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Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically-ill patients

Keith A. Corl, MD [a,b,c,*], Naomi R. George, MD [b], Justin Romanoff, MA [c], Andrew T. Levinson, MD, MPH [a], Darin B. Chheng, BS [b], Roland C. Merchant, MD, MPH, ScD [b,c], Mitchell M. Levy, MD [a], Anthony M. Napoli, MD [b]

[a] Department of Medicine, Division of Pulmonary Critical Care & Sleep, Alpert Medical School of Brown University, USA
[b] Department of Emergency Medicine, Alpert Medical School of Brown University
[c] School of Public Health of Brown University, Providence, RI, USA

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ABSTRACT

Purpose: Measurement of inferior vena cava collapsibility (cIVC) by point-of-care ultrasound (POCUS) has been proposed as a viable, non-invasive means of assessing fluid responsiveness. We aimed to determine the ability of cIVC to identify patients who will respond to additional intravenous fluid (IVF) administration among spontaneously breathing critically-ill patients.
Methods: Prospective observational trial of spontaneously breathing critically-ill patients. cIVC was obtained 3 cm caudal from the right atrium and IVC junction using POCUS. Fluid responsiveness was defined as a ≥ 10% increase in cardiac index following a 500 ml IVF bolus; measured using bioreactance (NICOM™, Cheetah Medical). cIVC was compared with fluid responsiveness and a cIVC optimal value was identified.
Results: Of the 124 participants, 49% were fluid responders. cIVC was able to detect fluid responsiveness: AUC = 0.84 [0.76, 0.91]. The optimum cutoff point for cIVC was identified as 25% (LR + 4.56 [2.72, 7.66], LR- 0.16 [0.08, 0.31]). A cIVC of 25% produced a lower misclassification rate (16.1%) for determining fluid responsiveness than the previous suggested cutoff values of 40% (34.7%).
Conclusion: IVC collapsibility, as measured by POCUS, performs well in distinguishing fluid responders from non-responders, and may be used to guide IVF resuscitation among spontaneously breathing critically-ill patients.

1. Introduction

Assessing fluid responsiveness is key to the successful resuscitation of critically-ill patients. While under-resuscitation is associated with worse clinical outcomes [1], there is a growing body of evidence that over-resuscitation may be harmful to patients with septic shock [2] and the acute respiratory distress syndrome [3]. As physicians re-examine the paradigm of aggressive intravenous fluid (IVF) resuscitation, there are calls for an individualized, evidence-based, IVF resuscitation strategy [4,5].

Despite the prevailing practice of early and aggressive IVF resuscitation in critically-ill patients, only 50% of patients will respond to an IVF bolus with an increase in their cardiac index [6-8]. Traditional methods of assessing fluid status, such as vital signs and physical examination, do not reliably identify fluid responders [9,10]. The use of a pulmonary artery catheter (PAC) is invasive, exposes patients to potential harm, and has questionable efficacy [11]. The Non-Invasive Cardiac Output Measurement device (NICOM™) offers an alternative to the PAC. NICOM has been validated against the PAC in multiple studies [12-14] and produces comparable hemodynamic data when compared to stroke volume variation [15]; however, its clinical use is limited to resource-rich practice environments. Consequently, an accurate, adaptable non-invasive alternative to help guide the IVF resuscitation of critically-ill patients is needed.

Emergency and critical care physicians have readily adopted point-of-care ultrasound (POCUS) for a spectrum of diagnostic and therapeutic uses [16-18]. Proficiency with POCUS among clinicians can be established with limited additional training [19,20], and the accuracy of POCUS has been demonstrated in multiple domains [21-23]. If a sonographic method of determining fluid responsiveness is shown to be valid, POCUS could obviate the need for other invasive or non-invasive methods.

