Utility of Ultrasound Measurements in Assessing Fluid Responsiveness

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Clinical Question
How can we utilize ultrasound measurements to accurately determine which patients are fluid responsive? Does any single ultrasound measurement accurately predict fluid responsiveness?

Introduction
Volume expansion is a cornerstone of resuscitation in the ED and is currently one of the main recommended components of septic shock management. The ability to predict fluid responsiveness has been a highly debated issue within emergency and critical care medicine. Early studies found inferior vena cava (IVC) diameter and variability could predict fluid responsiveness in intubated, mechanically-ventilated septic patients.1,2 The applicability of these findings to other populations is unknown and subsequent studies have called these findings into question.3 At the other end of the spectrum, the existence of a volume overloaded state may be detected by measuring indices in the liver and kidneys such as portal vein pulsatility,4,5 hepatic venous flow velocity,6 and intrarenal venous flow.7 Confirmation of increased stroke volume with passive leg raise or a small fluid challenge is currently one of the better, albeit imperfect, existing methods to ensure true volume responsiveness.8,9,10

More recent studies have evaluated other ultrasound measurements such as change in carotid corrected flow time, internal jugular vein distensibility, and left ventricular outflow tract velocity time integral in an attempt to find a method of determining volume responsiveness that is both accurate and easy to do at the bedside.8


Airapetian et al. sought to assess whether the respiratory variability of the IVC could be used to predict fluid responsiveness in spontaneously breathing (i.e., not intubated) patients. They conducted a prospective study performed in two ICUs from a single center in France. The cohort was made up of 59 consecutive patients who received volume expansion as ordered by an attending physician, generally based on criteria such as hypotension, oligoanuria, skin mottling, “and/or clinical and laboratory signs of extracellular dehydration.” Patients who had signs of hemorrhage, arrhythmias, an immediate need for the fluid challenge, compres sion stockings, or a contraindication to passive leg raising (PLR) were excluded. After baseline blood pressure (measured using an invasive arterial monitoring system), heart rate, cardiac output (CO), as calculated using the measured aortic area and velocity-time integral, VTI), and IVC diameters were recorded, the bed automatically induced a PLR of 30 degrees. Measurements were then repeated two minutes later, and the patient was returned to their initial semi-recumbent position. 500 mL of saline was then given over 15 minutes and measurements were then repeated again.

Responders (29/59, 49%) were defined as those who had a CO increase of 10% or more following the 500 mL bolus. Responders and non-responders had statistically similar baseline characteristics including percentage of non-surgical (versus surgical) admissions and rates of preexisting heart failure and chronic obstructive pulmonary disease. At baseline, responders had a higher aortic VTI (16 vs. 19 cm, p=0.03), smaller minimum IVC diameter on inspiration (IVCmin, 11 ± 5 vs. 14 ± 5 mm, p = 0.04), as well as greater IVC variability (cIVC 35 ± 16 vs. 27 ± 10 %, p = 0.04). Data analysis revealed that maximum IVC diameter upon expiration (IVCmax) did not predict fluid responsiveness (<2.1 cm: PPV of 57%, LR+ of 1.4), with an area under the receiver operating characteristic curve (AUROC) of 0.62 ± 0.07 (95 %CI 0.49-0.75). Similarly, the AUROC for cIVC at baseline was 0.62 ± 0.07 (95 %CI 0.49-0.74). However, at a threshold of cIVC >42% there was a specificity of 97% and a PPV of 90% (with a sensitivity of 31%) in distinguishing responders from non-responders.

The authors conclude that IVC diameter and IVC variability are not reliable predictors of fluid responsiveness in spontaneously breathing patients. Inspiratory variation >42% was a specific but non-sensitive predictor of fluid responsiveness.

Overall, this study’s biggest limitation is its small sample size. Another point of caution is that accurate ultrasound measurements are highly operator dependent particularly when measuring aortic VTI. In this study, CO was calculated using the average VTI over three to five consecutive measurements over one respiratory cycle. In addition, the high-level of inter-observer reliability suggests that the ultrasonographers were highly skilled, which may not be the case with all emergency physicians and may limit generalizability. It should be noted that the baseline MAP in this small cohort was 86±19 and 87±33 mmHg for responders and non-responders respectively, not hypotensive and actually higher than the typical MAP goal of 65 mmHg. There was also no comparator gold standard measurement used to confirm the CO measurements. In addition, this cohort of patients were ill, but also were thought to be stable enough not to need the fluid immediately, although this exclusion criteria as well as the inclusion criteria of “signs of extracellular dehydration” were poorly defined. While ultimately there is debate about the utility of IVC measurements in fluid responsiveness given its use as a surrogate value for central venous pressure, based on this study, a cIVC of >42% in spontaneously breathing patients may predict an increase in CO after fluid infusion.

