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Research paper

Central venous pressure, global end-diastolic index, and the inferior vena cava collapsibility/distensibility indices to estimate intravascular volume status in critically ill children: A pilot study

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ABSTRACT

Background: The assessment of the volume status in critically ill paediatric patients in intensive care units is vitally important for fluid therapy management. The most commonly used parameter for detecting volume status is still central venous pressure (CVP); however, in recent years, various kinds of methods and devices are being used for volume assessment in intensive care units.

Objectives: We aimed to evaluate the relationship between CVP, the global end-diastolic index (GEDI), and ultrasound measurements of the collapsibility and distensibility indices of the inferior vena cava (IVC) in paediatric patients undergoing Pulse index Contour Cardiac Output (PiCCO) monitoring.

Methods: Fifteen patients receiving PiCCO monitoring were prospectively included in the study. Forty-nine PiCCO measurements were evaluated, and simultaneous CVP values were noted. After each measurement, IVC collapsibility (in spontaneously breathing patients) and distensibility (in mechanically ventilated patients) indices were measured with bedside ultrasound.

Results: The mean age was 93.2 ± 61.3 months. Significant and negative correlations of the GEDI were found with the IVC collapsibility index (in spontaneously breathing patients) and the IVC distensibility index (in mechanically ventilated patients) ($r = -0.502$, $p < 0.001$; $r = -0.522$, $p = 0.001$, respectively). A significant and weakly positive correlation was found between the GEDI and CVP ($r = 0.346$, $p = 0.015$), and a significant and negative correlation was found between the IVC collapsibility index and CVP ($r = -0.482$, $p = 0.03$). The correlation between the IVC distensibility index and CVP was significant and negative ($r = -0.412$, $p = 0.04$).

Conclusion: The use of PiCCO as an advanced haemodynamic monitoring method and the use of bedside ultrasound as a noninvasive method are useful to evaluate the volume status in critically ill paediatric patients in intensive care. These methods will gradually come to the fore in paediatric intensive care.

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1. Introduction

Haemodynamic risks are known to be high in paediatric intensive care patients. A rapid fluid status assessment is valuable for the evaluation, treatment, and management of critically ill children with shock [1]. Therefore, planning appropriate fluid therapy and the use of inotropes, vasopressors, and inodilators are vitally

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important in this patient group [1]. Skin turgor, heart rate, mean arterial pressure, urine output, and central venous pressure (CVP) are commonly used parameters for assessing the intravascular volume status and planning fluid therapy in intensive care units (ICUs). However; increasingly more studies suggest that the measurement of these parameters is not free of interindividual variabilities, encouraging research to investigate new and objective reliable methods for volume assessments [2–4].

Pulse index Contour Cardiac Output (PiCCO) is the first pulse contour device indicated for measuring the cardiac output in haemodynamically unstable patients with unstable volume status [5]. PiCCO is an invasive method, which allows for continuous cardiac output monitoring and provides cardiac index values along with other parameters such as the preload and the systemic vascular resistance index [6]. The working principle of PiCCO is based on transpulmonary thermodilution and pulse contour technology. PiCCO assists paediatric intensive care physicians in planning fluid therapy and treatment with inotropes [7]. The global end-diastolic index (GEDI) is one of the PiCCO parameters that provide information about preload and the volume status of patients. The GEDI is a static volumetric parameter measured during transpulmonary thermodilution [8]. The GEDI can be defined as a virtual volume comprising the diastolic volumes of atria and ventricles [9]. Effective use of the GEDI can facilitate the management of circulatory dysfunction, allowing for the effective use of inotropes and vasopressors [10].

The use of bedside ultrasound by paediatric intensive care physicians has become so critical in recent years that it is now a component of physical examination in ICUs [11,12]. Inferior vena cava (IVC) is a highly elastic vein sensitive to changes in fluid status [13]. A critical parameter is the IVC diameter, which can be measured readily via noninvasive methods to estimate the fluid status of the patient [14]. IVC collapses in inspiration and distends in expiration during spontaneous breathing. Several studies have demonstrated that changes in the diameter of IVC can be used for estimating the fluid status of the patient; however, data obtained from children are limited [15–17]. The IVC collapsibility index in spontaneously breathing children and the IVC distensibility index in mechanically ventilated children are calculated by using maximum and minimum diameters of IVC. No well-described value ranges have been established for these indices in the paediatric age group yet; however, high values are associated with a requirement for volume replacement in patients.

