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Original Article

Fluid responsiveness in children with Septic shock is not a Reliable Predictor of outcome: Single Center Experience

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Abstract:
Background: Fluids are an integral line of management of septic shock as circulatory instability and myocardial dysfunction are the major causes of death in septic shock. Several indicators of fluid responsiveness (FR) have been proposed.
Aim of the Work: to assess predictive value of assessment of fluid responsiveness on outcome of children with sepsis.
Methods: This study was a prospective observational cohort study which was conducted on 25 children who were admitted to Pediatric Intensive Care Unit with septic shock at Children Hospital, Cairo University from February 2020 to May 2020. All underwent bedside echocardiography assessment of fluid responsiveness (FR) using inferior vena cava's (IVC) diameter: distensibility, collapsibility, variability indices and time velocity integral across aortic valve before and after fluid resuscitation.
Results: The mean age ± SD of the studied cohort was 33.72 ± 39.65 months, 17 (68%) were males and 8 (32%) were females. All patients presented by septic shock, of them 13 (52%) were fluid responsive and 12(48%) were fluid nonresponsive (p=0.118). FR was different between ventilated patients and non-ventilated patients as regards IVC variability % before and after IV fluids (p= 0.001) and (p=0.001) respectively, stroke volume and cardiac output after IV fluids (p =0.033) and (p=0.001) respectively. FR correlated with central venous pressure measurements (p=0.000017) and inotropic support (p=0.0074) but not with main diagnosis of septic shock, mechanical ventilation of patients or not and not with number of system failure. Ten (40%) of them were on mechanical ventilation and inotropes. Nineteen (76%) improved and 6 (24%) died. There was no correlation between FR and outcome (p= 0.316).
Conclusion: Bedside echocardiography may be a useful non-invasive method for follow up, evaluation of fluid responsiveness in children septic shock and to assess CI which helps in assessment of fluid response, make decision on medication, and help evaluate the different forms of shock, but it has no significant relation to the outcome of these children. Outcome of septic shock is multifactorial, depends on timing of diagnosis, fluid administration, inotropic support, and cardiac condition not fluid responsiveness only.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Inferior vena cava diameter variation; fluid responsiveness; sepsis; septic shock; pediatric intensive care; echocardiography; dynamic parameters.
Abbreviations: CI: cardiac index; CO: cardiac output; CONS: coagulase negative staphylococci; CVP: central venous pressure; FR: fluid responsiveness; IVC: Inferior vena cava; PICU: pediatric intensive care unit; SV: stroke volume; VTIAA: time velocity integral across aortic valve.

Introduction

One of leading causes of death in pediatric population around the world is sepsis, with estimated 7.5 million deaths each year (*2*). Septic shock is defined as sepsis with cardiovascular organ dysfunction *(3)*. The severity of the shock demands initiation of treatment rapidly and massively by fluids. It is critical to decide if the patient will benefit from fluids or not because

large amounts of fluids used conventionally may be unnecessary and may lead to fluid overload. Fluid overload prolongs mechanical ventilation and increases the mortality of critically ill patients in general and, more specifically, in patients with sepsis (*4*, *5*). Assessment of patient response to volume expansion presents a daily challenge for acute care physician, as fluid responsiveness (FR) and hemodynamic monitoring are the cornerstone to decide the use of fluids and vasoactive agents in septic shock patients, to guarantee sufficient delivery of oxygen to prevent or repair organ failure and to predict their effect on outcome. The static parameter central venous pressure (CVP) measures the preload but as the response of a patient to fluids depends on both preload and cardiac contractility that varies between patients, CVP has limited value in assessment of FR (*6*, *7*). Alternatively, dynamic parameters based on interactions of heart and lung have been used to assess FR to reduce unnecessary extra fluid loading through several echocardiographic indices in mechanically ventilated and critically ill patients (*8*). We aimed to assess the predictive value of assessment of FR on the outcome of children with sepsis.

Subjects and Methods

This study was a prospective observational cohort which was performed on 25 pediatric patients who were diagnosed to have septic shock who were admitted to Pediatric Intensive Care Unit (PICU) from February 2020 to May 2020 to evaluate the role of bedside echocardiography for assessment of FR in these critically ill children. The research was approved by the Faculty of Medicine, Cairo University Health Ethics Review Board (IRB Approval Number: MS-50-2019). The study conforms with the Code of Ethics of the World Medical Association, Declaration of Helsinki, for experiments involving humans (*9*).

