Abstract

**Background:** Prediction of Fluid Responsiveness (FR) is a critical step in management of patients with septic shock. Using ultrasound in detection of Inferior Vena Cava (IVC) diameters and collapsibility is established in mechanically ventilated patients; however its use in spontaneous breathing patients is still controversial. Few studies reported a correlation between internal jugular vein dimensions and Central Venous Pressure (CVP) but no data are available about the use IJV dimensions in detection of FR.

**Objective:** The aim of our study is to determine the possible rule of IVC diameters, collapsibility, and IJV dimensions in prediction of FR in spontaneously breathing patients.

**Methods:** Forty spontaneously breathing patients with septic shock were included in the study. Ultrasound examination was done before fluid resuscitation. IVC minimal and maximum diameters, IVC caval index (IVC maximum IVC minimum/IVC maximum), IJV aspect ratio (IJV vertical diameter/IJV transverse diameter) were measured before fluid resuscitation. Transthoracic Echocardiography (TTE) was done to determine Fluid Responsiveness (FR) which was defined as increase in subaortic Velocity Time Integral (VTI) >15% after fluid bolus. Sensitivity, specificity and Area Under Operating Characteristic (AUROC) curves were determined for all ultrasound parameters as well as CVP for detection of FR.

**Results:** Twenty six patients (65%) were fluid responders. AUROC (95% CI) for prediction of FR was: 0.57 (0.3-0.84) for CVP, and 0.64 (0.4-0.88) for IVC maximum diameter. AUROC (95% CI) was 0.93 (0.83-1.00) for IJV minimum diameter with a sensitivity of 90% and 70% respectively at a cut-off value of 0.9cm and was 0.96 (0.89–1.00) for caval index with a sensitivity and specificity of 92% and 86% respectively at a cut-off value of 35%. AUROC for IJV aspect ratio 0.53 (0.24-0.82).

**Conclusions:** IVC minimum diameter and caval index are useful methods to predicted FR in spontaneously breathing patients with septic shock.

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**Key Words:** Fluid responsiveness – IVC – CVP – FR.

Introduction

**SEPSIS** is a systemic, deleterious host response to infection. It is defined as systemic inflammatory response to infection. Severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are common squeals of sepsis. Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (and often more), and are increasing in incidence [1].

Sepsis induced hypotension is defined as a Systolic Blood Pressure (SBP) <90mmHg or Mean Arterial Pressure (MAP) <70mmHg or a SBP decrease >40mmHg or less than two Standard Deviations (SD) below normal for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypo perfusion is defined as infection-induced hypotension, elevated lactate, or oliguria [1].

Early quantitative resuscitation improved survival for Emergency Department patients presenting with septic shock, this strategy is termed early goal-directed therapy [2]. A large number of studies using similar forms of early quantitative resuscitation in different patient populations have shown significant mortality reduction compared to the institution’s historical controls [3].
The surviving sepsis campaign guidelines 2012 recommended an initial fluid challenge in patients with sepsis-induced tissue hypo perfusion with suspicion of hypovolemia to achieve a minimum of 30mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients. It recommended also that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables [1].

The cornerstone of resuscitation of hemodynamically unstable critically ill patients is often considered to be fluid loading. However, only roughly half of hemodynamically unstable patients respond to a fluid challenge, defined as an increase in stroke volume or cardiac output upon fluid loading [4,5]. Although rapid optimization of volume status has shown to improve outcome, extended fluid loading is associated with increased morbidity and mortality [6-9]. Little evidence is available for the type and exact dosing of fluid administration. Establishing volume status is complex, making accurate prediction of an increase in stroke volume upon fluid loading, so-called fluid responsiveness, difficult. Static cardiac filling pressures such as central venous pressure have shown to be incapable of predicting fluid responsiveness accurately. Dynamic parameters on the other hand, using mechanical ventilation-induced changes in preload to track subsequent changes in stroke volume, have shown promise and have been the subject of extensive research in critically ill patients. New methods have been conceived that can easily be used at the bedside in a large variety of patients [4].