CVP is the right ventricular filling pressure which provides information about the intravascular volume status [18]. Although the feasibility and efficacy of measuring CVP have been frequently questioned especially in recent years, CVP is still used commonly in paediatric intensive care units (PICUs) to evaluate the volume status in critically ill paediatric patients [19,20].

This pilot study focusses on the correlations between the GEDI, CVP, and bedside ultrasound measurements of the IVC collapsibility and IVC distensibility indices in patients monitored by PiCCO in our tertiary care PICU. We have wished to provide information about volume assessment in PICU patients in light of our results and of those published in the literature, aiming to draw attention to the importance of advanced haemodynamic monitoring and bedside ultrasound in ICUs.

2. Material and method

Fifteen patients monitored by PiCCO in our PICU in the period from February 2018 to September 2018 were prospectively included in the study. Haemodynamic monitoring was carried out using the PiCCO device (PiCCO, Pulsion Medical Systems, Munich, Germany) by inserting a central catheter in the internal jugular vein

or the subclavian vein via a 3F or 4F (as per the age of the patient) thermodilution catheter with a temperature sensor at the tip inserted in the femoral artery. The PiCCO system was calibrated with 10-mL cold saline every 8 h. A total of 49 PiCCO measurements were noted including the GEDI, systemic vascular resistance index, cardiac output, and cardiac index by using the PiCCO monitor. Simultaneous CVP values, which correspond to these parameters, were measured and recorded.

After each 8-h measurement, the IVC collapsibility (in spontaneously breathing patients) and distensibility (in mechanically ventilated patients) indices were measured with bedside ultrasound without any delays. To limit the inter-rater variability, all ultrasound measurements were carried out by the same PICU fellow (N.A.), who was experienced in bedside ultrasound and trained in point-of-care ultrasonography course organised by the Turkish Society of Paediatric Emergency and Intensive Care. A Mindray ultrasound device with a 2.1- to 5.1-MHz convex probe was used for ultrasound training in our department and was used for the measurements. Measurements were performed while the patient was in the supine position. IVC images were acquired in the sagittal section. Images of the IVC draining into the right atrium were obtained while the probe was in the subxiphoid area, using the liver as the acoustic window. The minimum IVC diameter on inspiration and the maximum IVC diameter on expiration were recorded using the M-mode just beyond the point, where the hepatic veins drain into IVC (Fig. 1). The maximum IVC diameter on inspiration and the minimum IVC diameter on expiration were measured using the same ultrasound scanning method. The IVC collapsibility index was calculated using the following formula [21]:

$$\text{IVC collapsibility index} = \left[\frac{\text{the maximum diameter on expiration} - \text{the minimum diameter on inspiration}}{\text{the maximum diameter on expiration}} \right]$$

In mechanically ventilated patients, the IVC distensibility index was calculated using the following formula [22]:

$$\text{IVC distensibility index} = \left[\frac{\text{the maximum diameter on inspiration} - \text{the minimum diameter on expiration}}{\text{the minimum diameter on expiration}} \right]$$


Fig. 1. M-mode measurement of the maximum and minimum IVC diameters in the sagittal section. IVC, inferior vena cava.

The Vasoactive-Inotropic Score (VIS) was calculated using the following formula [23]:

$$\text{VIS} = 1 \times \text{dopamine} [\mu\text{g}/\text{kg}/\text{min}] + 1 \times \text{dobutamine} [\mu\text{g}/\text{kg}/\text{min}] + 100 \times \text{epinephrine} [\mu\text{g}/\text{kg}/\text{min}] + 100 \times \text{norepinephrine} [\mu\text{g}/\text{kg}/\text{min}] + 10 \times \text{milrinone} [\mu\text{g}/\text{kg}/\text{min}] + 10,000 \times \text{vasopressin} [\text{U}/\text{kg}/\text{min}].$$

Age, body weight, and the Paediatric Index of Mortality-2 and the Paediatric Risk of Mortality-III scores of the patients were recorded. Based on CVP values, a total of 49 recordings obtained from the patients were classified into two categories as the hypovolaemic group and the normovolaemic group for comparison. CVP values of ≤ 8 mmHg were categorised as the hypovolaemic group and CVP values of > 8 mmHg were categorised as the normovolaemic group in a way compatible with the information in the literature [21]. Ethical approval for the study was obtained from the Cukurova University School of Medicine Clinical Research Ethics Committee (April 2018; 76).

