



Non-invasive Cardiac Output Monitoring and Assessment of Fluid Responsiveness in Children With Shock in the Emergency Department

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Introduction: The assessment of fluid responsiveness is important in the management of shock but conventional methods of assessing fluid responsiveness are often inaccurate. Our study aims to evaluate changes in objective hemodynamic parameters as measured using electrical cardiometry (ICON® monitor) following the fluid bolus in children presenting with shock and to evaluate whether any specific hemodynamic parameter can best predict fluid responsiveness among children with shock.

Materials and Methods: We conducted a prospective observational study in children presenting with shock to our emergency department between June 2020 and March 2021. We collected the parameters such as heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and hemodynamic data such as cardiac output (CO), cardiac index (CI), index of contractility (ICON), stroke volume (SV), stroke index (SI), corrected flow time (FTC), systolic time ratio (STR), variation of index of contractility (VIC), stroke volume variation (SVV), systemic vascular resistance (SVR), and thoracic fluid content (TFC) using the ICON monitor before and after fluid bolus (FB). We assessed percent change (Δ) and used paired-sample Student's *t*-test to compare pre- and post-hemodynamic data and Mann-Whitney *U*-test to compare fluid responders and non-responders. *P*-Values < 0.05 were considered statistically significant.

Results: We recorded 42 fluid interventions in 40 patients during our study period. The median IQR age was 10.56 (4.8, 14.8) years with male/female ratio (1.2:1). There was a significant decrease in Δ RR [−1.61 (−14.8, 0); *p* = 0.012], Δ DBP [−5.5 (−14.4, 8); *p* = 0.027], Δ MAP [−2.2 (−11, 2); *p* = 0.018], Δ SVR [−5.8 (−20, 5.2); *p* = 0.025], and Δ STR [−8.39 (−21, 3); *p* = 0.001] and significant increase in Δ TFC [6.2 (3.5, 11.4); *p* = 0.01] following FB. We defined fluid responders by an increase in SV by $\geq 10\%$

after a single FB of 20 ml/kg crystalloid. Receiver operating curve analysis revealed that among all the parameters, 15% change in ICON had an excellent AUC (0.85) for the fluid responsiveness.

Conclusion: Our study showed significant changes in objective hemodynamic parameters, such as SVR, STR, and TFC following FB in children presenting with shock. A 15% change in ICON had an excellent predictive performance for the fluid responsiveness among our cohort of pediatric shock.

Keywords: fluid responsiveness, shock, children, hemodynamic monitoring, electrical cardiometry

INTRODUCTION

Shock is a leading cause of morbidity and mortality in the pediatric patients worldwide (1, 2). The prevalence of sepsis and septic shock has been reported to be around 1–26% of shock cases with mortality rates ranging from 5 to 35% in hospitalized children globally (3, 4). Appropriate fluid resuscitation is crucial in the management of children with shock (5). The current American College of Critical Care Medicine (ACCM), Pediatric Advanced Life Support (PALS), and Surviving Sepsis Campaign Guidelines have focused on the implementation of early and goal-directed fluid therapy (6, 7). Many studies have shown that mortality in pediatric patients with septic shock has been significantly decreased with aggressive fluid administration (8, 9). However, overzealous fluid administration can also lead to fluid overload (FO) and has been associated with complications such as acute respiratory distress syndrome (ARDS), which results in poor outcomes including increased hospital length of stay and mechanical ventilator days (10–13). As a result, in the recent decades, a more restrictive approach for fluid resuscitation has emerged in adults and children vs. the usual aggressive fluid therapy (14–16).

Despite ongoing extensive research related to fluid management in septic shock, the optimal amount of fluid to administer in early resuscitation of pediatric shock remains uncertain (17). Therefore, it is imperative to assess the clinical and hemodynamic responses before and after each fluid bolus (FB) to guide resuscitation and to determine the presence or absence of FO. Traditional use of subjective findings such as pulse volume, capillary refill time, and clinical signs of hydration status to predict fluid responsiveness (FR) has been proven to be unreliable (18, 19). In the recent decades, objective hemodynamic parameters have gained popularity and have been shown to reliably predict FR in adults (20, 21). While there is a growing body of the literature on the use of non-invasive devices for objective hemodynamic monitoring, there is a paucity of the literature related to the assessment of FR using these measures in children with shock (22).