Inferior Vena Cava diameter (IVCd), or more specifically the variation in vena cava diameter during respiration as seen by echocardiography, is a dynamic mechanism by which fluid responsiveness can be measured. Much like SVV, IVCd variation during respiration is a function of increasing and decreasing intra-thoracic pressures during respiration and has proven to be an accurate metric of volume responsiveness in mechanically ventilated patients [10-12]. IVCd is measured subcostally, approximately 0.5-4cm below the junction of the IVC and the right atrium, in the longitudinal direction at a perpendicular angle to the IVC.

Variation in IVCd is calculated as "the change" in IVCd during inspiration as compared with baseline (during expiration). Normative values for IVCd have been described in several studies, and, depending on the clinical scenario, range from 8 to 40mm [13,14]. Variation of greater than 10-18% in IVCd during a respiratory cycle has been shown to be predictive of volume responsiveness in several studies, (sensitivity ranging from 50% to 100%; specificity ranging from 53% to 100%, predefined variation [15-17].

Bedside ultrasonic measurement of caval index greater than or equal to 50% is strongly associated with a low central venous pressure. Bedside measurements of caval index could be a useful noninvasive tool to determine central venous pressure during the initial evaluation of the Emergency Department (ED) patient [18].

**Objective:**

The aim of our study is to determine the possible rule of IVC diameters, collapsibility, and IJV dimensions in prediction of FR in spontaneous breathing patients.

**Patients and Methods**

After obtaining the ethical committee approval and patient relative consent, a prospective observational study was conducted in surgical ICU in Emergency Department in Cairo University Hospitals from Dec. 2012-Dec. 2013. Forty successive patients aged above 18 years, with septic shock (diagnosed as systemic inflammatory response of infectious origin complicated by circulatory failure in the form of MAP <65mmHg) on admission to the ICU were enrolled in the study. Exclusion criteria were technical difficulties for ultrasound examination of neck and abdomen, patients with right sided heart failure, patients with tricuspid valve lesions, and mechanically ventilated patients.

Patients were managed according to early goal directed therapy guidelines receiving 500ml normal saline every 15 minutes till reaching the goals of initial resuscitation.

All patients had an ultrasound examination before fluid administration. A long-axis sub-xiphoid view with a 2-4MHz curvilinear probe was done where a two-dimensional echocardiographic sector was used to visualize the inferior vena cava, approximately 3cm from the right atrium. Maximum and minimum IVC diameter values over a single respiratory cycle were collected. The IVC caval index was calculated as the relative decrease in
inferior vena cava diameter during a normal respiratory cycle (maximum IVC diameter-minimum IVC diameter/maximum IVC diameter).

Using the 6-13MHz probe of the, the image of the IJV was obtained in transverse view. Care was taken to position the probe perpendicular to the skin and the long-axis of the vessels at their level in the lower one-half of the neck applying the minimum pressure necessary to obtain the image to avoid distortion of the IJV. The aspect ratio (longest diameter/shortest diameter) for IJV was calculated.

The sub-aortic Velocity Time Index (VTI) was recorded by pulsed wave Doppler on a five-chamber apical view of transthoracic Echocardiography upon inclusion in the study and after 30ml/kg fluid bolus in order to identify fluid responders. VTI was measured in triplicate then the obtained values were averaged for its determination.

Participants were stratified into fluid responders (defined as patients in whom Velocity Time Index (VTI) increased >15% of the baseline value after resuscitation) and fluid non-responders (defined as patients in whom VTI didn't increase >15% after resuscitation).

Both groups were compared as regarding demographic data, acute physiology and chronic health evaluation score II (APACHE II), length of ICU stay, 28 days mortality, hemodynamic data (heart rate, blood pressure and CVP) and ultrasound indices (IVC and IJV diameters).

Sensitivity and specificity for all measured data (CVP, IVC minimum diameter, IVC maximum diameter, IVC collapsibility index, IJV aspect ratio in detection of fluid responders were determined.

