PAOP) of 12–15 mm Hg as reasonable targets (2). If only central venous pressure is available, levels of 8–12 mm Hg have been recommended to be targeted (2). Therefore, at the present time, cardiac filling pressures are considered as the gold standard for guiding fluid therapy in patients with sepsis and septic shock. However, the analysis of the available literature strongly suggests that neither PAOP nor central venous pressure are valuable for the guidance of fluid resuscitation in patients with circulatory failure including septic shock (4, 5).

It is noteworthy that none of the previous studies addressing this issue evaluated the significance of combining the knowledge of one filling pressure with that of the other one or with that of the stroke volume for predicting volume responsiveness. By examining a large number of volume challenges in the setting of severe sepsis or septic shock, the aims of our study were 1) to establish the degree of prediction of volume response of either

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PAOP or central venous pressure, or their combination, or their respective association with a low stroke volume index (SVI) and 2) to test the significance of the targets proposed in the recent international guidelines.

METHODS

Patients. Using our hemodynamic database, we analyzed all the consecutive fluid challenges performed between 2001 and 2004 in 96 mechanically ventilated patients hospitalized in our intensive care unit for severe sepsis and septic shock and monitored with a pulmonary artery catheter. The patients had been previously enrolled in two prospective studies, which received institutional review board (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) approvals. Written informed consents were obtained before inclusion in these two prospective studies.

Measurements. All patients were monitored using a pulmonary artery catheter (Swan-Ganz CCO catheter, 7.5 Fr; Baxter Edwards Critical-Care Division, Irvine, CA). The central venous pressure and the PAOP were measured at end-expiration. The correct position of the pulmonary artery catheter in West's zone 3 was checked using a method previously described (6). Continuous thermodilution cardiac output was measured automatically (Vigilance, Baxter Edwards Critical Care).

The decision to give fluid was based on the presence of at least one clinical sign of acute circulatory failure or associated signs of hypoperfusion. In all patients, the volume challenge consisted of the infusion of 500 mL of 6% hydroxyethyl starch in a period 20 mins.

Patients exhibiting an increase in cardiac index induced by the volume challenge of ≥15% and <15% were classified as responders and nonresponders, respectively.

Statistical Analysis. All hemodynamic variables were analyzed as continuous variables and expressed as mean ± SD. The normality of variables was tested using a Kolmogorov-Smirnov test for normality. All variables were normally distributed. The comparison before and after fluid infusion was done using a paired Student's *t*-test. To assess the ability of cardiac filling pressures to distinguish between positive and negative responses to fluid challenge, we first compared the values of each filling pressure measured immediately before the fluid challenge using an unpaired Student's *t*-test. Then receiver operating characteristic (ROC) curves were generated by varying the discriminating threshold of each variable. The area under the ROC curve was calculated and compared using a Hanley-McNeil test (7). The optimal threshold value (the value that maximizes the sum of the sensitivity and specificity) was also defined for each variable. The linear correlations were tested using the Spearman rank method. Statistical analysis was performed using Statview 5.0 software (Abacus concepts, Berkeley, CA) and MedCalc 8.1.0.0 software (MedCalc, Mariakerke, Belgium). For all comparisons, a p value of <.05 was considered significant.

Table 1. Evolution of hemodynamic parameters in responders and nonresponders

	Responders		Nonresponders	
	Pre-infusion	Postinfusion	Pre-infusion	Postinfusion
Heart rate, beats/min	109 ± 21	103 ± 21[a]	105 ± 22	102 ± 21
Stroke volume index, $mL \cdot m^{-2}$	31 ± 12	40 ± 13[a]	38 ± 11	39 ± 12
Cardiac index, $mL \cdot min^{-1} \cdot m^{-2}$	3.2 ± 1	3.9 ± 1[a]	3.7 ± 1	3.8 ± 1
Central venous pressure, mm Hg	8 ± 4	11 ± 4[a]	9 ± 4	12 ± 5[a]
PAOP, mm Hg	10 ± 4	14 ± 5[a]	11 ± 4	16 ± 5[a]
SVRI, mm $Hg \cdot L^{-1} \cdot min^{-1} \cdot m^{-2}$	22 ± 9	19 ± 7[a]	19 ± 8	19 ± 7
MPAP, mm Hg	23 ± 6	29 ± 6[a]	25 ± 7	29 ± 7[a]
PVRI, mm $Hg \cdot L^{-1} \cdot min^{-1} \cdot m^{-2}$	3 ± 3	3 ± 3	3 ± 3	3 ± 3

PAOP, pulmonary artery occlusion pressure; SVRI, systemic vascular resistance index; MPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index.