2.1. Statistical analysis

IBM SPSS Statistics, version 20.0, package program was used for the statistical analysis of the data. The categorical variables were summarised as numbers and percentages, while the numerical variables were presented as mean and standard deviation (with the median and minimum/maximum values when necessary). The Kolmogorov–Smirnov test was used for testing whether the numerical measurements met the normal distribution assumption. Pearson's correlation coefficient and respective p-values were obtained to evaluate the correlation between numerical measurements. The level of statistical significance was taken as 0.05 for all tests.

3. Results

The mean age was 93.2 ± 61.3 months. Seven (46.6%) patients were girls. The diagnoses of the patients were septic shock (eight patients), pulmonary acute respiratory distress syndrome (2 patients), cardiogenic shock due to scorpion stings (2 patients), and pulmonary oedema (3 patients). The demographic characteristics of the patients and their recorded PiCCO parameters are presented in Table 1. The mean VIS was 23.2 ± 8.58 , the mean CVP was 9 ± 2.18 mmHg, and the mean central venous oxygen saturation (S_{cvO_2}) was $71.86 \pm 6.75\%$. Significant and negative correlations of the GEDI were found with the IVC collapsibility index (in spontaneously breathing patients) and the IVC distensibility index (in mechanically ventilated patients) ($r = -0.502$, $p < 0.001$; $r = -0.522$, $p = 0.001$, respectively). There was a significant and weakly positive correlation between the GEDI and CVP ($r = 0.346$, $p = 0.015$) and a significant and negative correlation between the IVC collapsibility index and CVP ($r = -0.482$, $p = 0.03$). A significant

and negative correlation was found between the IVC distensibility index and CVP ($r = -0.412$, $p = 0.04$). When the $\text{CVP} \leq 8$ mmHg group and $\text{CVP} > 8$ mmHg group were compared, statistically significant differences were found in the GEDI, extravascular lung water index (ELWI), the IVC collapsibility index, and the IVC distensibility index between the groups ($p < 0.001$, $p = 0.003$, $p = 0.001$, and $p = 0.001$, respectively [Table 2]).

4. Discussion

Adequate fluid therapy is vital in reducing the risk of organ failure and mortality [19]. As intensive care professionals, we can use CVP measurements for this purpose [24]. CVP is a good indicator of the right atrial pressure and provides information about the intravascular volume, reflecting the right ventricular performance [18,25]. Despite a large number of publications suggesting that it is a subjective measurement because it can easily be affected by intrathoracic pressure changes and inter-rater variability, CVP is still a commonly used parameter [19,20]. A recommended treatment goal in the previous version of the paediatric septic shock guideline was that the perfusion pressure (mean arterial pressure–CVP) should be optimised [26]. However, in the recent paediatric sepsis guideline, the recommendation to optimise the CVP has been left out and only the optimisation of the mean arterial pressure has been recommended because supporting information about CVP is inadequate, CVP does not provide correct information about the left ventricular preload, and CVP is not a practical measure to be used in early stages of fluid resuscitation [27].

PiCCO provides data to determine the preload, myocardial contractility, the afterload, and pulmonary permeability as an invasive monitoring method. Some authors suggest that PiCCO is the gold standard to determine the fluid status of patients; however, most studies were conducted on adults and paediatric data are limited [28]. Grindheim et al [29], performed a prospective observational study which includes 31 children without cardiopulmonary disease, and they applied PiCCO monitoring to the patients. They reported values obtained by the PiCCO system in children have a wide range and should therefore be interpreted with caution. The authors noticed that all variables measured by PiCCO, especially ELWI, has a high interindividual variation especially in children weighing less than 15 kg. They declared that current reference values obtained from the published adult literature for GEDI and ELWI are not applicable in children; the former is too high, and the latter, too low and should not guide clinical practice [29]. The use of the GEDI has been shown to be more appropriate than the use of CVP in determining the cardiac preload in patients with septic shock [30]. In a study with 74 adult patients who underwent liver transplantation, no correlation was found between the GEDI and CVP. Also, the study reported that the use of the GEDI was a more appropriate measure in preload

Table 1
Patient demographics and PiCCO parameter measurements.