Statistical analysis:
Sample size calculation: It was assumed that IVC collapsibility index would be clinically relevant if the 95% Confidence Interval (CI) of its Area Under the Curve (AUC) was >0.75, corresponding to an AUC of a good clinical tool. For this purpose, 39 patients had to be included.

Continuous data were expressed as mean (standard deviation) and analyzed using non-parametric Mann-Whitney test. Categorical data were expressed as frequency (percent) and analyzed using Chi square test. p-value less than 0.05 was considered statistically significant. Sensitivity, specificity and area under the receiver operating characteristic curve (AUROC) of CVP, IVC minimum diameter, IVC maximum diameter, IVC caval index, and IJV aspect ratio were constructed to evaluate their ability to predict fluid responsiveness; Area Under the Curve (AUC) >0.75 was clinically relevant. The software used was SPSS.

Results

Regarding patient characteristics there was no significant differences between both study groups (responders and non-responders) in age, gender, mean APACHE score, mortality at 28 days, mean length of ICU stay (Table 1).

Regarding hemodynamic data; there was no significant difference between the two groups in baseline systolic blood pressure, diastolic blood pressure and mean arterial blood pressure, HR, Baseline CVP (Table 2).

There was no significant difference between responders and non-responders regarding the maximum IVC diameter measured by U/S upon inclusion in the study (p=0.22), while the minimum IVC diameter was significantly lower in the group of fluid responders compared the non-responder group (p=0.00). The caval index was significantly higher in the responder group compared to non-responder group (p=0.00) (Table 3).

Regarding IJV, there was no significant difference in the aspect ratio of the IJV between responders and non-responders (p=0.46) (Table 3).

The Area Under the Receiver Operating Characteristic Curve (AUROC) for the initial CVP reading in predicting fluid responsiveness was 0.57 (95% CI: 0.3-0.84, p=0.57), while for the maximum IVC diameter the AUROC was 0.64 (95% CI: 0.4-0.88, p=0.3) Fig. (1).

The AUROC for the minimum IVC diameter in predicting fluid responsiveness was 0.93 (95% CI: 0.83-1.03, p=0.02) and if the cut-off value is 0.9cm the sensitivity and specificity are 100% and 70% respectively Fig. (2).

The AUROC for caval index was 0.96 (95% CI: 0.89-1.04, p=0.001) and at a cut-off value of 35%, the sensitivity and specificity were 92% and 86% respectively Fig. (2).

The AUROC was 0.53 for IJV aspect ratio (95% CI: 0.24-0.82, p=0.7) Fig. (3), showing poor sensitivity and specificity.
Fig. (1): Receiver Operating Characteristic (ROC) curve for central venous pressure (on the left) and inferior vena cava maximum diameter (on the right) on prediction of fluid responsiveness in septic shock patients.

Fig. (2): Receiver Operating Characteristic (ROC) curve for minimum internal jugular vein (IVC) diameter (on the left) and caval index (on the right) on prediction of fluid responsiveness in septic shock patients.

Fig. (3): Receiver Operating Characteristic (ROC) curve for Internal Jugular Vein (IJV) aspect ratio on prediction of fluid responsiveness in septic shock patients.

Table (1): Demographic data and other patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Fluid responders n=26</th>
<th>Fluid non-responders n=14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.5±16.4</td>
<td>32.4±13.8</td>
<td>0.42</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17.3±6.6</td>
<td>15.1±6.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (42%)</td>
<td>7 (50%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Female</td>
<td>15 (58%)</td>
<td>7 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-days mortality</td>
<td>20 (77%)</td>
<td>12 (85.7%)</td>
<td>0.06</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>7.3±2.1</td>
<td>6.7±2.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

APACHE: Acute Physiology and Chronic Health Evaluation score.
LOS: Length Of ICU Stay.
N: Number of patients.
Data are presented as mean ± SD, number (frequency).
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predicting fluid responders and recommended their campaign guidelines 2013 are still recommending CVP preferentially used for septic shock patients be misleading if used to determine volume respon-
tion has superior performance, and should be not be used to guide fluid therapy in critically ill patients

mented review recommended that CVP should not be used to guide fluid therapy in critically ill patients [19].

