Published in final edited form as:

Ultrasound Med Biol. 2020 October ; 46(10): 2659–2666. doi:10.1016/j.ultrasmedbio.2020.07.001.

Change in Carotid Blood Flow and Carotid Corrected Flow Time Assessed by Novice Sonologists Fails to Determine Fluid Responsiveness in Spontaneously Breathing Intensive Care Unit Patients

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Abstract

Measurement of carotid blood flow (CBF) and carotid corrected flow time (ccFT) has been proposed as a non-invasive means of determining fluid responsiveness. We evaluated the ability of CBF and ccFT as assessed by novice sonologists to determine fluid responsiveness in intensive care unit patients. Three novice physician sonologists performed carotid ultrasounds before and after a fluid bolus and calculated changes in CBF and ccFT. Fluid responsiveness was defined as a 10% increase in cardiac index as measured using bioreactance. Of 112 participants, 56 (50%) were fluid responders. Changes in CBF and ccFT performed poorly at determining fluid responsiveness: 19 mL/min (AUROC 0.58, 95% CI: 0.47 – 0.68) and 6 ms (AUROC 0.59, 95%

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Conflicts of interest: Cheetah Medical Inc. donated NICOM sensor leads used in this study. They had no role in the study design, conduct, data collection, data analysis and interpretation, manuscript preparation or review.

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CI: 0.46 – 0.65) respectively. Novice physician sonologists are unable to determine fluid responsiveness using CBF or ccFT. Further research is needed to identify the key limiting factors in using carotid ultrasound to determine fluid responsiveness.

Keywords

Fluid responsiveness; carotid ultrasound; carotid blood flow; carotid corrected flow time; point-of-care ultrasound

Introduction

Despite advances in critical care medicine, determining which patients are fluid responsive remains a significant challenge.(Monnet and Teboul 2013, Monnet et al. 2016) Only half of intensive care unit (ICU) patients will increase organ perfusion in response to intravenous (IV) fluids.(Marik et al. 2009) Given evidence that excessive fluid administration is associated with patient harm, a reliable and easily adopted means of predicting fluid responsiveness to tailor IV fluid resuscitation in patients is needed.(Benes et al. 2015; Boyd et al. 2011; Byrne and Van Haren 2017; Kelm et al. 2015; Marik et al. 2017)

Measurement of carotid blood flow (CBF) and carotid corrected flow time (ccFT) using point-of-care ultrasound (POCUS) have been proposed as a feasible, non-invasive means of determining fluid responsiveness.(Mackenzie et al. 2015; Marik et al. 2013) CBF measurement is prone to variability due to sonologist technique and has demonstrated mixed results.(Ma et al. 2017; Marik et al. 2013; Radparvar et al. 2019) ccFT has been studied more widely and may perform better than CBF. It has been shown to increase following IV fluid administration or a passive leg raise (PLR), and decreases following the administration of nitroglycerin, hemodialysis or blood donation.(Antipervitch et al. 2017; Blehar et al. 2014; Chebi et al. 2018; Hossein-Nejad et al. 2015; Mackenzie et al. 2015; Pare et al. 2016; Shokoohi et al. 2017) Early studies evaluating ccFT against objective measures of patient hemodynamics show good test characteristics for distinguishing fluid responders from non-responders.(Jalil et al. 2018; Kim et al. 2018; Ma et al. 2017) A 2018 study of participants with undifferentiated shock found that a change in ccFT of 7 milliseconds (ms) could distinguish fluid responders from fluid non-responders with an area under receiver operating characteristic (AUROC) curve of 0.88.(Barjaktarevic et al. 2018) These promising initial results are tempered by the fact that in all of these studies carotid POCUS was performed by an expert physician sonologist. Given that most clinicians are not expert sonologists it is imperative to test the utility of carotid POCUS among individuals with ultrasound skills that more closely resemble those of a typical practicing clinician. One study that evaluated the performance of novice physician sonologists demonstrated that they were able to assess carotid blood flow in healthy volunteers after a five-minute instructional video.(Stolz et al. 2015) In a contrasting study, novice physician sonologists measurements of ccFT were shown to have poor inter-rater reliability and reproducibility when compared to an expert sonologist.(Doctor et al. 2017) Sonologist experience is a key factor that will determine if CBF and ccFT can be widely used by clinicians to determine fluid responsiveness in clinical practice.