	Mean \pm standard deviation	Median (minimum–maximum)
Age (months)	93.2 \pm 61.3	101 (16–186)
Body weight (kg)	22.87 \pm 12.75	20 (9.8–45)
PiM-2 score	47.1 \pm 21.85	40.1 (19–95.1)
PRISM-III score	22.4 \pm 6.79	20 (15–41)
GEDI (mL/m ²)	505.7 \pm 180.1	447 (265–1003)
SVRI (Dynes*cm ⁵ /m ²)	1277.2 \pm 356.6	1039 (702–2273)
ELWI (mL/kg)	11.73 \pm 3.27	11 (6–19)
Cardiac output (L/min)	3.7 \pm 1.72	3.29 (1.65–8.5)
Cardiac index (L/min/m ²)	4.57 \pm 0.98	4.6 (2.47–7.32)

PiCCO, Pulse index Contour Cardiac Output; PiM-2, Paediatric Index of Mortality-2; PRISM-III, Paediatric Risk of Mortality-III; GEDI, global end-diastolic index; SVRI, systemic vascular resistance index; ELWI, extravascular lung water index.

Table 2
Comparison of groups with CVP ≤ 8 mmHg and CVP > 8 mmHg.

	Measurements of CVP ≤ 8 mmHg (mean \pm standard deviation), median (minimum–maximum) n = 28	Measurements of CVP > 8 mmHg (mean \pm standard deviation), median (minimum–maximum) n = 21	p
CVP (mmHg)	5.84 \pm 2.23, 6 (5–8)	10.4 \pm 1.14, 12 (9–15)	<0.001
GEDI (mL/m ₂)	458 \pm 118.18, 429 (265–711)	918 \pm 53.2, 909 (857–1003)	<0.001
SVRI (Dynes \cdot cm ⁵ /m ²)	1164.27 \pm 364.3, 1038 (702–2273)	1267 \pm 296.3, 1417 (944–1523)	0.449
ELWI (mL/kg)	11.25 \pm 2.99, 11 (6–19)	16 \pm 2.55, 16 (12–19)	0.003
Cardiac output (L/min)	3.56 \pm 1.7, 2.94 (1.65–8.5)	4.86 \pm 1.6, 3.81 (3.69–7.23)	0.025
Cardiac index (L/min/m ²)	4.57 \pm 1.03, 4.71 (2.47–7.32)	4.56 \pm 0.37, 4.39 (4.35–5.21)	0.86
ScvO ₂ (%)	71.59 \pm 6.96, 70 (62–85)	74.2 \pm 4.26, 75 (68–78)	0.293
Vena cava inferior indices (%)			
Extubated patient-IVC collapsibility index (%)	42.24 \pm 8.55, 40 (28–43)	24.68 \pm 6.36, 25 (19–33)	<0.001
Intubated patient-IVC distensibility index (%)	22.40 \pm 3.34, 19 (10–25)	14.16 \pm 2.44, 13 (9–16)	<0.001

GEDI, global end-diastolic index; SVRI, systemic vascular resistance index; IVC, inferior vena cava; CVP, central venous pressure; ELWI, extravascular lung water index. Statistically significant p values by bold.

monitoring [10]. In adult patients undergoing PiCCO monitoring, low CVP was found to be correlated with high cardiac output. Furthermore, low CVP values were indicated to reduce 28-day mortality rates [31]. Renner et al [32], identified the GEDI as the most important parameter to predict fluid responsiveness in an animal experiment, and they reported that they did not find a correlation between the GEDI and CVP. Our study results showed the presence of a weak and positive correlation between GEDI and CVP values.