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This study investigated if IVC collapsibility measure using POCUS was able to detect fluid responsiveness among critically ill but spontaneously breathing patients. The study was a prospective observational study that enrolled a convenience sample of patients admitted to a medical ICU. A total of 124 patients were included who demonstrated signs of “acute circulatory failure” defined in this study as hypotension (systolic blood pressure <90 or MAP <65 mmHg for at least 30 minutes), persistent tachycardia (HR >120 for at least 30 minutes), and/or laboratory tests indicative of organ hypoperfusion (serum pH <7.3 or lactic acid >2).

The authors defined fluid responsiveness as an at least 10% increase in cardiac index following a 500 mL bolus of normal saline as measured by the Non-Invasive Bioreactance Cardiac Output Monitoring System (NICOM; Cheetah Medical, Newton Center, MA). The NICOM measures the change in phase of a 75kHz alternating current across the chest which predictably varies with blood flow through the aorta when compared to thermodilution with a pulmonary artery (PA) catheter as the gold standard and was subsequently validated in a multi-center follow up study.

The authors obtained subcostal long axis views of the IVC. IVC diameter was measured at maximum expiratory and minimum inspiratory diameter 3 cm caudal from the junction of the IVC and the right atrium. Caval index (cIVC) was defined as (IVC expiratory diameter – IVC inspiratory diameter)/IVC expiratory diameter.

The primary outcome was AUC for cIVC. The AUC was found to be 0.84 (CI 0.76 – 0.91) — indicative of a fair level of discrimination. The optimal cIVC found to maximize sensitivity and specificity for fluid responsiveness was 25%. Secondary investigations included comparison of this cutoff to previously suggested cutoff values and to evaluate if incorporating a passive leg raise helps detect fluid responsiveness. The authors found that a cIVC of 25%, which was lower than previously suggested cutoff values of 40-42%, produced a lower misclassification rate. Incorporating a passive leg raise did not result in fewer misclassifications compared to baseline cIVC alone.

One limitation of this study was that the exclusion criteria included “if the clinical team felt that they had active pulmonary edema” and if the clinical team “believed that further IVFs might pose a clinical risk.” The specific criteria used to determine patients excluded for these reasons are not given. Another limitation is that the authors report the median time from ED triage to first ultrasound was 17 hours during which a mean of 4060 mL of fluids was administered to each patient. In contrast, the mean fluid given during the study, including the 500 mL bolus to assess fluid responsiveness, was only 525 mL. This suggests that the vast majority of volume resuscitation occurred prior to study enrollment and ultrasound images thus limiting the applicability of the study to patients.

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who present to the ED prior to any volume resuscitation. It may make the results more applicable to patients on arrival to the ICU, however, similar to patients who have already received fluids in the ED.

The authors conclude that their results support the use of cIVC, as the AUC of 0.84 is indicative of fair discrimination. In addition, this AUC is reasonably higher than that for PLR, which indicates that cIVC outperforms PLR as a measure of fluid responsiveness. While debate still exists as to the optimal cutoff for cIVC to predict fluid responsiveness, this study also suggests that it may be a useful tool in guiding fluid resuscitation.


The authors of this study questioned whether point-of-care doppler ultrasound measuring the change in carotid corrected flow time (ΔccFT) during a passive leg raise (PLR) accurately predicted fluid responsiveness in ICU patients with undifferentiated shock. The flow time is the time from ejection of blood into the aorta until the closing of the aortic valve as measured at the carotid. It predates modern ultrasound and was developed in conjunction with heart sounds and ECG tracings to determine the cardiac cycle. As a surrogate measurement for stroke volume, it can be measured using a pulse waveform analysis of the carotid artery and it can be corrected for heart rate variability.

For their prospective observational study, Barjaktarevic et al. enrolled 77 consecutive patients with early (< 24 hours) undifferentiated shock (requiring vasopressors despite > 1L fluid resuscitation) as they presented to the UCLA medical or surgical ICUs. They excluded patients with heart failure, any rhythm other than normal sinus, pulmonary hypertension, recent history of thromboembolism, or increased intracranial pressure. A single physician sonographer measured ccFT before and after PLR and a second physician blinded to the clinical environment measured the same unprocessed images to assess inter-rater variability. Results from the two physicians were not significantly different when compared with a Bland-Altman plot demonstrating a mean difference score = 0ms at baseline and -0.2ms after PLR (95% limits of agreement from -6.6 to + 6.4ms).