ICON monitor, which is based on a novel technology of electrical cardiometry (EC), is one such non-invasive hemodynamic monitoring device and has been studied for the assessment of FR in adult patients with the promising results (23, 24). EC technique uses signals generated by the surface electrodes to measure the alterations in thoracic impedance. The changes in bio-impedance to the flow of erythrocytes in the aorta are

computed into an algorithm allowing continuous hemodynamic monitoring (25). In our pilot study, we aim to determine changes in subjective and objective measures of hemodynamic status before and after FB in children with shock using ICON monitor. We also sought to assess whether changes in objective parameters could predict FR in these children.

MATERIALS AND METHODS

Study Design and Selection of Participants

We conducted a prospective observational pilot study in children presenting with shock to our emergency department (ED) from June 2020 to March 2021. We conducted the study at the Children's Hospital of San Antonio (CHofSA), a freestanding, 200-bed, tertiary care children's hospital. The Baylor College of Medicine Institutional Review Board and CHofSA feasibility committee approved the study. Due to the prospective observational nature of the study, a waiver of informed consent was obtained.

In our study, we used ICON® non-invasive hemodynamic monitor to measure objective hemodynamic parameters before and after FBs in children with shock in the ED. ICON® monitor has been utilized to monitor patient hemodynamics in our pediatric intensive care unit (PICU) since 2018. Hence, we were interested to determine whether it may be feasible to expand the use of ICON® monitor to the ED. After a short training period for the research team and ED staff, we began using the monitor on ED patients with shock to explore the workflow and obtain fluid resuscitation responses by measuring subjective and objective parameters.

Inclusion Criteria

1. Children aged 0–17 years who presented in shock or presumed shock and required FB in our ED.
2. Children in whom all the hemodynamic parameters were available and feasible using ICON® monitor.

Exclusion Criteria

1. Children with suspected infection with SARS CoV-2 who were designated as patients under investigation (PUI).
2. Children in whom any hemodynamic data using ICON® monitor were not feasible or not available.

Unfortunately, during the study period, we were facing the COVID-19 pandemic wave. During the study period, our hospital policies required all PUI to be considered as suspected COVID 19 and did not allow trainees to be involved with the care of PUI and patients with COVID-19. We therefore excluded the PUI.

We defined shock *a priori* based on a combination of clinical and/or laboratory parameters such as hypothermia or hyperthermia, tachycardia or tachycardia out of proportion to the degree of fever, tachypnea, hypotension, delayed capillary refill time, dry mucosa, and elevated lactate levels which warranted fluid resuscitation. In our ED, it is a standard protocol for the triage nurse to alert the ED attending about any patient presenting in shock or presumed shock. The ED attending then decides about the administration of FB based on his/her assessment of the patient's clinical status suggestive of shock or presumed shock. Therefore, in our study, we included pediatric patients presenting with shock or presumed shock who were administered FB. In our ED, it is a routine practice to monitor the patients' clinical and hemodynamic parameters obtained *via* standard monitoring before and after FB interventions. We expanded the current standard of care with an application of the ICON® monitor to obtain additional hemodynamic parameters after the decision to administer fluid was made. The providers were blinded to the information collected by the monitor to reduce the risk

of introducing bias into the treatment of the patients. We did not initiate or change real-time clinical management of the patient based on hemodynamic parameters obtained using the ICON® monitor.

Non-invasive Monitoring

ICON® monitor measurements require the placement of four skin sensors on the left side of the body as shown in **Figure 1**. After attaching the four sensors (two upper and two lower), we confirmed 100% signal strength before capturing hemodynamic parameters for accuracy. The upper sensors apply a harmless low amplitude, high-frequency alternating current. The changes in pulsatile red blood cell flow and change of thoracic electrical bio-impedance during the cardiac cycle are captured between the pair of the sensors. The complex mathematical algorithm built into the device calculates beat-to-beat parameters such as cardiac output, stroke volume, and many other hemodynamic parameters (25).

Hemodynamic Measurements

We collected hemodynamic variables before and within 10 min after each FB in children with shock. We obtained demographic characteristics such as age and gender, clinical parameters such as heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure

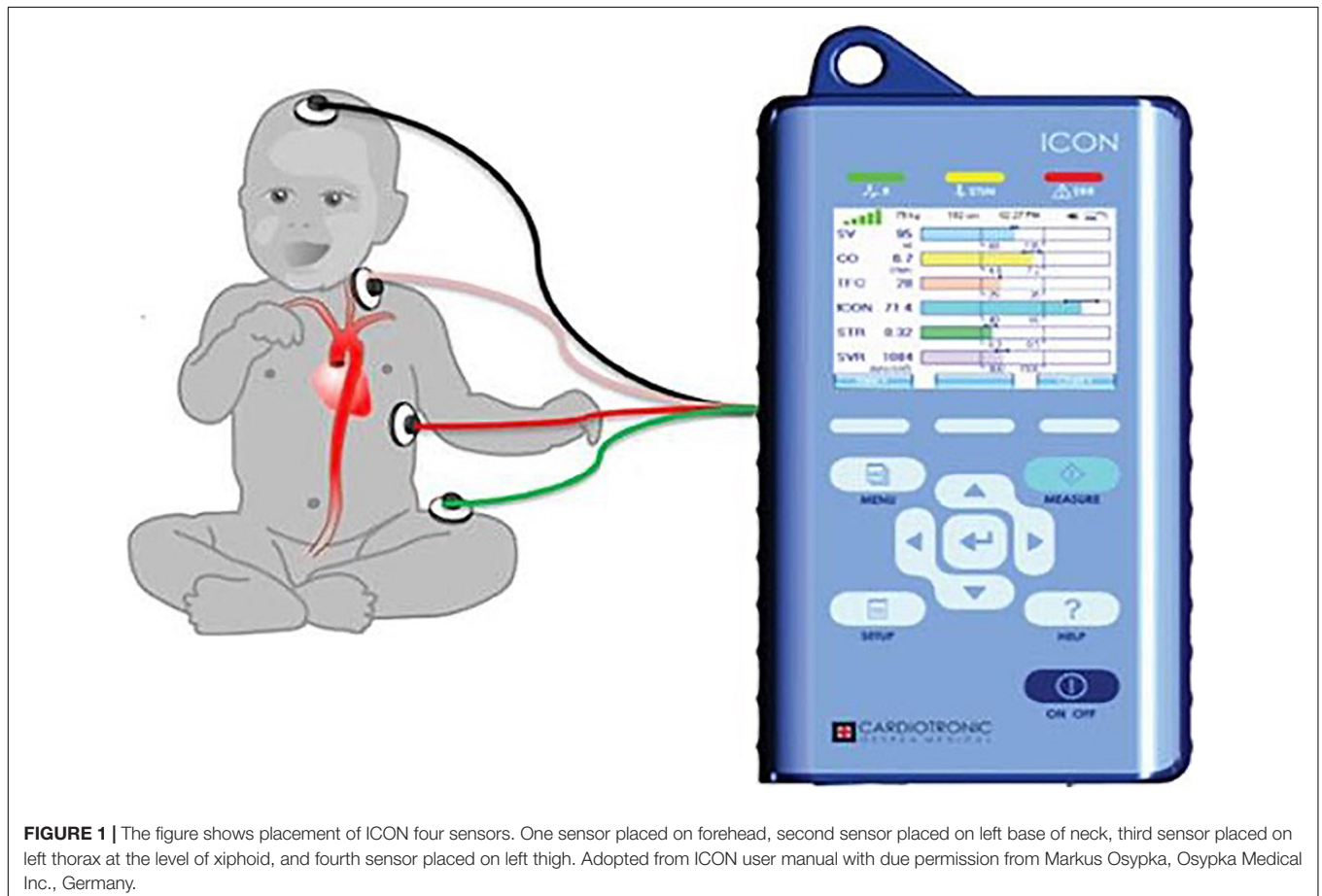


FIGURE 1 | The figure shows placement of ICON four sensors. One sensor placed on forehead, second sensor placed on left base of neck, third sensor placed on left thorax at the level of xiphoid, and fourth sensor placed on left thigh. Adopted from ICON user manual with due permission from Markus Osypka, Osypka Medical Inc., Germany.

(MAP), and hemodynamic parameters from ICON device such as cardiac output (CO), cardiac index (CI), index of contractility (ICON), stroke volume (SV), stroke index (SI), corrected flow time (FTC), systolic time ratio (STR), variation of index of contractility (VIC), stroke volume variation (SVV), systemic vascular resistance (SVR), and thoracic fluid content (TFC).

Similar to the prior studies in adults, we defined the fluid responders *a priori* as those who exhibited an increase in SV by $\geq 10\%$ after a single FB of 20 ml/kg crystalloid (18).

Statistical Analysis

We conducted a statistical analysis using R-project (R Core Team, Vienna, Austria). We presented numeric data in median interquartile range (IQR) values. We calculated percent change (Δ) for pre- and post-hemodynamic data and compared the data using paired-sample Student's *t*-test. We used Mann-Whitney *U*-test to compare hemodynamic parameters between fluid responders and non-responders. Furthermore, we plotted sensitivity and specificity for the cut-off points 5, 10, 15, and 20% for all variables to create receiver operating characteristic (ROC) curves to assess their predictive performances. *p*-values < 0.05 were considered statistically significant.