The primary aim of our study was to determine the ability of novice physician sonologists to accurately determine fluid responsiveness in spontaneously breathing ICU patients using POCUS measurements of CBF and ccFT. The secondary aim was to determine the optimum changes in CBF and ccFT that would distinguish fluid responders from non-responders.

Materials and Methods

Study design and setting

This prospective observational study was conducted in the ICUs of two tertiary-care medical centers from November 2016 to July 2018. Patients were eligible for participation if they were > 18 years old, spontaneously breathing, and had acute circulatory failure at any time within the first 72 hours from hospital presentation, which was defined as: persistent hypotension (systolic blood pressure < 90 mm Hg or mean arterial pressure < 65 mm Hg for 30 minutes), persistent tachycardia (heart rate > 120 beats per minute for 30 minutes), decreased urine output (< 0.5 mL/kg/hour), or serum markers of organ hypoperfusion (lactic acid > 2 meq/L or acidemia with a serum pH < 7.3). (Muller et al. 2012) Patients were excluded if they had atrial fibrillation or flutter, suspected or confirmed cardiogenic, obstructive or neurogenic shock, were incarcerated or pregnant, or in cases where the treatment team believed that administering an IV fluid bolus might be harmful. Patients with a history of carotid artery disease were not excluded from participation. The study was approved by the study hospitals' Institutional Review Board and informed consent was obtained from either patients or their surrogates prior to study participation.

Sonologists

Three novice physician sonologists without prior carotid ultrasound experience, enrolled in a medical critical care fellowship, performed all the POCUS assessments of CBF and ccFT at both ICUs. One of the novice physicians sonologists had received formal ultrasound training during an emergency medicine residency, the remaining two had no formal ultrasound training in their internal medicine residencies. Before enrolling subjects, the novice sonologists received a 6-hour hands-on training session on carotid ultrasound directed by an expert sonologist, and subsequently demonstrated proficiency in 10 directly-observed POCUS assessments of CBF and ccFT as evaluated by the expert sonologist. The expert sonologist had over 28 years of experience relating to the clinical use, medical education, research, and policy development surrounding POCUS.

Study protocol and ultrasound measurements

Determination of fluid responsiveness—Following enrollment, each participant's hemodynamic profile was measured at one-minute intervals throughout the study using bioreactance (NICOM™ CHEETAH Medical, Tel Aviv, Israel). NICOM leads were applied to each participant's thorax and then participants were placed in a supine position for a three-minute NICOM calibration period. One of the three novice sonologists performed two POCUS assessments of CBF and ccFT, before and after a 500 mL IV fluid bolus of 0.9% normal saline via pressure bag. Fluid responsiveness was defined as a ≥ 10% increase in cardiac index immediately following the fluid bolus, as measured using bioreactance. During the study, the novice sonologists were blinded to the NICOM results.

CBF and ccFT measurements—While the participants were supine, the novice sonologists visualized the common carotid artery using POCUS in the long-axis view using a 13 – 6 MHz linear array transducer (Sonosite Edge ultrasound; Sonosite, Bothell, WA). As part of the protocol, the novice sonologists preferentially visualized the right common carotid artery over the left. The carotid bulb was identified visually by a symmetric widening in the carotid artery. The anterior-posterior diameter of the common carotid artery was measured one centimeter from the carotid bulb in the sagittal plane, and used for all assessments of CBF and ccFT. The novice sonologists then obtained a pulse wave Doppler tracing of the common carotid artery proximal to the carotid bulb by placing the Doppler gate in the center of the artery, parallel to the artery wall. Cycle and systole times were then measured over a single waveform on the carotid tracing in real-time using electronic calipers on the ultrasound machine. The novice sonologist obtained a series of at least 10 waveforms before selecting a single waveform. Cycle time, the length of a single cardiac cycle, was measured as the distance between two consecutive systolic upstrokes, while systole time was measured from the start of a systolic upstroke to the following diastolic notch (Figure 1a, b). Still images of flow time (FT) and systole time were uploaded to a secure server for later review. CBF was calculated in real time as $\text{CBF (milliliter/minute)} = (\text{heart rate}) \times (\text{velocity time integral}) \times \pi \times (\text{carotid diameter})^2/4$, using the average of three waveforms (Figure 1c). (9) Sonosite Edge software performed this calculation automatically and the results were uploaded to the secure server. ccFT was calculated using Wodey's formula: $\text{ccFT (millisecond)} = \text{FT}_{\text{measured}} + 1.29 (\text{heart rate} - 60)$. (Barjaktarevic et al. 2017; Mohammadinejad and Hossein-Nejad 2018) Changes in CBF and ccFT were then calculated by subtracting the CBF or ccFT measured before versus after administration of the IV fluid bolus.