They divided the patients into responders and non-responders based on whether stroke volume increased 10% or more on PLR as measured by NICOM. Using a two-sample t-test they found a significant difference in the ΔccFT between responders (14.1ms +/- 19ms[SD]) and non-responders (-4.0ms +/- 8ms) with p < 0.001. They used a cutoff of 7ms to calculate a ROC curve for predicting fluid responsiveness with ΔccFT and found that it was 68% sensitive and 96% specific. Subgroup analyses of mechanical ventilation, PEEP > 5cmH2O, and respiratory rate demonstrated no significant impact on test performance.

The authors conclude ΔccFT is “an acceptable and reproducible” measure of fluid responsiveness in patients with undifferentiated shock, and this evidence is supportive but weak. It is plausible that this test should be reproducible given that a longitudinal view of the carotid with a linear probe is not difficult to achieve but the conclusion is undermined by having only two operators and only one set of images. The importance of doppler ultrasound agreement with NICOM as a gold standard is also questionable because NICOM was not validated in this specific population. The mathematical significance of the findings lacks a clinically-relevant outcome like duration of ICU admission, duration of vasopressor use, volume of crystalloid given, rates of renal failure, or mortality, and the significant variance in the ΔccFT shows overlap between responders and non-responders.


The authors of this study sought to elucidate if respiratory changes in internal jugular vein (IJV) diameter in mechanically-ventilated septic patients can predict fluid responsiveness. In mechanically-ventilated patients, the positive pressure from the ventilator causes distension of the extrathoracic vasculature during inspiration. Measuring this respiratory change in diameter of the IVC has been previously suggested to be an accurate measurement of fluid responsiveness. The internal jugular vein is an easily accessible vessel using ultrasound and is thought to be technically easier to image than the IVC.

In this prospective study, Guarracino et al. enrolled 50 patients aged 18 years or older who presented with sepsis and required intubation. They excluded patients with cardiac disease, atrial fibrillation, or any sign of IJV thrombosis. All patients were mechanically-ventilated with a mandatory minute ventilation setting and similar parameters (PEEP, FiO2, TV). During acquisition of measurements patients remained in a semi-recumbent position with the head of bead at 30 degrees elevation. All enrolled patients had an indwelling radial artery catheter to monitor hemodynamics including pulse pressure (PP), cardiac index (CI), and MAP. Pulse pressure variation (PPV) was defined as the ratio of the maximum difference in PP averaged over three respiratory cycles. All patients were given a 7 mL/kg crystalloid infusion over 30 minutes. Ultrasound measurements were performed just prior to and immediately following the fluid administration. The authors determined that responders would be patients who had a PPV > 13%. For their ultrasound measurements, a single operator used a 12-MHz linear transducer placed at the level of the cricoid cartilage to evaluate the diameter of the IJV in the anterior-posterior plane using M-mode. An IJV distensibility index (%) was calculated using the following formula: (maximal IJV inspiratory diameter - minimum IJV expiratory diameter) / minimum IJV expiratory diameter x 100. IJV distensibility measurements were performed by personnel blinded to the patient’s response to volume expansion.

The authors found that 30 patients were responders and 20 were non-responders. The median IJV distensibility index prior to fluid administration in the responders was 24.15% (IQR 20 to 29) and 9.8% (IQR 7.6 to 13.8) in the non-responders (p-value <0.0001). This difference between IJV distensibility was not present following volume expansion (p-value=0.07). The authors utilized ROC curves to determine the...
sensitivity and specificity for IJV distensibility and PPV to predict fluid responsiveness. They found that the sensitivity and specificity for predicting fluid responsiveness with an IJV distensibility > 18% was 80% (95% CI 61.4 - 92.3) and 95% (95% CI 75.1 – 99.9), respectively. The data also showed that the responders had a median PPV that was greater than the non-responders, 22.5% vs 12.2% (p-value < 0.0001). A PPV > 12.5% was shown to predict fluid responsiveness with a sensitivity and specificity of 96% and 95%, respectively. Using an IJV distensibility index >9.9% and a PPV >12%, the authors found that the sensitivity and specificity for predicting fluid responsiveness was 100% and 95%, respectively. Interobserver variability was assessed by taking two measurements of IJV diameter before and after fluid administration in the first 15 patients and showed significant agreement in measurements.

