Introduction

Sepsis is defined as life-threatening organ dysfunction due to a deregulated host response to infection which can result in grave complications such as septic shock which is a subset of infection with circularity and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. One of the lines for the treatment is to administer intravenous fluids as the first step to improve blood pressure [2]. A fluid challenge will cause an increase in stroke volume only when patients’ cardiac preload is in the low volume status [3], [4]. Determining the optimal amount of fluid to be administered remains a critical issue through continued inquiry. Analysis of large databases suggests that there may be a U-shaped response curve, where limited amounts as well as large amounts of fluid administration are associated with worse outcomes. The best response was observed when fluid resuscitation was administered in volumes between 15 and 45 mL/kg [5]. However, studies have shown that not every patient advantages from aggressive intravenous hydration [6]. Only 40% of hypotensive patients with sepsis respond to it with improvement in blood pressure [2], [7]. Those who do not respond are liable to develop high intravascular pressure, pulmonary edema, or acute heart failure with high associated mortality [8], [9], [10].

Therefore, precise fluid resuscitation and careful assessment of fluid responsiveness should be fastidiously evaluated and always weigh between the benefits and the risks of intravenous fluids [11]. Static indicators of fluid responsiveness such as central venous pressure (CVP) and pulmonary capillary wedge pressure are poor predictors of fluid responsiveness [12], [13]. In contrast, indices relying on the cardiopulmonary interactions in mechanically ventilated patients have been shown to be good predictors of fluid responsiveness [13]. Respiratory variation in aortic blood peak velocity had high sensitivity and specificity to predict fluid responsiveness [14], [15]. However, measurements of aortic blood flow velocity need a transesophageal ultrasound which is an invasive procedure. Several studies had been done to evaluate the noninvasively respiratory variation of brachial artery peak velocity to predict fluid responsiveness in mechanically ventilated patients and concluded that it is a feasible tool for predicting fluid responsiveness, with
efficiency similar to other well-known dynamic parameters of preload [16], [17]. Measures of carotid artery flow or inferior vena cava (IVC) diameter (IVC-d) were recently shown to predict fluid responsiveness [16], [17], [18].

**Aim of the study**

Our aim is to assess the fluid responsiveness by measuring carotid Doppler peak velocity and respiratory variation in IVC-d against the increase in the cardiac index by echocardiographic calculations as a reference in mechanically ventilated patients in septic shock.

**Methods**

This is a multicenter, prospective, and cohort study on 30 critically ill mechanically ventilated patients in septic shock. We included in our study only patients who were mechanically ventilated and in septic shock for which the treating intensivist was considering fluid challenge and titration of vasopressor doses based on patients’ response to therapy. The study was performed in Cairo University Intensive Care Unit, Assalam International Hospital, and Al Safa Hospital for 1 year. We excluded patients <18 years, shock other than septic shocks, known cardiac disease, end-stage renal disease who required hemodialysis, intra-abdominal hypertension, and carotid artery stenosis >55%. All the patients were subjected to IV fluid bolus by 7 ml/kg crystalloid solution over 30 min. Static and dynamic indices were obtained before fluid bolus (T0) and after fluid bolus (T1) by a well-trained echocardiography operator. Patients who achieved an increase of 15% or more in the cardiac index were classified as “responders” (R), and those with an increase of <15% in CO or those with no increase were classified as “non-responders” (NR). CVP, mean arterial pressure, pulse pressure, difference between diameters of IVC during inspiration and expiration (ΔIVC-d) in single respiratory cycle, and difference between velocities of carotid Doppler peak velocity in single respiratory cycle (ΔCDPV) were all measured by the same well-trained echocardiography operator then data were calculated and followed (Figure 1).