Statistical analysis—Participant demographic and clinical characteristics were extracted from the electronic health record at the time of enrollment, and summarized using descriptive statistics. For continuous clinical characteristics, variables were described using medians and the interquartile range (IQR) while frequencies and percentages were used for categorical variables. Differences in characteristics across fluid responders were assessed for using Fisher's exact test and Wilcoxon rank-sum test for categorical and continuous variables, respectively. Values for the optimum changes in CBF and ccFT in determining fluid responsiveness were identified by maximizing the sum of sensitivity and specificity in the area where the curves for these values intersect when graphed against the probability of fluid responsiveness. This was based on an unadjusted logistic regression model of fluid responsiveness against either change in CBF or change in ccFT. Test performance characteristics of these optimum change values were generated: AUROC curve, sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-), along with their respective 95% confidence intervals (CI). All analyses were conducted using Stata 14.2 (StataCorp, College Station, TX).

Results

Participant characteristic and fluid administration

We assessed 482 ICU patients to enroll 145 participants. Fourteen participants withdrew from the study, 13 before initiation of the study and one following the first carotid ultrasound. Ultrasound images for 11 patients were not properly captured and uploaded to the server for review, including one participant in whom the study was terminated after developing atrial fibrillation following administration of the IV fluid bolus. Eight patients were excluded from the data analyses, five due to NICOM error and three who were mechanically ventilated, yielding a final study sample of 112 participants (Appendix Figure 1). Participant characteristics are shown in Table 1. The median age of the participants was 53 years, and 63% were male. The most common etiology for acute circulatory failure included sepsis, septic shock, diabetic ketoacidosis, hyperosmolar hyperglycemic state and gastrointestinal hemorrhage. Fifty-six (50%) participants were fluid responders. Fluid responders had a significantly higher mean arterial pressure at the time of enrollment, as compared to fluid non-responders (74 mm Hg versus 65 mm Hg, $p = 0.02$). There were no other statistically significant differences between study groups. The median amount of fluid administered prior to study enrollment in both groups was 3 L (IQR 2 – 4 L). The IV fluid boluses were administered over a median infusion time of 8 minutes (IQR 7 – 11 minutes) among both fluid responders and non-responders. The carotid POCUS measurements were initiated within a median of 1 minute (1 – 2 min IQR) following the IV fluid bolus for both fluid responders and non-responders.

Outcomes

There were no differences in the changes in CBF (11 vs. 51 mL/min; $p = 0.17$) and ccFT (10 vs. 4 ms; $p = 0.29$) between fluid responders and non-responders (Table 2). The optimum change in CBF to detect fluid responsiveness was 19 mL/min and the optimum change in ccFT was 6 ms. Both failed to distinguish fluid responders from non-responders: AUROC of 0.58 (95% CI: 0.47 – 0.68) and 0.59 (95% CI: 0.46 – 0.65) respectively (Figure 2). CBF and ccFT test performance characteristics are provided in Table 3. Changes in CBF and ccFT following administration of an IV fluid bolus were inconsistent, decreasing in some fluid responders or non-responders, while increasing in others (Appendix Figure 2). Employing a gray zone approach that identified values for changes in CBF and ccFT with a sensitivity or specificity fixed at 90% for determining fluid responsiveness did not improve test characteristics (Table 3).

