Comparative evaluation of central venous pressure and sonographic inferior vena cava variability in assessing fluid responsiveness in septic shock

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Objective: Fluid infusion, the most critical step in the resuscitation of patients with septic shock, needs preferably continuous invasive hemodynamic monitoring. The study was planned to evaluate the efficacy of ultrasonographically measured inferior vena cava collapsibility index (IVC CI) in comparison to central venous pressure (CVP) in predicting fluid responsiveness in septic shock. Materials and Methods: Thirty-six patients of septic shock requiring ventilatory support (invasive/noninvasive) were included. Patients with congestive heart failure, raised intra-abdominal pressure, and poor echo window were excluded from the study. They were randomly divided into two groups based on mode of fluid resuscitation - Group I (CVP) and Group II (IVC CI). Primary end-points were mean arterial pressure (MAP) of ≥65 mmHg and CVP >12 mmHg or IVC CI <20% in Groups I and II, respectively. Patients were followed till achievement of end-points or maximum of 6 h. Outcome variables (pulse rate, MAP, urine output, pH, base deficit, and ScvO2) were serially measured till the end of the study. Survival at 2 and 4 weeks was used as secondary end-point. Results: Primary end-point was reached in 31 patients (15 in Group I and 16 in Group II). Fluid infusion, by either method, had increased CVP and decreased IVC CI with resultant negative correlation between them (Pearson correlation coefficient –0.626). There was no significant difference in the amount of fluid infused and time to reach end-point in two groups. Comparison in outcome variables at baseline and end-point showed no significant difference including mortality. Conclusion: CVP and IVC CI are negatively correlated with fluid resuscitation, and both methods can be used for resuscitation, with IVC CI being noninferior to CVP.

Keywords: Central venous pressure, fluid responsiveness, hypovolemia, septic shock, sonographic inferior vena cava variability

Introduction

Septic shock is a complex interplay of microbial and host defense system (cytokine storm), leading to capillary damage resulting into edema and hypotension. Fluid therapy corrects hypovolemia, improves microcirculation, modulates inflammation, and decreases the need for vasoactive agents.[1-4] However, fluid acts as a double-edged sword as excessive fluid impairs diffusion at the cellular level and has been associated with increased mortality with acute respiratory distress syndrome net cohort demonstrating a positive association between cumulative fluid balance...
and mortality.[5,6] Fluid needs to be used judiciously as a drug in these cases, and intensivists need to have a regular watch over fluid balance of patient. Different types of shock have different pathophysiology, which can be unraveled by different patterns of combination of hemodynamic variables and can totally modify treatment strategy. Hemodynamic monitoring helps speed up treatment decisions and also assess response to them.

Till date, no parameter is ideal, and therefore, the inference needs to be drawn in clinical context. Central venous pressure (CVP), a traditional guide to fluid therapy, needs an invasive procedure to measure the pressure of right atrium which is being used as a surrogate for volume of left ventricle.[7] Its value is altered by intrathoracic pressures, left and right ventricular contractility and may affect the assessment of intravascular volume.[8]

With more emphasis on noninvasive tools, nowadays, more and more simple methods are being developed for fluid assessment. One of them has been the change in inferior vena cava (IVC) diameter with respiration which has shown promising results as a guide to fluid therapy in various other studies.[9‑13] However, IVC collapsibility index (IVC CI) is also affected by intrathoracic pressures and right heart dysfunction similar to CVP. Marked inter-rater variability and lack of expertise in carrying out ultrasonographic (USG) IVC assessment further add to drawbacks of this method.[14] Studies have shown an increase in CVP and decrease in IVC collapsibility with fluid infusion. Correlating these two methods, workers have also shown a negative correlation with fluid infusion, however, with certain limitations.[12,15] Keeping these things in mind, the study was planned to evaluate the efficacy of ultrasonographically measured IVC variability and to find correlation, if any, of same with CVP in predicting fluid responsiveness in patients with septic shock.