[a] $p < .05$ pre-infusion vs. postinfusion.

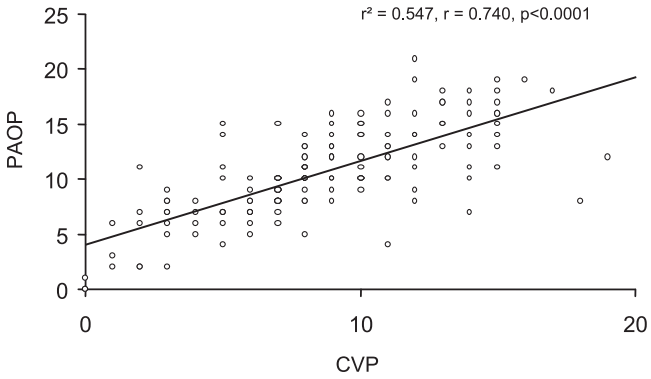

Figure 1. Relationship between central venous pressure (*CVP*) and pulmonary artery occlusion pressure (*PAOP*) before fluid loading in the overall population. Linear correlation: $r^2 = .547$, $r = .740$, $p < .0001$.

RESULTS

A total of 150 fluid challenges were performed in 96 patients (73 men, 23 women; mean age, 62 ± 14 yrs). All the patients were mechanically ventilated with a mean positive end-expiratory pressure of 7 ± 3 cm H_2O. All the patients had clear evidence of sepsis: bacterial pneumonia (67 patients), abdominal sepsis (25 patients), and meningitis (four patients). In 118 of 150 instances (79%), patients received a vasopressor (75% in responders vs. 81% in nonresponders, not significant): norepinephrine in 106 instances (0.02–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine in 12 instances (5–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In no case was the dose of vasopressor changed during the fluid challenge.

In 65 of 150 instances (43%), the volume challenge resulted in an increase in cardiac index of ≥15% (responders). Table 1 shows the mean changes in hemodynamic variables in both groups after volume expansion. Figure 1 shows a significant correlation between central venous pressure and PAOP ($r^2 = .547$, $p < .05$).

Central Venous Pressure

The pre-infusion central venous pressure was not significantly lower in responders than in nonresponders (8 ± 4 vs. 9 ± 4 mm Hg). A large overlap of individual values was observed between the groups (Fig. 2).

The optimal threshold value for prediction of volume responsiveness was 8 mm Hg. The area under the ROC curve was 0.58 (95% confidence interval [CI], 0.49–0.67]. A pre-infusion central venous pressure of <8 mm Hg predicted fluid responsiveness with a sensitivity of 62% (95% CI, 49–73%), a specificity of 54% (95% CI, 43–65%), a positive predictive value (PPV) of 51%, and a negative predictive value (NPV) of 65%.

In the Surviving Sepsis Campaign guidelines (1), a central venous pressure of ≥8 mm Hg was recommended to be tar-

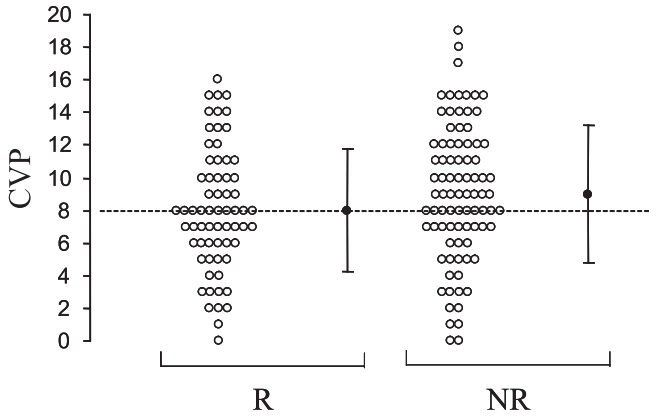

Figure 2. Individual values (*open circles*) and mean ± SD (*closed circles*) of pre-infusion central venous pressure (*CVP*) (both expressed in millimeters of mercury) in responders (*R*) and nonresponders (*NR*).