RESULTS

During the study period between June 2020 and March 2021, total number of ED visits in our children's hospital was 23,060.

Out of these patients, 1,792 presented with shock. During the Coronavirus disease 2019 (COVID-19) pandemic, the ICON device was not used in many patients who visited our ED during the study period. Therefore, in total, we were able to record 42 fluid interventions in 40 patients out of these 1,792 during our pilot study (Figure 2).

Patient's Characteristics

The median (IQR) patient age was 10.56 (4.8, 14.8) years with male/female ratio 1.2:1. Out of 40 patients included in our study, 32 (80%) had clinical findings and the remaining 8 (20%) had clinical and laboratory findings suggestive of shock. The hypovolemic shock was present to some degrees in 72% and septic shock in 28% of patients. The most common underlying etiology of shock was hypovolemia due to gastrointestinal condition (48%) (Table 1). All patients received FBs with crystalloids *via* infusion pump. The preferred crystalloid was normal saline in 32/42 (76%) and ringer's lactate in 10/42 (24%). The mean weight-based volume of fluid administration was 16.24 ml/kg (standard deviation 5.6) with a mean duration of 47.26 min (standard deviation 15.8) to bolus completion.

Effects of Fluid Therapy and Fluid Responsiveness

We observed a significant decrease in ΔRR [-1.61 ($-14.8, 0$); $p = 0.012$], ΔDBP [-5.5 ($-14.4, 8$); $p = 0.027$], ΔMAP [-2.2 ($-11, 2$); $p = 0.018$], ΔSVR [-5.8 ($-20, 5.2$); $p = 0.025$], and