Analyses of the three novice physician sonologists' data in assessing test performance of CBF and ccFT to determine fluid responsiveness failed to improve test characteristics (Appendix Table 1). Neither the change in CBF nor ccFT as assessed by the novice physician sonologists individually detected fluid responsiveness. AUROCs for the three sonologists individually ranged from 0.56 to 0.75 for CBF, and 0.55 to 0.63 for ccFT. A secondary analyses of the ability CBF and ccFT to detect fluid responsiveness stratified by participant age (< 45 years old vs > 45 years old) failed to statistically improve testing characteristics (Appendix Table 2).

Discussion

POCUS assessment of blood flow through the carotid artery has been proposed as a feasible non-invasive means to determine fluid responsiveness.(Marik et al. 2013) To date, studies that support its use typically have used expert physician sonologists to obtain POCUS images.(Barjaktarevic et al. 2018; Jalil et al. 2018; Kim et al. 2018; Ma et al. 2017) The results of our study suggest that novice physician sonologists are unable to reliably determine fluid responsiveness among spontaneously breathing ICU patients using carotid POCUS measurement of the change in CBF or ccFT (AUROC 0.58 and 0.59, respectively). The optimum change in ccFT to determine fluid responsiveness estimated in this study was 6 ms, which is similar to a prior threshold derived by an expert physician sonologist, and 19 mL/min for CBF.(Barjaktarevic et al. 2018) Both values showed very poor accuracy in distinguishing fluid responders from non-responders.

Our findings stand in contrast to initial work that suggests carotid POCUS may be a feasible way for clinicians to determine fluid responsiveness.(Barjaktarevic et al. 2018; Blehar et al. 2014; Jalil et al. 2018; Kim et al. 2018; Marik et al. 2013; Shokoohi et al. 2017) While these earlier studies used expert physician sonologists to acquire POCUS carotid data, our study used novice sonologists. Sonologist proficiency is likely the key driver of our negative findings. The reliability and reproducibility of carotid POCUS measured ccFT can be poor when compared between novice and expert physician sonologists.(Doctor et al. 2017) The finding that a change in CBF failed to determine fluid responsiveness is not surprising since this measurement is recognized to be skill dependent. The inability to maintain an appropriate and consistent angle of inclination before and after an IV fluid bolus can lead to erroneous CBF measurements.(Ma et al. 2017) ccFT, in contrast, has been advocated as a measurement that is robust to this source of error.(Blehar et al. 2014; Doctor et al. 2017) However, an individual analysis of the three novice physician sonologists (Appendix Table 1) showed notable variations between them: AUROC for change in CBF ranged from 0.56 to 0.75, while the AUROC for change in ccFT was 0.55 to 0.63. The range of results among our novice physician sonologists implies that POCUS skill likely affected the observed results.

Time elapsed between the IV fluid bolus and carotid POCUS measurements may also explain why the novice physician sonologists were unable to determine fluid responsiveness. Fluid responsiveness is a time-dependent phenomenon; meaning that patients who initially show a significant increase in cardiac index following an IV fluid bolus may only do so for a short period of time.(Glassford et al. 2014) While a 2019 study suggests the effects of an IV fluid bolus can dissipate over 30 minutes, clinical experience suggests that the effects of an IV fluid bolus vary widely among patients and in some cases may dissipate quickly.(Roger et al. 2019) Although the novice physician sonologists usually measured CBF and ccFT shortly after the fluid bolus (median 1 minute), 40% (45 of 112) of the measurements were not obtained within the first minute. Additionally, because the time measurements were recorded at the start of the carotid POCUS measurements, instead of after they were completed, the time elapsed was in fact longer. These time delays could have been enough to negate the accuracy of change in CBF and ccFT. Advancements in technology that

automates carotid POCUS and are able to capture measurements the moment an IV fluid bolus is completed may eliminate this potential source of error.