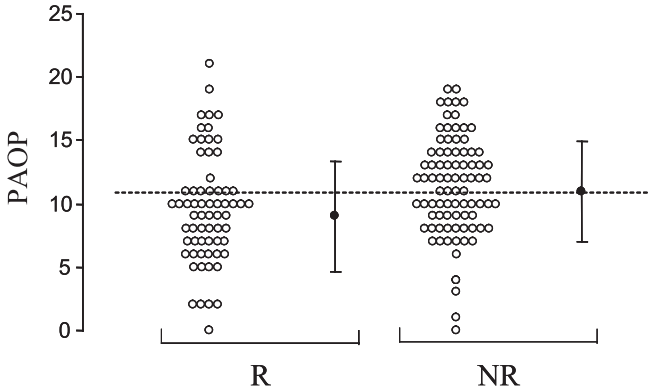

Figure 3. Individual values (*open circles*) and mean ± SD (*closed circles*) of pre-infusion pulmonary artery occlusion pressure (*PAOP*) (both expressed in millimeters of mercury) in responders (*R*) and nonresponders (*NR*).

geted in spontaneous breathing patients and a central venous pressure of 12 mm Hg in mechanically ventilated patients. In our study, because all patients received mechanical ventilation, we also tested this value. A pre-infusion central venous pressure of <12 mm Hg was observed 114 times (76%). For those patients, fluid responsiveness was observed only 53 times (46%). Overall, fluid responsiveness was poorly predicted by a central venous pressure of <12 mm Hg: sensitivity, 82% (95% CI, 70–90%); specificity, 28% (95% CI, 19–39%); PPV, 47%; NPV, 67%.

The prediction was still poor for a very low value of central venous pressure (<5 mm Hg): sensitivity, 23%; specificity, 80%; PPV, 47%; NPV, 58%. However, these latter findings must be cautiously interpreted because the condition of central venous pressure of <5 mm Hg was relatively rare (only 23 times), probably because our patients had been resuscitated before the insertion of the pulmonary artery catheter.

PAOP

The pre-infusion PAOP was significantly lower in responders than in nonresponders (10 ± 4 vs. 11 ± 4 mm Hg, $p < .05$), but a large overlap of individual values was observed between the groups (Fig. 3).

The area under the ROC curve was only 0.63 (95% CI, 0.55–0.70) and was not statistically greater than that generated for central venous pressure: difference between areas, 0.053 (95% CI, 0.01–0.12; $p = .12$).

The optimal threshold value was 11 mm Hg. A pre-infusion PAOP value of <11 mm Hg predicted fluid responsiveness with a sensitivity of 77% (95% CI, 65–87%), a specificity of 51% (95% CI, 40–62%), a PPV of 54%, and a NPV of 74%.

In the updated guidelines of the American College of Critical Care (2), a PAOP of ≥12 mm Hg was recommended to be targeted. A pre-infusion PAOP of <12 mm Hg was observed 92 times (61%). For those patients, fluid responsiveness was only observed 50 times (54%). Overall, the fluid responsiveness was poorly predicted by a PAOP of <12 mm Hg: sensitivity, 77% (95% CI, 65–87%); specificity, 51% (95% CI, 40–62%); PPV, 54%; NPV, 74%.

Combination of Central Venous Pressure and PAOP

From our data, 8 mm Hg of central venous pressure and 11 mm Hg of PAOP were the optimal threshold values. If a patient had a central venous pressure of <8 mm Hg and a PAOP of <11 mm Hg, he or she was likely to be responder, with a sensitivity of 35%, a specificity of 71%, a PPV of 54%, and a NPV of 63%.

Combination of Cardiac Filling Pressures and SVI

Central Venous Pressure and SVI. The significance of central venous pressure to predict a hemodynamic response to volume in patients with low SVI (<30 $mL \cdot m^{-2}$) was evaluated in that population (condition observed in 61 instances). The area under the ROC curve was only 0.54 (95% CI, 0.40–0.67%). When a pre-infusion central venous pressure of <8 mm Hg was associated with a low SVI (<30 $mL \cdot m^{-2}$), the positive prediction was higher than in the overall population but still unsatisfactory: sensitivity, 38%; specificity, 63%; PPV, 61%; NPV, 39%.

PAOP and SVI. The value of PAOP to predict a hemodynamic response to volume in patients with a low SVI (<30 $mL \cdot m^{-2}$) was also evaluated. The area under the ROC curve was only 0.59 (95% CI, 0.45–0.72%). When a pre-infusion PAOP of <12 mm Hg was associated with an SVI of <30 $mL \cdot m^{-2}$, the positive prediction of volume responsiveness was higher but still poor: sensitivity, 78%; specificity, 46%; PPV, 69%; NPV, 58%.

DISCUSSION

Our study demonstrates that in septic patients receiving mechanical ventilation, cardiac filling pressures are poor predictors of fluid responsiveness, even when each filling pressure was interpreted in combination with the knowledge of the other filling pressure or with SVI. Therefore, we definitely believe that the use of PAOP or central venous pressure as targets for volume resuscitation in patients with sepsis must be discouraged. Accordingly, targeting volume therapy to a central venous pressure

between 12 and 15 mm Hg (1) or to a PAOP between 12 and 15 mm Hg (2) does not seem realistic. In our patients, fluid responsiveness was exhibited in only 46% when central venous pressure was <12 mm Hg and in only 54% when PAOP was <12 mm Hg.