POCUS can estimate central venous pressure (CVP) [24]; however, CVP is a static measure of volume status and has little clinical value in guiding the resuscitation of critically-ill patients [25]. Measurement of

* Corresponding author at: Division of Pulmonary, Critical Care & Sleep Department of Medicine, and Department of Emergency Medicine, Rhode Island Hospital, 55 Claverick Street, Second floor, Room 268, Providence, RI 02903, USA.
E-mail addresses: keith_corl@brown.edu (K.A. Corl), justin_romanoff@alumni.brown.edu (J. Romanoff), andrew_levinson@brown.edu (A.T. Levinson), rmerchant@lifespan.org (R.C. Merchant), mitchell_levy@brown.edu (M.M. Levy), Anapoli@lifespan.org (A.M. Napoli).

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the collapsibility of the inferior vena cava (cIVC) during respiration, also known as the caval index, has been proposed as a non-invasive means to measure a patient's response to an IVF volume challenge or following a passive leg raise (PLR). Research has demonstrated that cIVC can be used to predict fluid responsiveness in mechanically ventilated patients (receiving tidal volumes of 10 ml/kg) [26-28]. However, evidence supporting the use of cIVC in spontaneously breathing critically-ill patients has been limited to smaller trials [29-31]. In 2016, the Society of Critical Care Medicine (SCCM) released updated guidelines for the use of POCUS in the evaluation of critically-ill patients. With a lack of robust evidence, the guideline panel was unable to make a recommendation for or against the use of cIVC among spontaneously breathing patients [23]. Despite this absence, the 2015 Surviving Sepsis Campaign bundle calls for an assessment of patient volume status and suggests POCUS as a clinical option [32]. Many emergency physicians and intensivists have already adopted the practice of using POCUS to guide IVF resuscitation (with or without an IVF challenge or PLR) among spontaneously breathing critically-ill patients into their practice [33,34] despite the limited evidence.

The primary aim of this study was to assess the ability of cIVC to detect fluid responsiveness among spontaneously breathing critically-ill patients undergoing resuscitation, as measured using NICOM. Secondary aims were to establish an optimum cutoff value for cIVC, compare this value to previously suggested cutoffs, and determine if incorporating a PLR with cIVC assists in detecting fluid responsiveness.

2. Methods

2.1. Study setting and population

This prospective observational investigation was performed in the emergency departments and medical intensive care units (ICUs) of two urban adult academic hospitals in the United States. From August 2014 until July 2016, we enrolled a convenience sample of spontaneously breathing patients with signs of acute circulatory failure being admitted to the ICU. Patients were enrolled within 36 h of presentation to the emergency department during the resuscitative phase of care. Acute circulatory failure was defined as hypotension (systolic blood pressure < 90 mmHg, or a mean arterial pressure < 65 mmHg for ≥30 min); decreased urine output (<0.5 ml/kg/h); persistent tachycardia (heart rate > 120 bpm for ≥30 min); and/or serum markers suggesting organ hypo-perfusion (acidosis with a serum pH < 7.3 or lactic acid >2 meq/l) as previously described by Muller et al. and Airapetian et al. [29,30]. Exclusion criteria were primary traumatic, cardiogenic, obstructive, or neurogenic shock; age < 18 years old; incarceration; pregnancy; and/or hospitalization for >36 h. Patients also were excluded if they were receiving non-invasive positive pressure ventilation, if the clinical team felt that they had active pulmonary edema, or that believed that further IVFs might pose a clinical risk. The local institutional review board approved the study protocol (204,814 45CFR 46.110), and all patients or their surrogates gave written consent prior to study involvement.

2.2. Study protocol

Following enrollment, the NICOM™ (Cheetah Medical, Tel Aviv, Israel) device leads were applied to the study participant according to manufacturer specifications. The patient's cardiac index was recorded at one-minute intervals throughout the study. Patients were placed supine for a three-minute NICOM calibration period. Following NICOM calibration, two baseline ten-second videos of the IVC were recorded one minute apart. A three-minute PLR was performed, after which the research sonographer recorded a 10-s IVC video. The patient was then returned to the supine position for a minimum of 3 min. Finally, a 500 ml normal saline fluid bolus was administered with the assistance of a pressure bag through the participant's largest gauge IV. Immediately upon completion of the fluid bolus, a single ultrasound video of the IVC was repeated. If a participant's clinical condition required vasopressors, they were held at a constant rate throughout the study.