Carotid peak systolic velocity was measured using a 5–10-mHz linear array transducer. Devices used were: GE LOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia. At 50% in this patient and Toshiba Xario™ 200- Japan: Maximum and minimum peak systolic velocities were measured in a single respiratory cycle, and the respiratory variation in carotid Doppler peak velocity “ΔCDPV” was calculated with the following formula:

\[
\frac{\text{MaxCDPV} - \text{MinCDPV}}{\text{MaxCDPV} + \text{MinCDPV}} \times 100,
\]

expressed as a percentage [18]. IVC-d measurement was performed with a two views IVC using 2–6 MHz curved transducer with longitudinal two views at a subxyphoidal long axis just caudal to the hepatic vein inlet. Devices used were: GE LOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia, and Toshiba Xario™ 200- Japan. Maximum and minimum diameters over a single respiratory cycle were recorded and respiratory variation in IVC-d was calculated with the formula:

\[
\frac{\text{Max IVC-d} - \text{Min IVC-d}}{\text{Max IVC-d} + \text{Min IVC-d}} \times 100,
\]

expressed as a percentage [19].

Cardiac output was measured using a 1.5–7-mHz phased array transducer. Devices used were: GE LOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia, and Toshiba Xario™ 200- Japan. Two views were obtained: Long parasternal view and apical five chambers view. Measurement of LVOT diameter was obtained in the parasternal long axis view during systole while assess LVOT Velocity Time Integral: Using pulsed wave Doppler in the apical five chamber view. Stroke volume was calculated with the formula: Stroke volume = left ventricle outflow tract “LVOT” area × LVOT velocity time interval “VTI” = \( \text{Pi} \times 3.14 \times (\text{LVOT diameter/2})^2 \times \text{LVOT VTI} \) [20]. Then, cardiac output was calculated by formula: Cardiac output = stroke volume × heart rate. The parameters on the ventilator were kept constant during data recording. Inotropes or vasopressors rate was not changed and stimulation of the patients was avoided.

Data were summarized by descriptive statistics using mean, standard deviation, median, minimum and maximum in quantitative data, and using frequency (count) and relative frequency (percentage) for categorical data. Mean values and standard deviation were compared using simple t-test (for two variables) or ANOVA test (for more than two variables). Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [21]. For comparing categorical data, Chi-square (\( \chi^2 \)) test was performed. Exact test was used instead when the expected frequency is <5 [22]. Correlations between quantitative variables were done using Spearman correlation coefficient [23]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of

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**Figure 1:** Measurement of variation in carotid peak systolic velocity. At 50 % in this patient.
significant parameters for detection of responders. Data were coded and entered using the statistical package Statistical Package for the Social Sciences version 25. P ≤ 0.05 was considered statistically significant.

Results

In our study, we included 30 patients in septic shock on controlled mechanical ventilation according to the inclusion criteria, positive culture results, and need of vasoactive drug infusion. Stroke volume, CVP, IVC-d, and CDPV were measured in all patients before and after fluid boluses. Baseline characteristics of the patients are shown in Table 1.

Table 1: Characteristics and baseline parameters before all fluid challenges between responders and non-responders

| Variable          | Responsive (n: 21) | Non-responsive (n: 9) | p-value |
|-------------------|-------------------|----------------------|---------|
| Age (years)       | 64.95 ± 12.59     | 68.22 ± 21.18        | 0.191   |
| Gender            |                   |                      |         |
| Male              | 10 (48%)          | 6 (67%)              | 0.440   |
| Female            | 11 (52%)          | 3 (33%)              |         |
| APACHE II         | 16.05 ± 3.23      | 18.44 ± 3.81         | 0.164   |
| SOFA score 0      | 11.48 ± 2.82      | 12.11 ± 2.80         | 0.625   |
| SOFA score 5      | 12.95 ± 3.68      | 12.56 ± 3.97         | 0.790   |
| TLC (×10^3/μl)    | 17.19 ± 8.38      | 18.60 ± 10.18        | 0.859   |
| Lactate (mmol/l)  | 6.36 ± 3.64       | 8.04 ± 4.67          | 0.397   |
| Mortality rate    | 17 (81%)          | 7 (77.8%)            | 1       |
| Comorbidities     |                   |                      |         |
| Hypertension      | 3 (62%)           | 5 (56%)              | 1       |
| Diabetes mellitus | 8 (38%)           | 5 (56%)              | 0.443   |
| Ischemic heart disease | 9 (43%) | 5 (56%) | 0.694 |
| Immuno compromised | 8 (38%)         | 5 (56%)              | 0.443   |
| Malignancy        | 5 (29%)           | 4 (44%)              | 0.431   |
| Chronic kidney disease | 3 (14%) | 3 (33%) | 0.329 |
| COPD              | 4 (19%)           | 1 (11%)              | 1       |