Another reason why our study did not reveal a relationship between change in ccFT and fluid responsiveness may have been that ccFT was measured over a single waveform, rather than as an average over multiple waveforms. In a study by Ma, et al., a single waveform measurement of ccFT did not correlate with cardiac output measured by right heart catheterization and thermodilution.(2017) An average of three waveform measurements of ccFT performed only marginally better. Studies comparing ccFT to an objective measure of fluid responsiveness have both used one and three beat averages.(Barjaktarevic et al. 2018; Kim et al. 2018) Not only does the variation in clinical practice introduce a potential source of error, the work by Ma, et al. perhaps challenges the physiologic premise for using the change in ccFT as surrogate for cardiac output.(2017)

Finally, the participants' underlying carotid artery disease and vessel stiffness may have affected our results. Population based studies show that more than 50% of patients 55 years of age or older have carotid plaque. (Sturlaugsdottir R et al. 2016) We intentionally did not exclude patients with a history of carotid artery disease in an effort to make our results generalizable to a larger ICU population. Our stratified analysis of participants less than 45 years old, who generally have minimal-to-no carotid plaque did not improve test characteristics for CBF, and marginally improved the point estimate of the AUROC (0.68; 95% CI 0.52–0.84) for ccFT (Appendix Table 2). The small sample size (n = 40) and wide confidence intervals limit any conclusions that might be drawn from this analysis. Further study in this age group is warranted.

A strength of our study is that we used a 500 mL IV fluid bolus to test fluid responsiveness, as opposed to using a passive leg raise (PLR) to simulate a fluid bolus. While a meta-analysis of the use of a PLR to simulate a fluid bolus strongly supports this practice, these findings may be overstated because of publication bias.(Cherpanath et al. 2016) Secondary analyses of a large multicenter trial using PLR suggests that the sensitivity and specificity of a PLR simulated fluid bolus may be significantly lower than previously reported (84% and 62%, respectively).(Vistisen et al. 2017) In addition, a 2018 study demonstrated that PLR tests repeated within the same critically ill patients lack precision; over 35% of patients demonstrated results that were not reproducible.(Chopra et al. 2019) Our use of a fluid bolus differs from work by Barjaktarevic, et al, and could in part explain the discordant results. (2018)

Our study has limitations. First, POCUS measurements were obtained only once before and after IV fluid administration by one of the three novice physician sonologists. This design therefore did not permit calculation of inter- and intra-rater reliabilities. Second, an expert physician sonologist did not supervise or repeat the carotid POCUS measurements. This would have allowed for a direct comparison between novice and expert test performance, and allowed us to address the impact sonologist experience had on the ability of the novice physician sonologist to predict fluid responsiveness using CBF and ccFT. While we acknowledge this limitation, prior work has demonstrated that expert sonologists perform well using carotid POCUS to determine fluid responsiveness.(Barjaktarevic et al. 2018; Kim

et al. 2018) Additionally, while the novice physician sonologists had to each demonstrate proficiency in 10 directly-observed POCUS assessments of CBF and ccFT as evaluated by the expert sonologist before study enrollment, there was no widely accepted standard they had to each demonstrate. Study designs that involve expert supervision of novice physician sonologists likely bias the results towards the expert's skill level. We also note that training our novice sonologist for 6 hours may have produced a study group of novices with a greater skill level than the typical physician using carotid POCUS in clinical practice. In a study by Doctor et al. that found poor reliability and reproducibility of ccFT between novice sonologists, the novices received a 1-hour didactic session followed by 5 proctored carotid exams.(2017) Therefore, our study design may bias the findings away from our null hypothesis. Third, while all of our participants were spontaneously breathing and most were not in significant respiratory distress, we did not control for respiratory effort. Although, POCUS measurements of fluid responsiveness that rely on the venous system's interaction with the right heart, such as inferior vena cava collapsibility (cIVC) are more subject to heart-lung interactions, left sided measurements of cardiac output such as CBF and ccFT may be affected as well. If respiratory effort alters the flow of blood through the carotid artery, the magnitude of the effect may be relatively small. An observational study found no difference in ccFT measured at end inspiration or end expiration (Doctor et al. 2017). Fourth, some experts are skeptical that NICOM does not accurately measure true patient hemodynamics.(Joosten et al. 2017) Currently, no form of non-invasive hemodynamic monitoring has demonstrated superiority over other modalities, and NICOM has been validated against invasive measurements of hemodynamics using thermodilution in a variety of patient settings.(Huygh et al. 2016; Raval et al. 2008; Squara et al. 2007) While acknowledging the potential limitations of NICOM, the completely non-invasive nature of bioimpedance is a strength. Previous methodologically sound research of carotid POCUS has used the NICOM technology, making our selection of NICOM to measure patient hemodynamics reasonable.(Barjaktarevic et al. 2018)