The authors concluded that utilizing IJV distensibility can predict fluid responsiveness in septic, mechanically ventilated patients. They further described that combining IJV distensibility with PPV can improve the sensitivity and specificity for predicting fluid responsiveness. The major limitations of this study are the size of the study, restriction to only mechanically ventilated septic patients, and lack of analysis of patients with cardiac disease. Furthermore, the authors used PPV as their gold standard for fluid responsiveness, which, while validated in a small sample of similar patients, is far from a widely accepted gold standard. Additionally, while identifying patients who respond to fluids is beneficial more clinically relevant endpoints should be evaluated as well, such as mortality and ICU length of stay.


Murthi et al. attempted to address the large variation between POCUS volume response measurements by using multiple different methods on the same patients. They utilized a convenience sample of patients in surgical and trauma ICU and performed testing on 242 patients. Ultimately 199 patients completed the study and were used for data analysis. 68% of patients were trauma/emergency surgery patients while the rest were a combination of other surgical services. The average injury severity score was 25. The majority of patients were mechanically ventilated (68%) with multiple different ventilatory modes used. The patients were identified as anyone who would be receiving a fluid infusion including crystalloid, blood products, or albumin. Ultimately, 64% received crystalloid while 21% received blood products. Within 30 minutes prior to infusion and within 30 minutes after infusion completion a TTE was performed in addition to multiple other testing modalities. They defined an increase in stroke volume by >15% as evidence of a volume response. The team used 6 different POCUS measures of volume responsiveness: 1) Left ventricular outflow tract velocity time integral (LVOT VTI), 2) relative positional change in IJV diameter at 0 degrees and 90 degrees head of bed, 3) respiratory variation in IJV diameter at 90 degrees head of bed, 4) respiratory stroke volume variation, 5) passive leg raise stroke volume variation, 6) respiratory variation of the IVC.

Overall, they found LVOT VTI to be the most predictive single measure of volume responsiveness with their interpretation of the ROC indicating the best threshold to detect volume responders is a VTI <18cm, and the best threshold for non-responders is a VTI >22cm. This resulted in a sensitivity of 75% and specificity of 70%. They also found respiratory variation of the IJV at 90 degrees head of bed (the left IJV measured at mid-neck in this study) was associated with an increased stroke volume after a fluid infusion. The authors found that the combination of these 2 metrics into a value called the CAVS (combined assessment of volume status) increased the area under the receiver operator curve to 76% (higher than either alone).

Importantly, they found that IVC variation was not associated with volume responsiveness although only 78% of patients had an IVC that was able to be measured. Subgroup analysis also showed that mechanically ventilated patients (not controlling for ventilator mode) had more accurate measures across all modalities. In addition, they found that pre-bolus EF and diastolic function were not associated with volume responsiveness.

The authors argued that studies on POCUS assessment of volume status should not use absolute thresholds, but rather ranges. This would help one of the main weaknesses of this study and many others like this, study population heterogeneity. Other weaknesses of the study included the limited ability to properly assess the IVC (only seen in 78% of patients) and inability to assess stroke volume (11% could not assess SV) as many patients were either obese or had undergone abdominal/thoracic surgeries that resulted in subcutaneous air. Passive leg raise could not reliable be measured as well and was largely excluded from the study as many patients had injuries that would prevent safe mobility of the legs. This study also had a limited sample size with disease processes largely limited to surgical hypovolemic states (54% were trauma patients).

Conclusions
The studies reviewed above demonstrate potential utility for several ultrasound methods of assessing volume responsiveness. Overall, measurements that are easier to obtain, such as IVC variability and IJV distensibility, may be less reliable, especially in spontaneously breathing patients. Other limitations include the inability of these measurements to exclude patients who might be volume responsive, notably in patients with elevated right-atrial pressure. Multiple measurements used in combination, as demonstrated in the latter two articles above, may be more reliable measures of volume responsiveness. Many studies are weakened by small sample sizes and the exclusion of highly relevant patient populations, such as those with heart failure and pulmonary hypertension. There remains a need for a controlled trial using a validated gold-standard measurement of fluid responsiveness to determine the...
The best ultrasound method to not only predict a response to volume but to differentiate between volume need and volume “tolerance.”

**Answer**

Measurements of IVC diameter and distensibility, carotid corrected flow time, UJV distensibility, and LVOT VTI can predict volume responsiveness, but each method has its own sensitivity, specificity, and limitations that can make its application and interpretation cumbersome. Recent existing studies demonstrate that a single, easily acquired ultrasound measurement that reliably predicts fluid responsiveness in the broad spectrum of patients managed in EDs and ICUs remains elusive. LVOT VTI demonstrates promise independently and with the use of PLR, but could use a direct, prospective, high-quality study validating it in conjunction with PLR.

**References**