A review article published 2014 stated that cardiac filling pressures i.e. CVP and PAoP may be misleading if used to determine volume responsiveness. Assessment of cardiopulmonary interactions has superior performance, and should be preferentially used for septic shock patients [20].

Despite the rising evidence that dynamic measurements for fluid responsiveness in septic shock are better than static ones, surviving sepsis campaign guidelines 2013 are still recommending CVP as a target of fluid therapy. The guidelines mentioned dynamic measurements to be superior in predicting fluid responders and recommended their use. But the lack of literature available regarding

Table (2): Baseline hemodynamic data.

<table>
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<tr>
<td>HR (b/min)</td>
<td>112±21</td>
<td>127±24</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>81.9±5.9</td>
<td>762±7.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>40.7±4.6</td>
<td>42.1±6</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>53.8±3.7</td>
<td>52.1±5.4</td>
</tr>
<tr>
<td>CVP (cm H2O)</td>
<td>5.5±3.8</td>
<td>7.3±5.6</td>
</tr>
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HR : Heart Rate.  DBP : Diastolic Blood Pressure.  SBP : Systolic Blood Pressure.  MBP : Mean Blood Pressure.  CVP : Central Venous Pressure.  Data are presented as mean ± SD.

Table (3): Baseline ultrasound indices.

<table>
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<th>Responders n=26</th>
<th>Non-responders n=14</th>
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<tr>
<td>IVC max. diameter (cm)</td>
<td>1.4±0.5</td>
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</tr>
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<td>IVC min. diameter (cm)</td>
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<td>Caval index (%)</td>
<td>57±18.2</td>
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<tr>
<td>Aspect ratio of IJV</td>
<td>1.6±0.4</td>
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<tr>
<td>VTI</td>
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IVC : Inferior Vena Cava.  IJV : Internal Jugular Vein.  CCA : Common Carotid Artery.  VTI : Velocity Time Index.  Data are presented as mean ± SD.

Discussion

The results of this study showed that the minimum IVC diameter and caval index are good predictors of fluid responsiveness. These parameters were significantly different between the two groups of fluid responders and non-responders. A minimum IVC diameter of 0.9cm predicted fluid responsiveness with a sensitivity of 100% and specificity of 70%. A caval index of 35% had 92% sensitivity and 86% specificity.

These results are compatible with the substantial volume of literature that supports that CVP and other static parameters are poor predictors of fluid responsiveness. A systematic review of literature which included 24 studies and 803 patients showed that CVP is a poor predictor of fluid responsiveness. The AUROC in pooled data was 0.56 (95% CI, 0.51 to 0.61) and the pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index was very weak correlation \( r=0.18 \) (95% CI, 0.08 to 0.28). The authors of the aforementioned review recommended that CVP should not be used to guide fluid therapy in critically ill patients [19].

In the issue of IVC diameter and caval index, the results of the current study generally conform with the current literature about the usefulness of IVC diameter and collapsibility index as predictors of the response to fluid therapy. But some conflict is still present about the accuracy of these parameters in spontaneously breathing patients and about the cut-off values at which they showed highest sensitivity and specificity in determining fluid responsiveness.

A systematic review of literature involved 8 studies and 235 patients evaluated the use of caval index in predicting fluid responsiveness. This review included two studies on spontaneously breathing patients (as the current study) [21,22] and six studies on mechanically ventilated patients. In the two studies on spontaneously breathing patients (the larger study included 40 patients as equal as the sample size of this study) the AUROC for the caval index in detection of fluid responsiveness was 0.56 (95% CI: 0.31, 0.81) and 0.77 (95% CI: 0.6, 0.88) respectively which is lower than in the results of this study 0.96 (95% CI: 0.89-1.04).

The pooled results of the aforementioned systematic review in all patients (including spontaneously breathing patients and mechanically ventilated patients) showed cut-off values that varied between 12% and 40%. Sensitivity and specificity in the overall population were 0.76 (95% CI: 0.61-0.86) and 0.86 (95% CI: 0.69-0.95) respectively. AUROC was 0.84 (95% CI: 0.79-0.89).