The use of bedside ultrasound by emergency and intensive care physicians has gained increasing momentum, especially in the last 5 years [33]. First, Natori et al [34], described the correlation between the IVC diameter and the right atrial pressure in 1979. Increasingly more studies in the following years have shown that changes in the IVC diameter have occurred long before vital sign changes in conditions of fluid loss [35]. Several adult studies are available in the literature, demonstrating that the IVC collapsibility index, which is calculated using the maximum and minimum diameters of IVC, correlates well with CVP [15,16]. The number of studies on paediatric patients is limited, but these studies are gradually increasing in the literature [17]. However, the reference values defined for the IVC collapsibility index and the maximum and minimum diameters of IVC belong to the adult population. Again, paediatric data about these reference values are limited [14]. Despite many studies on adults reporting a variety of reference value ranges, the accepted normal range for the IVC collapsibility index is 35–50% [36]. In adults, an IVC collapsibility index of $>50\%$ is associated with a reduced right atrial pressure and severe dehydration, leading to the interpretation that the patient needs fluid therapy [37]. In a paediatric study, Kutty et al [38], enrolled 120 healthy children and measured IVC diameters, the IVC collapsibility index, and right atrial volumes by echocardiography. The authors found out that the measurement of IVC diameters, the IVC collapsibility index, and right atrial volumes were feasible in healthy children. Another study by Babaie et al [21], about the prediction of fluid status in paediatric patients evaluated 70 children in the age range from 1 month to 12 years. A negative correlation was reported between CVP and the IVC collapsibility index, and the mean IVC collapsibility index was found to be $35 \pm 16\%$. Mugloo et al [39], evaluated 50 newborns and reported that the IVC collapsibility index and CVP were negatively correlated. Consistent with the findings reported in the literature; we found a significant and negative correlation between the IVC collapsibility index and CVP in our study. Our pilot study results demonstrated a significant and negative correlation between the GEDI and the IVC collapsibility index.

Positive-pressure ventilation elevates the pleural and the right atrial pressure values and reduces the venous return to the heart by increasing the intrathoracic pressure during inspiration. These factors act on the diameter and the distensibility of IVC [40]. Consequently, unlike spontaneously breathing, the IVC diameter distends during inspiration and collapses during expiration in an intubated patient [41]. Therefore, it is recommended that the IVC distensibility index should be used instead of the IVC collapsibility index in patients receiving positive-pressure mechanical ventilation [42]. A study on mechanically ventilated adult patients in septic shock demonstrated that the IVC distensibility index values of $>18\%$ indicated the likelihood of a fluid deficit [43]. Previous studies examined the effectiveness of the use of the IVC distensibility index in predicting fluid responsiveness in critically ill children [42]. Although the results are contradictory, recent studies have shown that the IVC distensibility index is a reliable measure of predicting fluid responsiveness in mechanically ventilated children [42,44,45]. Both Babaie et al [21], and Mugloo et al [39], used the IVC collapsibility index measurements in their studies on intubated patients. In our study, we used the IVC distensibility index measurement in intubated patients. We found that the mean IVC collapsibility index and the mean IVC distensibility index were $42.24 \pm 8.55\%$ and $22.40 \pm 3.34\%$, respectively, in the CVP ≤ 8 mmHg group in our study. Our results showed significant and negative correlations of CVP both with the IVC collapsibility index and the IVC distensibility index.

The main limitation of our study is the sample size. The number of both the patients and, therefore, the recorded measurements are limited in our study because, first, PiCCO is an invasive monitoring method that can be applied in a select patient group and second, we have a limited number of PiCCO catheters in our units. We plan to continue carrying out our study; however, we have wished to share our preliminary results with a review of the literature, considering the present efforts as a pilot study. Besides our study is an observational study. We do not have a control group, and the measurements are not blinded. We know these conditions could cause a high risk of bias.

In conclusion, PiCCO as an advanced monitoring method and the collapsibility and distensibility indices of IVC as noninvasive measurements are increasingly coming to the fore in evaluating the volume status in critically ill paediatric patients in ICUs.

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Conflict of interest

No conflict of interest was declared by the authors.

CRedit authorship contribution statement

Nagehan Aslan: Conceptualisation, Methodology, Writing - Original draft preparation. **Yasemin Coban:** Data curation. **Didar Arslan:** Data curation. **Wang Wu:** Visualisation, Investigation. **Ozden Ozgur Horoz:** Supervision. **Yasar Serdemir:** Software, Validation. **Dincer Yildizdas:** Writing - Reviewing and Editing.

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