All data are expressed as mean (standard deviation). TLC: Total leukocytes count, APACHE II: Acute Physiology and Chronic Health Evaluation II, range from 0 to 71, SOFA: Sequential Organ Failure Assessment score, range from 0 to 24, with higher scores indicating a greater risk of mortality.

Pneumonia was the most common cause of sepsis in our study (42.4%) followed by soft-tissue infection and urosepsis in six patients each (18.2% for each). Acute Physiology and Chronic Health Evaluation II score was calculated for all patients within 24 h of diagnosis of septic shock (16.8 ± 3.5). Sequential Organ Failure Assessment (SOFA) score was calculated for all patients within 24 h of diagnosis of septic shock (16.8 ± 3.5). Sequential Organ Failure Assessment score, range from 0 to 24, with higher scores indicating a greater risk of mortality.

Discussion

Our study showed that ∆CDPV was more precise and easier in interpretation than other older methods (CVP and respiratory variation in IVC-d) for evaluating fluid responsiveness in septic shock and mechanically ventilated patients. Furthermore, the ∆CDPV has a high correlation with stroke volume index (SVI) increase after fluid boluses. Cardiac output and stroke volume measured by echocardiography had the highest significant values among the whole parameters that were measured either static or dynamic (p = 0.007 and 0.01), respectively, with sensitivity and specificity 81%, specificity 66.7%, and p = 0.046. There were no correlation between IVC parameters and carotid artery parameters. ROC curve was calculated for the use of ∆CDPV as a diagnostic tool of fluid responsiveness in septic shock. The optimal cutoff point was ≥26% with a good sensitivity (Table 3).

Table 2: Responders versus non-responders main parameters before and after fluid boluses

| Variable   | Responsive (n: 21) | Non-responsive (n: 9) | p-value |
|------------|--------------------|-----------------------|---------|
| ∆CVP       | 5.86 ± 5.22        | 7.22 ± 4.82           | 0.689   |
| Before IV fluids  | 5.26 ± 4.42   | 6.95 ± 6.55           | 0.722   |
| After IV fluids   | 10.62 ± 5.73  | 5.82 ± 5.26           | 0.011*  |
| SV          | 104.81 ± 50.89    | 115.56 ± 82.56        | 0.529   |
| Before IV fluids  | 141.33 ± 84.39 | 95.22 ± 61.67         | 0.022*  |
| After IV fluids   | 11.91 ± 9.41  | 12.18 ± 5.83           | 0.449   |
| ∆D-IVC      | 13.51 ± 9.56      | 9.28 ± 7.22           | 0.104   |
| Before IV fluids  | 24.43 ± 11.87  | 24.78 ± 10.49         | 1       |
| After IV fluids   | 33.22 ± 11.00  | 23.67 ± 10.27         | 0.045*  |

Data were written as mean (standard deviation). ∆CDPV: Respiratory variation in carotid Doppler peak velocity; SV: Stroke volume; ∆D-IVC: Respiratory variation in inferior vena cava diameter; CO: Cardiac output; CVP: Central venous pressure.
specificity (86% and 89%), respectively, and this proves that it should be the reference tool for any new tests evaluating fluid responsiveness. Similarly, Philippe Vignon et al. found that an increase of aortic blood flow of 10% or more during passive leg rising has a good sensitivity and specificity (97% and 94%, respectively) in identifying fluid responders [24]. Moreover, another study concluded that respiratory variations in VTI can predict fluid responsiveness in ventilated patients, at a threshold of 20%. Even though they proved that the respiratory variations in peak aortic flow predict fluid responsiveness in patients with septic shock under mechanical ventilation have a high sensitivity with a calculated threshold of 12% [25]. Furthermore, Feissel et al. reported high accuracy, sensitivity, and specificity (100% and 89%, respectively) of respiratory variation in aortic blood velocity (cutoff value >12 %) for prediction of fluid responsiveness in mechanically ventilated septic shock patients [26]. In the same time, CDPV shows the second higher specificity for fluid responsiveness after cardiac output measured by echocardiography. (p = 0.012, AUROC of 0.73, 95% CI: 0.531–0.934 with sensitivity and specificity of 0.81 and 0.66) according to the statistical calculations: (Figure 2).