Materials and Methods

This prospective, randomized study was carried out in the Intensive Care Unit (ICU) of our institute and the Institutional Review Board approved the study protocol. Selection of patients was done from the emergency department, medical and surgical wards. Thirty-six patients with septic shock who needed ventilatory support (invasive or noninvasive) and fulfilled inclusion and exclusion criteria during 1-year period from first July 01, 2011, to June 30, 2012, were enrolled in the study [Figure 1]. The criteria for inclusion were fulfillment of two out of four criteria for systemic inflammatory response syndrome, probable or suspected septic etiology, systolic blood pressure <90 mmHg or mean arterial pressure (MAP) <70 mmHg despite adequate fluid challenge (20 ml/kg of normal saline infused over half hour), and positive pressure ventilation. Criteria for exclusion were pregnancy or other causes of raised intra-abdominal pressure, patients in whom USG could not be done because of poor echo window or dressings, acute coronary syndrome, cardiac dysrhythmias (as a primary diagnosis), congestive heart failure, pulmonary embolism, status asthmaticus, contraindication to central venous catheterization, burn injury, requirement of immediate surgery, and do-not-resuscitate status.

After admission to the ICU, patients were put on a ventilator and central venous catheterization was done. Ventilatory mode and positive end-expiratory pressure applied were recorded for each patient. Echocardiography of patients was done to assess cardiac contractility and to rule out congestive heart failure. Patients were divided into two groups (Groups I and II) depending on the method of fluid resuscitation, and randomization was done by envelope method. Group I patients (18) were resuscitated according to CVP and Group II patients (18) were resuscitated according to IVC CI. CVP was measured by central venous catheters inserted in either subclavian or internal jugular vein with its tip positioned in superior vena cava just proximal to the right atrium. It was measured at zero point which

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**Figure 1: Overview of patient enrollment and hemodynamic support**
corresponds with phlebostatic axis. Phlebostatic axis was taken as the line where a coronal plane midway between the back and sternum (in practice, the midaxillary line) intersects a cross-sectional plane through the fourth intercostal space. The CVP was measured in the end-expiratory phase of respiration using a column of saline which was later on converted into mmHg by dividing it by 1.3. The IVC assessment was made using hand-carried USG unit (Micro Maxx with P17 1–5 MHz phased array probe; Sonosite) with the patient in the supine position using an acoustic window inferior to the xiphoid, angling to the right. The cross-sectional image of the IVC was visualized at the right atrial/hepatic vein/IVC junction and then rotated so that a long axis view of the IVC was obtained. M mode was applied at approximately 1 cm distal to the IVC-hepatic vein junction where the anterior and posterior walls were clearly visualized. For the sake of simplicity, maximum and minimum diameters were measured in each respiratory cycle. IVC CI was calculated as (maximum diameter on inspiration − minimum diameter on expiration)/minimum diameter on expiration and expressed in percentage [Figure 2]. Video recordings of measurements were later on cross-checked by a senior radiologist (Jyotsna Sen) at our institute.

$$\text{IVC CI} = \frac{\text{IVC}_i - \text{IVC}_e}{\text{IVC}_e}$$

Both of these variables were recorded in each patient every half-hourly till initial 3 h and then hourly for next 3 h or till end-point was reached. Patients were given a fluid bolus 500 ml of crystalloid half-hourly after measuring CVP and IVC CI till target levels of CVP or IVC CI were achieved in respective groups. Vasopressors were started in situations of nonachievement of desired MAP despite reaching end-point CVP or IVC CI values.

Primary end-points were MAP of \(\geq 65\) mmHg and CVP >12 mmHg or IVC CI <20\% in Groups I and II, respectively. Patients were observed till either primary end-points were reached or up to maximum of 6 h. Patients were followed till 4 weeks and survival at 2 and 4 weeks was used as secondary end-point in the study. Outcome variables (pulse rate [PR], MAP, urine output, pH in arterial blood gas, base deficit, and ScvO\(_2\)) were serially measured in both groups at 0, 3 h, and end of the study.

**Statistical analysis**

Both descriptive and analytical statistics were used in the study as appropriate. The values were expressed as mean ± standard deviation. IVC CI values >100\% were taken as 100\% for the sake of statistical analysis. Correlation between CVP and IVC CI was calculated by Pearson correlation coefficient. Kaplan–Meier estimates were used to graphically represent mortality difference and time to resuscitation between study groups. Paired \(t\)-test was used to calculate any difference in outcome parameters after fluid resuscitations in both groups. Unpaired \(t\)-test was used for comparison of intergroup data. \(P < 0.05\) was considered statistically significant.