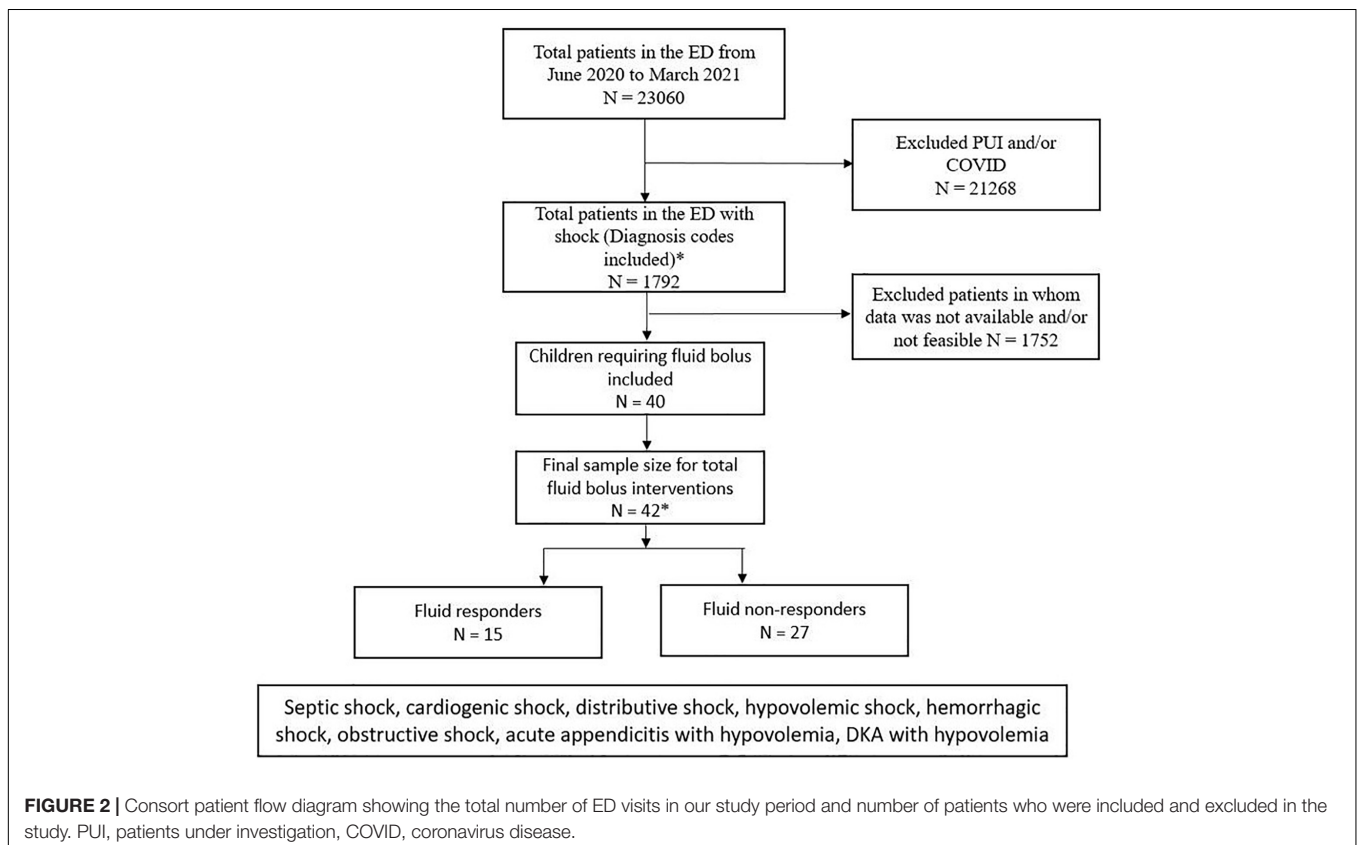


TABLE 1 | Demographic data and clinical characteristics.

Patient's characteristics	Percentage (%) or Median (IQR)
Age (years)	10.56 (4.8, 14.8)
Gender (male: female)	1.2:1
Type of shock	
Hypovolemic	30 (72%)
Septic	12 (28%)
Underlying etiology/Primary diagnosis/System involved	
Gastrointestinal	20 (48%)
Endocrine/Metabolic	9 (22%)
Neurological	7 (16%)
Genitourinary	2 (6%)
Respiratory	1 (2%)
Musculoskeletal	1 (2%)
Hematology/Oncology	2 (4%)

IQR, interquartile range.

Δ STR [−8.39 (−21, 3); $p = 0.001$] and a significant increase in Δ TFC [6.2 (3.5, 11.4); $p = 0.01$] following FB. About 35% of FBs led to $> / = 10\%$ change in TFC. There were no significant differences in HR, SBP, SV, SI, CO, CI, SVV, FTC, ICON, and VIC post-FB (Table 2).

Fluid responsiveness was seen in 15/42 interventions. Between responders vs. non-responders, fluid responders had a significant decrease in Δ HR [−3.7 (−16.6, −0.72) vs. 1.32 (−5.1, 9.9); $p = 0.002$], Δ SVV [−34 (−50, −2.9) vs. 25 (−19.5, 83.7); $p = 0.002$], Δ SVR [−12.8 (−22.7, −7.7) vs. 0 (−12.8, 9.2); $p = 0.31$], and Δ STR [−19.3 (−24.6, −12) vs. −5 (−14.8, 8.8); $p = 0.03$]. Furthermore, fluid responders had a significant increase in Δ SI [16 (15.8, 24.2) vs. −3 (−9, 0.91); $p = 0.00000011$], Δ CO [14.2 (4, 23) vs. −2.2 (−12.9, 6.2); $p = 0.006$], Δ CI [14.5 (5.2,

23) vs. −3.5 (−12.8, 5.6); $p = 0.003$], Δ FTC [7.65 (2.6, 9.4) vs. 0 (−6, 3.8); $p = 0.002$], and Δ ICON [16.7 (13.5, 25) vs. −9 (−23, 5.1), $p = 0.003$] as compared to non-responders. There were no significant differences between age, Δ RR, Δ SBP, Δ DBP, Δ MAP, Δ TFC, and Δ VIC between these two groups (Table 3).

Receiver Operating Characteristic Curve Analysis

We compared areas under ROC curves (AUCs) after fluid expansion for Δ HR, Δ SVR, Δ SVV, Δ STR, Δ SI, Δ CO, Δ CI, Δ FTC, and Δ ICON. The AUC denoted better classifiers for Δ SI (AUC=0.99), Δ ICON (AUC=0.85), and Δ CI (AUC=0.73). The optimal threshold value for CI, SI, and ICON calculated by the ROC curve analysis was 15% (Figure 3).

DISCUSSION

Our prospective observational pilot study focused on subjective and objective methods of assessing hemodynamic status and FR in children presenting to the ED in shock. To our knowledge, this is the first pediatric report of the use of electrical cardiography which demonstrated a significant change in objective indices of hemodynamic status following FB in children with shock. Additionally, the study demonstrated the changes in specific hemodynamic indices such as CI, SI, and ICON as measured by electrical cardiography best-predicted FR in children with shock. The overall goal of fluid administration in patients with shock is to increase cardiac preload and subsequently stroke volume (15, 17). However, the studies in critically ill patients that examined FR demonstrated only 40–50% of patients responded to volume expansion (19, 26, 27). Furthermore,

TABLE 2 | Comparison between pre- and post-FB hemodynamic variables.