Our results were nearly similar as Song et al. who conducted an analytical study on 40 patients post-operative elective coronary artery bypass surgery and divided patients as responders if SVI increased ≥15% after volume administration by IV bolus 6 ml/kg. The CDPV was calculated as the difference between the highest and lowest values of peak velocity over a single respiratory cycle as our study and shows that the AUC of CDPV was 0.85 (p < 0.001, 95% CI: 0.72–0.97) with sensitivity and specificity of 0.83 and 0.82) [27]. It has a higher sensitivity and specificity compared to our study as the population of the study was more homogeneous than our patients (Post-CABG vs. Septic shock). On the same stream, Miguel et al. concluded that the ΔCDPV had an AUROC of 0.88 (95 % CI 0.77–0.95) and has a superior predicting power for fluid responsiveness compared to stroke volume variation [14]. Besides the previous studies, an observational study was done on 49 patients of which 27 patients were classified as responders for the fluid challenge (responder group) and 22 as non-responders. There were no statistically significant differences in demographic and clinical variables while ΔCDPV was found to be the best predictor of fluid responsiveness value for fluid responders (in comparison with stroke volume variation, ultrasound assessments of respiratory variations in IVC-d [ΔIVC], and brachial artery peak velocity). It was associated with 78% sensitivity and 90% specificity and AUC of 0.910 [28].

On the other hand, respiratory variation of IVC-d showed no significant change before and after fluid challenge (11.91 ± 9.41 % vs. 13.51 ± 9.56%, respectively, with p = 0.87). Our results were similar to the study done by Peter Bentzeret who carried out a large meta-analysis (n = 173 patients) which showed that 95% CI for likelihood ratios—the probability of the test to be positive in patients with the disease to probability to be positive in patients without disease – are wide values – the percentage of variation across studies – are high which indicate a high degree of heterogeneity [29]. Furthermore, Muller et al. found that in 40 spontaneously breathing shocked patients, the respiratory variations of IVC performed are not better than static indices of preload, such as measuring the pulmonary artery occlusion pressure. In this trial, respiratory variability in IVC-d (>40%) was mostly fluid responsive, but lower values were not. Therefore, it does not have a significant threshold value [30]. However, on contrary to those studies, some studies such as Barbier et al. who studied the validity of respiratory variations in IVC to predict fluid responsiveness in mechanically ventilated patients and found that these measurements were initially validated in patients on mechanical ventilation, with 12 and 18% cutoff values separating fluid non-responders from responders [31]. This discrepancy can be explained as IVC-d can be affected by multiple factors, for example, operators variance, the IVC can moving in and out of the plane of US beam with respiration, mimicking a false changes in measures. Moreover, work of breathing with any spontaneous ventilation has a significant impact on IVC size over the respiratory cycle [32].
Conclusions

Our study showed that ΔCDPV was a more precise and easier assessment tool with better sensitivity and specificity for evaluation of fluid responsiveness than the IVC-d in patients with septic shock on mechanical ventilation. Furthermore, ΔCDPV has a high correlation with SVI increasing parameters assessed by echocardiography after fluid boluses. On the other hand and in comparison, CVP showed low accuracy in predicting fluid responsiveness. Echocardiography was still our gold standard method for fluid assessment as it showed very high specificity and sensitivity for fluid response.

Limitations

Other than the need for a well-trained operator for assessment of the IVC, carotid Doppler, and echography within a short time after admission of included patients for proper assessment of fluid response; there were no other limitations.

Further studies

We need further studies and meta-analysis to focus on carotid Doppler measurement against IVC-d or against echocardiography assessment to clarify the best method for evaluation of fluid responsiveness.

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