**Results**

Thirty-six patients of septic shock on a ventilator were randomly divided into two groups based on mode of fluid resuscitation - Group I (CVP) and Group II (IVC CI). There was no significant difference between two groups in baseline characters (age, Acute Physiology and Chronic Health Evaluation [APACHE] score on presentation, PEEP applied, and mean fluid infused) during the study [Table 1]. Etiology of sepsis was found in 24 cases (pneumonia, scrub typhus-induced ALI, abdominal sepsis, and cellulitis in 8, 6, 5, and 5 cases, respectively), while in 12 cases, the cause of sepsis was not found [Table 2].

![Figure 2: Calculation of inferior vena cava collapsibility index ([A–B]/B) (%) using ultrasonography](image_url)
IVC CI values on admission were very high and variable; to eliminate its effects on results, all values >100% were taken to be 100%. With fluid infusion, CVP values increased and IVC CI values decreased in both groups. Correlating CVP and IVC CI among patients, we found moderately negative correlation with a Pearson correlation coefficient −0.626 in total observations [Figure 3]. Coefficient was higher in patients who were resuscitated with IVC CI [Figures 4 and 5] as a tool (−0.535 in Group I and −0.709 in Group II). We did subgroup analysis to find the effect of ventilation on correlation (Group A = Invasive [17], Group B = Noninvasive [19]). Correlation coefficient was found to be comparable in both subgroups (−0.588 in invasive subgroup and −0.562 in noninvasive subgroup).

With resuscitation, PR, MAP, pH, and base deficit improved significantly in both groups, but urine output and ScvO₂ increased in Group II only [Table 3]. Survival at 2 and 4 weeks was used as a secondary outcome, and there was no significant difference in both groups [Table 4 and Figure 6].

Discussion

The incidence of sepsis and its complications is increasing despite the evolution of scientific technology. Septic shock and multiple organ dysfunction syndrome still remain a treatment challenge for both primary care physicians and intensivists. The treatment remains mainly supportive, and mortality increases disproportionally with the development of organ failure emphasizing the need for its prevention.

Since the concept of the ICUs in the 1950s, the hemodynamic monitoring has traveled a long way but is still at crossroads. More invasive techniques became popular with time. CVP has been used and recommended since long for fluid resuscitation in septic shock.[3,16] However, since CVP is unable to predict exact volume status, it should not be used to make clinical decisions regarding fluid management.[17] In recent times, the pendulum has swung toward noninvasive, simple techniques which are less time consuming. Portable sonographic machines have increased the popularity of variation in IVC dimensions with respiration and fluid infusion in intensive care. Initially, IVC diameter

| Table 3: Comparison of outcome variables at baseline and end of study |
|---------------------------------------------------------------|
|                  | Baseline |      |          |          |
|                  |          |      |          |          |
| Pulse rate       |          |      |          |          |
| Group I          | 125.66±19.90 | 108.11±14.16 | 0.002 |
| Group II         | 126.11±17.55 | 105.05±16.59 | 0.001 |
| P value          | 0.944     | 0.556 |          |          |
| Mean blood pressure (mm Hg)   |          |      |          |          |
| Group I          | 52±10.52 | 68.56±15.88 | 0.001 |
| Group II         | 51.05±9.09 | 69.83±13.12 | 0.001 |
| P value          | 0.772     | 0.795 |          |          |
| pH               |          |      |          |          |
| Group I          | 7.27±0.10 | 7.35±0.11 | 0.0022 |
| Group II         | 7.22±0.14 | 7.28±0.13 | 0.012 |
| P value          | 0.305     | 0.086 |          |          |
| Base Deficit     |          |      |          |          |
| Group I          | -9.40±5.95 | -7.61±6.33 | 0.026 |
| Group II         | -13.32±6.30 | -11.29±6.97 | 0.030 |
| P value          | 0.087     | 0.113 |          |          |
| UrineOutput (ml/hr) |          |      |          |          |
| Group I          | 45.83±38.19 | 59.59±46.60 | 0.410 |
| Group II         | 51.44±54.08 | 80.94±80.40 | 0.022 |
| P value          | 0.721     | 0.347 |          |          |
| ScvO₂ (%)        |          |      |          |          |
| Group I          | 69.45±13.21 | 72.16±12.34 | 0.273 |
| Group II         | 69.67±12.04 | 75.02±11.24 | 0.034 |
| P value          | 0.966     | 0.479 |          |          |