Conclusion

Our study demonstrates that novice physician sonologists are unable to use POCUS assessment of CBF and ccFT to determine fluid responsiveness in spontaneously breathing intensive care unit patients. Physician sonologist experience as well as the timing of carotid POCUS measurements following the IV fluid bolus could explain the poor performance. Until further research identifies key aspects of sonologist proficiency and ultrasound timing, clinicians should use caution when using carotid POCUS to determine fluid responsiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study including the statistical analysis was supported by HL134625 (AA) and the Division of Pulmonary, Critical Care and Sleep Medicine at the Warren Alpert School of Medicine at Brown University.

Appendices

Appendix Table 1.

Analyses of measurements from individual novice physician sonologists

Novice Sonologist	Change in CBF	n	AUROC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
1	54	42	0.68 (0.47 – 0.84)	61.1 (38.6 – 79.7)	75.0 (55.1 – 88.0)
	< 54				
2	35	25	0.75 (0.41 – 0.93)	71.4 (45.4 – 88.3)	72.7 (43.4 – 90.3)
	< 35				
3	–48	45	0.56 (0.37 – 0.73)	66.7 (46.7 – 82.0)	47.6 (28.3 – 67.6)
	< –48				

Novice Sonologist	Change in ccFT	n	AUROC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
1	18	42	0.55 (0.35 – 0.73)	61.1 (38.6 – 79.7)	45.8 (27.9 – 64.9)
	> 18				
2	11	25	0.63 (0.31 – 0.86)	50.0 (26.8 – 73.2)	72.7 (43.4 – 90.3)
	< 11				
3	6	45	0.56 (0.37 – 0.73)	62.5 (42.7 – 78.8)	52.4 (32.4 – 71.7)
	> 6				

AUROC-area under receiver operating characteristic curve, CBF-carotid blood flow, ccFT-carotid corrected fluid time, CI-confidence interval, n-number

Appendix Table B.

Subgroup analyses of CBF and ccFT performance by age

Change in CBF	age	Fluid Responder		AUROC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
		No	Yes			
< 19	45	13	8	0.55 (0.39 – 0.72)	55.6 (33.7 – 75.4)	59.1 (38.7 – 76.7)
19		9	10			
< 19	> 45	17	14	0.57 (0.45 – 0.69)	63.2 (47.3 – 76.6)	50.0 (34.1 – 65.9)
19		17	24			

Change in ccFT	age	Fluid Responder		AUROC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
		No	Yes			
< 6	45	7	11	0.68 (0.52 – 0.84)	55.6 (33.7 – 75.4)	59.1 (38.7 – 76.7)
6		15	7			
< 6	> 45	18	19	0.51 (0.39 – 0.63)	63.2 (47.3 – 76.6)	50.0 (34.1 – 65.9)
6		16	19			

AUROC-area under receiver operating characteristic curve, CBF-carotid blood flow, ccFT-carotid corrected fluid time, CI-confidence interval, n-number

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Figure 1a – c.

Doppler tracing of the common carotid artery. 1a. Cycle time and 1b. systole time used to calculate carotid corrected flow time (ccFT). 1c. Three waveform calculation of carotid blood flow (CBF).

Figure 2. Dot plot of corrected carotid flow time (ccFT) and carotid blood flow (CBF) by fluid responder status. Optimal changes in ccFT and CBF are displayed.

Table 1.