Parameters	Pre-FB median (IQR)	Post-FB median (IQR)	Δ Median (IQR)	p -values
HR (bpm)	107 (92, 131)	103.5 (85, 127)	−0.72 (−8, 4.2)	0.453
RR (/min)	22 (19, 24)	20 (18, 24)	−1.61 (−14.8, 0)	0.012
SBP (mmHg)	116 (105, 125)	112.5 (100, 123)	−5 (−14.5, 7)	0.104
DBP (mmHg)	73 (64, 84)	69 (55, 80)	−5.5 (−14.4, 8)	0.027
MAP (mmHg)	88 (83, 96)	84.5 (73, 93)	−2.2 (−11, 2)	0.018
SV (ml)	51.5 (27, 77)	54.5 (35, 72)	0.7 (−9, 15)	0.814
SI (BSA)	38 (35, 48)	41 (34, 48)	2.16 (−7.5, 16)	0.242
CO (l/min)	5 (3.5, 7.3)	4.7 (3.8, 6.3)	2.4 (−8.4, 16)	0.858
CI (BSA)	4.2 (3.2, 4.8)	4.2 (3.3, 5)	1.1 (−8, 16)	0.2577
SVV (%)	12.5 (8, 17)	13 (8, 17)	0.0 (−5, 4)	0.509
FTC (ms)	312 (298, 327)	323.5 (302, 333)	2.31 (−0.8, 8)	0.282
TFC	28.5 (20, 34)	31 (23, 37)	6.2 (3.5, 11.4)	0.005
SVR (dyn.s/cm ⁵)	1387 (958, 1913)	1374 (942, 1704)	−5.8 (−20, 5.2)	0.025
STR	0.37 (0.33, 0.45)	0.34 (0.3, 0.38)	−8.39 (−21, 3)	0.001
ICON	72.8 (56.6, 96.3)	71 (51, 103)	4 (−21.6, 16.6)	0.858
VIC (%)	13.5 (9, 27)	16.5 (11, 26)	0.0 (−33, 57)	0.433

FB, fluid bolus; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; FTC, corrected flow time; TFC, thoracic fluid content; SVR, systemic vascular resistance; STR, systolic time ratio; ICON, index of contractility; VIC, variation of index of contractility; Δ , percentage change; bpm, beats per minute; /min = per minute; ml, milliliters; BSA, body surface area; %, percentage; ms, milliseconds; dyn.s/cm⁵, dynes/sec/cm⁵; significant value, $p < 0.05$. (Paired-sample Student's t -test). Bold values correspond to significant p -values.

the conventional subjective parameters such as vital signs and physical examination pose several limitations and alone are not reliable in assessing FR, especially in children (28, 29). On the other hand, objective parameters such as CO, CI, SV, SI, and SVR may provide much more accurate hemodynamic status (30). More recently, non-invasive cardiac output monitors are also being utilized to provide continuous data of patients' hemodynamic status that could help in guiding fluid therapy and to predict FR (22, 31). Several studies have demonstrated the usefulness of these non-invasive devices in adults (23, 24, 32), yet the effectiveness of such devices remains controversial in pediatric patients. Some studies support the use of these newer non-invasive techniques in children. A study by Norozi et al. demonstrated a good correlation ($r = 0.84$) between CO measurements obtained by non-invasive cardiac output monitor and invasive direct Fick oxygen method in children with various congenital heart conditions (33). However, in another study that compares SVV measured by NICOM (non-invasive cardiac output monitor), traditional transesophageal echocardiography reported its ineffectiveness to predict FR in children undergoing cardiac surgery (34). In another study by Ballesterio Yolanda et al. on a pediatric animal model with hemorrhagic shock, CI measured by bioactance technique did not show significant changes after volume expansion (35).

In our study, we observed a significant decrease in RR, MAP, SVR, and STR and an increase in TFC, while CO, CI, SV, and SI remained unchanged. TFC is a newer objective parameter that has shown to identify pulmonary congestion which might not be evident on chest x-rays (36, 37). One study in critically ill children with respiratory failure and shock demonstrated that high TFC values correlate with pulmonary plethora and predicted patient outcomes (37). Another study in patients with heart failure suggested that TFC may identify patients at risk for decompensation (38). TFC measurements using EC have shown to be correlated with the presence of respiratory distress in infants (39). Hence, our pilot study that determined a significant increase in TFC may identify this as an important area of future study. A significant increase in TFC following FB in our study may be related to increased pulmonary interstitial edema following FB.