2.3. Measurements

Fluid responsiveness was defined as a ≥ 10% increase in cardiac index following an IVF bolus as measured by NICOM [35]. IVC POCUS was performed using a Sonosite Edge (Bothell, WA) by one of three study physicians (AL, KC, and NG) who had completed residency, fellowship, or post fellowship training that included POCUS [21]. Ultrasound images of the IVC were obtained in a subcostal long axis view with a low frequency (1–5 Hz) phased array probe. Measurements were recorded throughout the native respiratory cycle, study participants were not asked to take a deep inspiratory breath. The junction of the IVC and the right atrium and/or presence of hepatic veins were assessed to differentiate the aorta from the IVC. Images were obtained in 2D B-mode, recorded on 10-s clips, and uploaded to a secure server for review.

Ultrasound images were reviewed using the OsiriX Imaging Software (© Pixmeo, Switzerland) platform. During review images were frozen during maximum expiratory and minimum inspiratory diameter, the IVC was measured using the software's calipers 3 cm caudal to the junction of the IVC and the right atrium, for each still image. Maximum and minimum diameters were identified by visual inspection. cIVC (or caval index) was defined as the degree to which the IVC collapses relative to its largest diameter: cIVC = (IVC expiratory diameter – IVC inspiratory diameter)/IVC expiratory diameter [24]. Ultrasound reviewers were blinded to the NICOM results.

2.4. Data analysis

We calculated a sample size of 124 patients (90% power with a one-sided type I error rate of 0.05) needed to detect a difference between the true area under the receiver operating characteristic curve (AUC) for cIVC of at least 0.88 and an AUC of 0.70 (considered to signify a fair level of discrimination). This sample size was targeted to help ensure that confidence intervals (using the normal approximation to the binomial distribution) for baseline cIVC sensitivity and specificity would have radii <10%.

Baseline patient clinical and demographic characteristics were summarized using descriptive statistics. Differences between fluid responders and non-responders were assessed using Pearson's chi-squared test, Fisher's exact test, the Student's *t*-test, and the Mann-Whitney *U* test, with two-sided *P* values less than 0.05 indicating statistical significance. The intraclass correlation coefficient (ICC) for absolute agreement using one-way random-effects analysis of variance (ANOVA) and two-way random-effects ANOVA were calculated for the baseline cIVC measurements to determine intra- and inter-rater reliability. The ICCs for intra- and inter-rater reliability of cIVC were found to be 0.92 (95% CI [0.89, 0.95]) and 0.67 (95% CI [0.56, 0.76]), respectively.

The relationship between the baseline cIVC and change in cardiac index was examined, and ROC analysis was employed to evaluate the baseline cIVC's ability to predict fluid responsiveness. We considered four functions of sensitivity and specificity for producing a cIVC cutoff value for optimally predicting fluid responsiveness (the sum and product of the sensitivity and specificity, maximizing the minimum of sensitivity and specificity, and minimizing the distance between the ROC curve and the point associated with 100% sensitivity and 100% specificity). We repeated these analyses to determine if IVC inspiratory or expiratory diameter, or if the change in cIVC before and after a PLR or a 500 ml IVF bolus, were predictive of fluid responsiveness. To assess if the addition of a PLR aided in the baseline cIVC's ability to detect fluid responsiveness, we created algorithms for using cIVC in conjunction with PLR. For these algorithms, we first assessed the prediction of fluid responsiveness by cIVC and PLR separately. Next, we evaluated if following a PLR there was a 5% change in cIVC that would reclassify