The conclusion of this systematic review was that the diameter of IVC measured with ultrasonography is of great value in predicting fluid responsiveness, particularly in patients on controlled mechanical ventilation and those resuscitated with

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IVC : Inferior Vena Cava.  IJV : Internal Jugular Vein.  CCA : Common Carotid Artery.  VTI : Velocity Time Index.  Data are presented as mean ± SD.
The results of this study are in the same context but the patients are all spontaneously breathing and resuscitated with crystalloids.

Regarding the IJV aspect ratio, few studies tried to link this ultrasound measured parameter to CVP reading. No studies to the best of our knowledge reported the validity of these parameters in prediction of fluid responsiveness.

The only study that mentioned the IJV aspect ratio was aiming to evaluate the accuracy of ultrasound imaging of the internal jugular vein aspect ratio to estimate the CVP target of 8mmHg of the EGDT protocol of sepsis. The AUROC was 0.84 (95% CI, 0.72-0.96) [24]. Although the same population was targeted in that study and the current study, the current study differently was aiming to assess the accuracy of aspect ratio in predicting fluid responsiveness. This explains the difference between the results (in this study results, the AUROC is 0.53 for IJV aspect ratio [95% CI: 0.24-0.82]).

Limitations faced during this study were that this study was performed in ICU where many septic patients receive fluids before admission either in the operating room or in the emergency room. This leads to decrease in the number of patients that were valid to be enrolled in the study. So, this study was best to be done in Emergency Department.

Another limitation was that a good percentage of patients were burn patients; some difficulty was present in visualizing the IJV and IVC when they were involved in the burnt area.

Conclusion:

IVC minimum diameter and Cavai index are useful methods to predict fluid responsiveness in spontaneously breathing patients with septic shock.

References


الملخص العربي

يعتبر تحميل السوائل عن طريق الوريد حجر الزاوية في إعداد التسمم البكتيري الشديد والصمة التسممية. ومع ذلك، فقط ما يقرب من نصف المرضى غير مستقرين يستجيبون لحميل السوائل. على الرغم من أن تحسن الحالة مرتبطة بحميل جيد السوائل إلا أن تحميل السوائل واسع النطاق قد يتطلب مع زيادة معدلات الانتهاء والوفيات، القيمة من الدليل مستوفة للهجة والجرعة المناسبة لتناول السوائل عن طريق الوريد لتلك الحالات مما يجعل الحفاظ على الحالة الحميمة والتتبّي بالاستجابة للسوائل أمرًا صعبًا.

الضغوطات الثانية التي تعبير عن امتلاء القلب مثل الضغط الوريدي المركزى لا تستطيع التنبؤ بدقة بدرجة الاستجابة للسوائل. في حين أن المعايير المتغيرة التي تعمّد على التغيير في ضغ القلب نتيجة تغيرات التنفس الصناعي قد أظهرت نتائج واعدة في هذا السياق وكانت مادة البحث العلمي المكلف فيما يخص التنبؤ بالاستجابة للسوائل.

وقد أجريت هذه الدراسة في وحدة العناية المركزى الجراحية في مستشفيات جامعة القاهرة ككشف عن دقة مؤشرات الموجات فوق الصوتية الجديدة (مثل التغير في قطر الوريد الأجوف السفلي) لتجهيز العلاج بالسوائل والتتبّي بالاستجابة السوائل في التسمم البكتيري الشديد والصمة التسممية المرضى الذين ينتمون بشكل تقالي.

وقد أظهرت نتائج هذه الدراسة أن قطر الأصغر للوريد الأجوف السفلي فضلاً عن التغير في القطر، يعد كلها مقياساً فائقاً للتنبؤ بالاستجابة العلاج بالسوائل. كما أظهرت ارتباطاً ضعيفاً بين هذه المعايير والضغط الوريدي المركزى مما يؤكّد ضعف قيمة هذا المقياس للتنبؤ بالاستجابة للسوائل.