Participant demographics and clinical characteristics stratified by fluid responsiveness

	Fluid non-responders (n = 56)	Fluid responders (n = 56)	<i>p</i> value [‡]
Demographics			
Age (years), median (IQR)	54 (33 – 69)	53 (44 – 64)	0.86
Male, n (%)	40 (71.4)	31 (55.4)	0.12
BMI (kg/m ²), median (IQR)	27.6 (22.3 – 32.0)	27.8 (23.3 – 32.1)	0.33
Clinical characteristics			
Heart rate	110 (95 – 117)	103 (90 – 114)	0.20
Respiratory Rate	25 (22 – 31)	27 (21 – 32)	0.98
Mean arterial pressure (mm Hg)	65 (54 – 81)	74 (62 – 110)	0.02
APACHE II score, median (IQR)	16 (11 – 22)	15 (10 – 19)	0.27
Resuscitation			
IV fluid prior to enrollment (L), median (IQR)	3.0 (2.0 – 4.0)	3.0 (2.0 – 4.0)	0.68
IV fluid administered during study (L), median (IQR)	0.5 (0.5 – 0.5)	0.5 (0.5 – 0.5)	0.32
Duration of fluid bolus (min), median (IQR)	9 (7 – 11)	8 (7 – 13)	0.90
Required vasopressors, n (%)	10 (17.9)	5 (8.9)	0.27
Medical history, n (%)			
Hypertension	33 (58.9)	30 (53.6)	0.70
Diabetes mellitus	31 (55.4)	28 (50.0)	0.71
Cardiomyopathy	8 (14.3)	5 (8.9)	0.56
Alcohol Abuse	14 (25.0)	18 (32.1)	0.53
Chronic obstructive pulmonary disease	9 (16.1)	12 (21.4)	0.63
Pulmonary embolism	3 (5.4)	2 (3.6)	> 0.99
Pulmonary hypertension	6 (10.7)	1 (1.8)	0.11
Hospital discharge diagnosis, n (%)			
Severe sepsis/septic shock	20 (35.7)	12 (21.4)	0.14
DKA/HHS	18 (32.1)	18 (32.1)	> 0.99
Gastrointestinal hemorrhage	6 (10.7)	8 (14.3)	0.78
Alcohol withdrawal	3 (5.4)	3 (5.4)	> 0.99
Respiratory failure (pneumonia)	1 (1.8)	1 (1.8)	> 0.99
Outcomes, n (%)			
ICU length of stay (days)	2 (1–3)	1 (1–2)	0.27
Hospital length of stay (days)	4.5 (3–8)	4 (2–7)	0.16
Survival to discharge	53 (94.6)	52 (92.9)	> 0.99

[‡]p-values are based on Fisher's exact test for binary variables and Wilcoxon rank-sum test for continuous variables

APACHE II-Acute Physiology and Chronic Health Evaluation II, bpm-beats per minute, BMI-body mass index, DKA-diabetic ketoacidosis, HHS-hyperosmolar hyperglycemic state, ICU-intensive care unit, IQR-interquartile range, IV-intravenous, kg-kilogram, L-liter, m²-meters squared, mm Hg-millimeters of mercury, min-minute, n-number,

Table 2.

Carotid measurements and noninvasive cardiac output monitoring results before and after an IV fluid bolus