Our results are in agreement with other clinical studies showing that neither central venous pressure nor PAOP were reliable predictors of volume responsiveness (8–15). In a few studies, pre-infusion central venous pressure (10, 16) or PAOP (16, 17) was lower in responders, but a large overlap of individual values was observed between the groups, such that no threshold value could be defined.

One would have expected that the knowledge of both PAOP and central venous pressure or that the knowledge of either cardiac filling pressure in combination with stroke volume would give a better prediction of volume responsiveness than the knowledge of a single filling pressure. In fact, our data do not support that hypothesis.

One potential explanation for these findings is that filling pressures are poor indicators of cardiac preload (18) because they are highly dependent on ventricular compliance, which is frequently altered in critically ill patients. It is interesting to note that even in healthy volunteers, PAOP and central venous pressure have been reported as poor markers of preload responsiveness (19). More importantly, there is a physiologic reason explaining that even the most accurate marker of ventricular preload will never be a reliable predictor of volume responsiveness. Indeed, the slope of the Frank-Starling curve (ventricular preload vs. stroke volume) depends on the systolic function. In this respect, in the middle range of preload, a given value of preload can be associated with either some preload reserve and hence volume responsiveness for a normal heart (steep part of the curve) or with the absence of preload reserve in the case of a failing heart (flat part of the curve). This explanation probably accounts for the superiority of dynamic indices attempting to approach the slope of the Frank-Starling curve over "static" markers of preload (4, 5). In this regard, the magnitude of respiratory changes of surrogates of stroke volume have been emphasized as reliable indices of volume responsiveness in patients on sinus rhythm receiving controlled ventilation (4, 5), including septic patients (8, 13, 20). In the light of the present study and of the existing literature, further guidelines of volume resuscitation could incorporate these functional indices, at least in patients who do not experience any inspiratory effort.

Our study has some limitations. First, it was a retrospective analysis of fluid challenges, and some patients experienced more than one volume challenge. Even if it is only theoretical, we cannot exclude that this could have some influence on the results. However, it is unlikely that two different volume challenges were performed in a patient while he or she was in the same hemodynamic conditions. Second, it could be argued that examining the effect of infusion of a limited volume is not relevant to assess volume responsiveness in patients experiencing an increased vascular capacitance and capillary leak. In reference to the preexisting literature, the amount of 500 mL of colloid was rather high than low (4). By choosing this amount, we attempted to prevent the possibility of not identifying volume responders. Moreover, we observed an increase in central venous pressure and PAOP in both groups after fluid loading, suggesting an increase in preload. Therefore, it is unlikely that the amount of fluid was too small to not detect patients who would be responders, although we cannot totally exclude this possibility. Third, although the increase in preload was likely to play a major role in the response to fluid, we cannot exclude the possibility that preload independent mechanisms (changes in vascular tone or myocardial function) had occurred in responders during the fluid challenge, as suggested by the study of Kumar et al. (21) in healthy volunteers. However, in our study, fluid challenge consisted of 500 mL of colloid infusion over 20 mins, whereas it consisted of 3000 mL of saline infusion in the study by Kumar et al (21). Fourth, because of the retrospective study design, we could not focus on the consequences of fluid infusion on regional perfusions. Fifth, the criterion used to classify patients in the responders group was an increase in cardiac index of ≥15%, a benchmark that was frequently used by previous investigators who expected to be far above the errors in measurement of cardiac index by thermodilution (4, 8, 22, 23). Finally, we studied patients hospitalized in our ICU who had been previously resuscitated. In this regard, only a few patients exhibited low values of cardiac filling pressures. Thus, we cannot exclude that knowledge of cardiac filling pressure at the initial phase could be valuable for guiding volume therapy. However, even in this case, it remains true that deliberately attempting to reach the target value of 8 mm Hg of central venous pressure or 12 mm Hg of PAOP, or both, would have resulted in futile volume expansion in a great number of patients. On the other hand, for ethical reasons, our policy is not to perform volume challenges in patients with a PAOP value of >20 mm Hg, conditions in which the absence of response to volume would be expected.

In conclusion, our study demonstrates that in septic patients receiving mechanical ventilation, cardiac filling pressures afford a poor prediction of fluid responsiveness. In the light of these results, targeting volume therapy to central venous pressure and PAOP values should be discouraged, at least after the early phase of sepsis has concluded.

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