| Table 4: Survival in both groups at 2 and 4 weeks |
|-----------------------------------------------|
| Survival at 2 weeks (n) | Survival at 4 weeks (n) |
| Group I          | 9                        | 9                        |
| Group II         | 8                        | 7                        |

n=Number of patients.
was explored as a static parameter and was shown to decrease with dehydration indicating the need of fluid resuscitation.\[18\] As understanding of the physiology of IVC mechanics improved, intensivists started using variability in diameter with respiration. IVC CI, a dynamic tool, has been shown in studies to predict preload responsiveness.\[9,10,19\]

In our study, we used both CVP and IVC CI to evaluate the efficacy of IVC CI and tried to find correlation, if any, between two modalities. The study is in conformity with other studies on the correlation of CVP with IVC CI on fluid resuscitation.\[12,13\] With fluid resuscitation, CVP increased and IVC CI decreased and they were negatively correlated (−0.626) with higher correlation in Group II (−0.709 in Group II vs. −0.535 in Group I). This may be partly explained by more fluid infused, although not significantly different, in Group II than Group I (3.56 ± 1.42 L vs. 2.91 ± 0.60 L). These findings are comparable to the previous studies.\[12\] Mode of ventilation had no effect on same (−0.586 in Subgroup I vs. −0.562 in Subgroup II).

With resuscitation, there was no significant difference in outcome variables (PR, mean blood pressure, pH, and base deficit) and mortality in both groups at baseline and after resuscitation. The difference in urine output may be explained by the fact that more fluid, although not significantly different, was infused in Group II.

Target ScvO\(_2\) >70% was used by River et al. in early goal-directed therapy;\[3\] however, the incidence of low ScvO\(_2\) has been shown to be less in septic patients by other workers.\[20-22\] As ScvO\(_2\) was >65% at baseline in majority of patients, an increase in its value with resuscitation got nullified despite a significant increase in Group II. We had a higher mortality of 52.7% in our study population with mean APACHE of 21 (approximately) in both groups, which is in contrast with a predicted mortality of 40% (corresponding to mean APACHE score of 21).\[23\]

Although the sample size is small, the study demonstrates that measurement of IVC CI is noninferior to CVP for fluid resuscitation in patients of septic shock on ventilation, despite their respective limitations. Therefore, IVC CI can be used to fluid resuscitate patients of septic shock, whenever or wherever there is difficulty or challenges in measuring or interpreting CVP. Measurement of IVC CI with USG, thus, is an important tool in the armamentarium of intensivists to make decisions about fluid resuscitation and its adequacy on patients’ bedside.

**Limitations of the study**

The wide variation in IVC CI was a major limitation of the study. Poor acoustic window, especially in noninvasively ventilated patients, due to spontaneous respiratory efforts and uncooperativeness of patients was commonly encountered. Therefore, if the operator is inexperienced, one can have false values leading to both over and under estimation. We tried to overcome it by having the values measured by a single operator (M) and later on reviewed by a senior radiologist (Jyotsna Sen). However, still one cannot completely rule out aberrations in measurement on this account.

Outcome parameters might have been influenced by the use of vasopressors. Since we did not study the duration and dosing of vasopressors used, we are not in a position to state their role in reaching end-points.

Lactate levels and clearance were not measured, but rather a surrogate marker of it (base deficit) was calculated in patients. Similarly, although there was an improvement in ScvO\(_2\) after resuscitation, its baseline values were above 65%. In addition, the cause for higher mortality among subjects could not be deciphered.
Finally, due to single center and small sample size, extrapolation of our findings to a large subset of population should be judiciously addressed.

Conclusion

With fluid infusion, a negative correlation was observed between CVP and IVC CI. Correlation coefficient was more in Group II; however, because of small sample size, we are not in a position to generalize this fact. Both methods resulted in improved resuscitation outcomes, with IVC CI being noninferior to CVP, can be used effectively in fluid resuscitation.

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Conflicts of interest
There are no conflicts of interest.

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