	Fluid non-responders (n = 56)	Fluid responders (n = 56)	<i>p</i> value [‡]
Hemodynamic measurements			
Mean arterial pressure (mm Hg), median (IQR)	65 (54 – 81)	74 (62 – 110)	0.02
Heart rate, median (IQR)	110 (95 – 117)	103 (90 – 114)	0.20
Baseline stroke volume (mL), median (IQR)	76 (66 – 93)	73 (62 – 87)	0.31
Post IV fluid bolus stroke volume (mL), median (IQR)	77 (62 – 96)	91 (73 – 103)	0.013
Change in baseline stroke volume (mL), median (IQR)	0 (–3 – 4)	13 (10 – 20)	0.001
Baseline cardiac index (L/min/m ²)	3.5 (3.0 – 4.2)	3.3 (2.8 – 3.7)	0.048
Post IV fluid bolus cardiac index (L/min/m ²), median (IQR)	3.5 (2.9 – 4.2)	4.0 (3.3 – 4.4)	0.013
Change in cardiac index (L/min/m ²), median (IQR)	0 (–.01 – 0.2)	0.6 (0.4 – 0.9)	0.001
Carotid ultrasound measurements			
Baseline CBF (mL/min), median (IQR)	605 (500 – 840)	591 (454 – 831)	0.63
Post IV fluid bolus CBF (mL/min), median (IQR)	656 (485 – 835)	698 (507 – 854)	0.41
Change in CBF (mL/min), median (IQR)	11 (–70 – 80)	51 (–55 – 183)	0.17
Baseline ccFT (ms), median (IQR)	319 (296 – 338)	321 (300 – 338)	0.49
Post IV fluid bolus ccFT (ms), median (IQR)	318 (304 – 346)	326 (307 – 345)	0.44
Change in ccFT (ms), median (IQR)	10 (–4 – 25)	4 (–10 – 20)	0.29

[‡]p-values are based on Fisher's exact test for binary variables and Wilcoxon rank-sum test for continuous variables

CBF-carotid blood flow, ccFT-carotid corrected flow time, IQR-intra-quartile range, IV-intravenous, L-liter, m²-meters squared, mL-milliliter, mm Hg-millimeters of mercury, ms-millisecond, min-minute, n-number

Table 3.

Test performance characteristics for changes in carotid blood flow (CBF) and corrected carotid flow time (ccFT) to determine fluid responsiveness

Change in CBF	Fluid responders (n = 56)	Non-responders (n = 56)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV% (95% CI)	NPV % (95% CI)	+ LR % (95% CI)	- LR % (95% CI)	Accuracy % (95% CI)
19	34	26	60.7 (47.6 – 72.4)	53.6 (40.7 – 66.0)	56.7 (44.1 – 68.4)	57.7 (44.2 – 70.1)	1.31 (1.28 – 1.34)	0.73 (0.71 – 0.75)	57.1 (47.9 – 65.9)
< 19	22	30							
-164	50	51	90	8.9 (3.9 – 19.3)	49.5 (40.0 – 59.1)	45.5 (21.3 – 72.0)	1.31 (1.28 – 1.34)	0.73 (0.71 – 0.75)	57.1 (47.9 – 65.9)
< -164	6	5							
208	12	6	21.4 (12.7 – 33.8)	90	66.7 (43.7 – 83.7)	53.2 (43.2 – 63.0)	2.00 (1.86 – 2.16)	0.88 (0.87 – 0.89)	55.4 (46.1 – 64.2)
< 208	44	50							

Change in ccFT	Fluid responders (n = 56)	Non-responders (n = 56)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV% (95% CI)	NPV % (95% CI)	+ LR % (95% CI)	- LR % (95% CI)	Accuracy % (95% CI)
6	30	25	53.6 (40.7 – 66.0)	55.4 (42.4 – 67.6)	54.5 (41.5 – 67.0)	54.4 (41.6 – 66.6)	1.20 (1.18 – 1.23)	0.84 (0.82 – 0.86)	54.5 (45.2 – 63.4)
> 6	26	31							
39	50	50	90	10.7 (5.0 – 21.5)	50.0 (41.4 – 59.6)	50.0 (25.4 – 74.6)	1.00 (1.00 – 1.00)	1.00 (0.99 – 1.00)	50.0 (40.9 – 59.1)
> 39	6	6							
-21	6	5	10.7 (5.0 – 21.5)	90	54.5 (28.0 – 78.7)	50.5 (40.9 – 60.0)	1.20 (1.15 – 1.27)	0.98 (0.97 – 0.98)	50.9 (41.8 – 60.0)
> -21	50	51							

CBF-carotid blood flow, ccFT-carotid corrected fluid time, CI-confidence interval, NPV-negative predictive value, n-number, + LR-positive likelihood ratio, - LR-negative likelihood ratio, PPV-positive predictive value