Predicting FR in children can be challenging. The predictive abilities of various hemodynamic parameters have previously been evaluated in a systematic review (40). Our results show that Δ CI, Δ SI, and Δ ICON had good predictability for FR in children. In our study, AUCs of CI, SI, and ICON were 0.73, 0.99, and 0.85, respectively. In a study on adult patients undergoing laparoscopic cholecystectomy, AUCs for CI and SI for FR were 0.83 and 0.90, respectively (41). In a study on post-operative pediatric patients, AUC for SI was 0.88 (42). Our findings of AUC for HR for FR correlate with the prior similar results (43, 44). Though commonly used as a parameter to assess fluid status, HR is a worse predictor of FR. In our study, changes in CI and ICON showed a high predictive performance for FR. It is possible that FB improved myocardial contractility through Frank-Starling mechanism, and therefore, CI and ICON showed an excellent predictive performance.

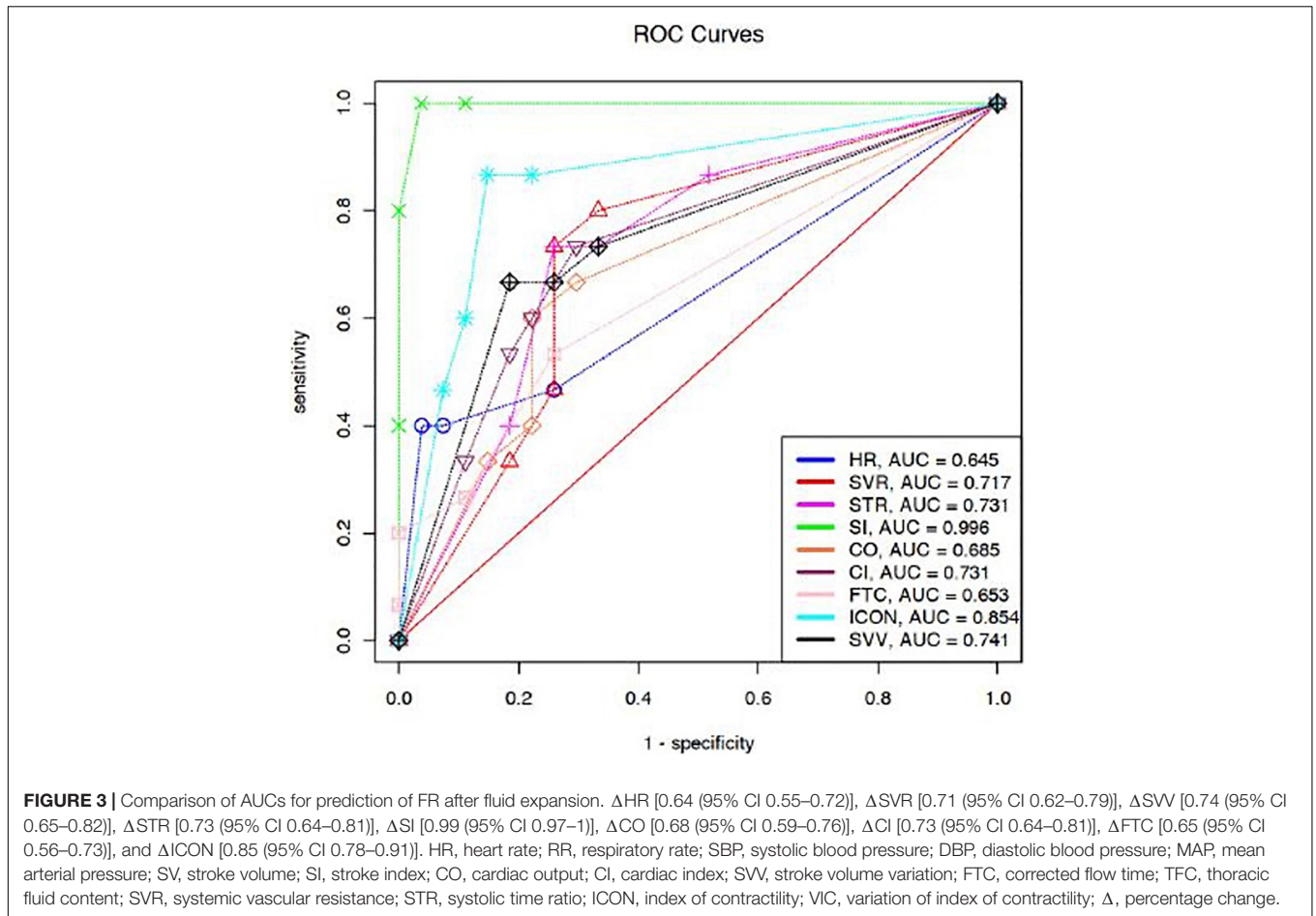
Limitations

Our study had several limitations. It is a prospective observational pilot study conducted in a single center, and our sample size is small. A major challenge we encountered that led to a smaller sample size was the necessary exclusion of patients with COVID-19 or PUI during the unprecedented pandemic due to PPE restrictions and institutional guidelines to protect students from potential exposure. In addition, this cohort does not represent consecutive patients due to the limitations of availability and feasibility to perform monitoring in the unpredictable ED setting. Furthermore, considering these limitations in patient recruitment, our sample included most patients with mild-to-moderate shock and may not be representative of the most critically ill patients. Additionally, this may have impacted the rate of fluid administration with the mean bolus duration longer than optimum for shock resuscitation guidelines. Therefore, the results of this study cannot be generalized to all patients with pediatrics with shock. Despite the limitations of our pilot, the parameters we found to be statistically significant demonstrate the promising results that using a non-invasive monitor to assess objective hemodynamic changes in children with shock has the potential to aid ED physicians in predicting FR and better guide fluid management.

TABLE 3 | Changes in hemodynamic variables in responders vs. non-responders.

Parameters	Responders <i>n</i> = 15 median (IQR)	Non-responders <i>n</i> = 27 median (IQR)	<i>p</i> -values
Age (years)	7.9 (2, 11)	12.3 (5.6, 15.6)	0.15
Δ HR (bpm)	-3.7 (-16.6, -0.72)	1.32 (-5.1, 9.9)	0.002
Δ RR (/min)	-6.2 (-15.5, 0)	0 (-12.7, 4.5)	0.169
Δ SBP (mmHg)	-0.85 (-4.9, 4.9)	-6.6 (-12, 7.5)	0.293
Δ DBP (mmHg)	-2.4 (-5.8, 8.9)	-9.8 (-16.2, 6.43)	0.253
Δ MAP (mmHg)	-1.1 (-4.6, 1.8)	-6.5 (-12.8, -0.6)	0.100
Δ SI (BSA)	16 (15.8, 24.2)	-3 (-9, 0.91)	0.00000011
Δ CO (l/min)	14.2 (4, 23)	-2.2 (-12.9, 6.2)	0.006
Δ CI (BSA)	14.5 (5.2, 23)	-3.5 (-12.8, 5.6)	0.003
Δ SVV (%)	-34 (-50, -2.9)	25 (-19.5, 83.7)	0.002
Δ FTC (ms)	7.65 (2.6, 9.4)	0 (-6, 3.8)	0.002
Δ TFC	6.6 (5.4, 12)	5.8 (1.5, 10.5)	0.216
Δ SVR (dyn.s/cm ⁵)	-12.8 (-22.7, -7.7)	0 (-12.8, 9.2)	0.031
Δ STR	-19.3 (-24.6, -12)	-5 (-14.8, 8.8)	0.003
Δ ICON	16.7 (13.5, 25)	-9 (-23, 5.1)	0.0003
Δ VIC (%)	0 (-39, 44)	0 (-23, 71)	0.617

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; FTC, corrected flow time; TFC, thoracic fluid content; SVR, systemic vascular resistance; STR, systolic time ratio; ICON, index of contractility; VIC, variation of index of contractility; Δ , percentage change; bpm = beats per minute; /min = per minute; millimeters of mercury, mmHg; ml, milliliters; BSA, body surface area; %, percentage; ms, milliseconds; dyn.s/cm⁵, dynes/sec/cm⁵; significant value, $p < 0.05$. Bold values correspond to significant *p*-values.



CONCLUSION

The results of our pilot study suggest that integration of objective assessment with subjective data using advanced non-invasive monitoring could help to evaluate patients' hemodynamic status and FR in children with shock in ED settings. The findings of excellent predictive performance (AUC 0.85) of changes in ICON for FR could potentially aid treating physicians in avoiding fluid overload, developing optimal management plans, and using objective clinical decision-making for children with shock. Larger, multi-center, prospective, randomized studies are needed to further evaluate the validity of non-invasive devices in predicting FR in children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Baylor College of Medicine IRB.

Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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