Participants

This study included 25 children who met the criteria of septic shock according to International Pediatric Sepsis Consensus conference definitions for Sepsis (*10*) admitted to the PICU, Cairo University Pediatric hospital. We included children with pediatric septic shock, but not children with ascites, associated cardiac arrhythmias, pre-existing dilated or restrictive cardiomyopathy, severe valvular heart disease and /or hemodynamically significant intracardiac shunt, and those with infective endocarditis.

Methods

Data were collected from the patients' medical record. All enrolled children underwent assessment of static and dynamic tests at time of admission to PICU before fluid challenge (20 cc /kg either 0.9% normal saline or lactated ringer's over 5 minutes) and after fifteen minutes of fluid challenge.

Static tests for hemodynamic monitoring: Heart rate, blood pressure: systolic (SBP), diastolic (DBP) and mean(MAP) = [(SBP-DBP) /3] + DBP, capillary refill time and central venous pressure measured by central venous line at left or right internal jugular vein or the right or left subclavian vein.

Dynamic tests for hemodynamic monitoring:

Assessment of cardiac index: using transthoracic echocardiography (General Electric ultrasound machine made in Germany) with 6 mega Hertz echo probe for pediatric patients. Hemodynamic parameters were obtained by a trained intensivist using 2 dimensional and pulsed wave Doppler echocardiography to measure the following:

- Left ventricular outflow tract (LVOT) diameter measured in the long axis parasternal view.
- Time velocity integral of the flow wave across the aortic valve (VTIAA) obtained by imaging the Doppler aortic outflow signal.
- Stroke volume was calculated using the following equation: Stroke volume = $\pi \times$ VTI × (LVOT diameter/2) ^{2} (*11*).
- Cardiac output= stroke volume × heart rate.
- Cardiac index= cardiac output/ body surface area.

IVC ultrasound Parameters:

- IVC collapsibility index (in the longitudinal subcostal view)= the maximum diameter of IVC during expiration minus the minimal diameter during inspiration divided by the diameter during expiration in spontaneously breathing patients (*12*).

- IVC Distensibility index = the maximum diameter of IVC during inspiration minus the minimal diameter of IVC during expiration divided by the diameter of IVC during expiration in mechanically ventilated patients (*12*).
- IVC variability index will be calculated by the difference of the max IVC diameter (IVD max) and minimum IVC diameter (IVCD min) during the respiratory cycle divided by the mean IVC diameter (*12*).

Statistical Analysis

Data coding and entry were done using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, median, standard deviation, minimum and maximum for quantitative variables and frequencies while relative frequencies (percentages) were used for categorical variables. For normally distributed quantitative variables, the unpaired t test was used for comparison, while for non-normally distributed quantitative variables, the non-parametric Mann-Whitney test was used. Paired t test was used to compare the before and after results. Chi square (X^2) test was performed to compare categorical data; alternatively. Fisher's Exact test was used when the expected frequency is less than 5. Pearson correlation coefficient was used to determine correlations between quantitative variables. P-values less than 0.05 were considered statistically significant.

Results

Demographics and clinical characteristics of the studied group:

The study included 25 children with septic shock recruited from PICU. Their mean ± SD age was 33.72±39.65 months, of them 17 (68%) were males and 8 (32%) females. The underlying diagnoses of PICU admission were pneumonia 10 (40%), meningitis 5 (20%) followed by postoperative 4 (16%), myocarditis 5 (20%) and neuromuscular disease in 1 (4%). (Table 1).

Table 1. Clinical data of the included patients during PICU admission.

	Mean ±SD	Median	Minimum	Maximum
Age (months)	33.72±39.65	18.00	2.00	144.00
Surface area	0.51±0.23	0.43	0.24	1.40
Weight Z score for age	-0.65±0.818	9.00	4.00	50.00
HB	10.66±2.26	11.00	6.10	15.80
WBC	16.47±10.75	15.30	2.00	42.00
PLT	357.29±200.65	342.00	22.00	702.00
CRP	117.74±96.82	106.00	18.80	425.00
PH	7.41±0.12	7.40	7.02	7.65
pco2	35.08±10.10	33.00	13.90	70.00
Hco3	21.84±5.05	22.50	6.60	30.00
SBP	113.34±12.97	112.00	88.00	132.00
DBP	70.57±11.57	74.00	45.00	84.00
Mean BP	85.48±18.67	84.00	55.00	107.00
Temp	37.39±0.43	37.30	37.00	38.50
HR	138±22.4	135	92	179
RR	35.94±11.39	35.00	20.00	70.00
CRT (sec)	2.91±0.82	3.00	2.00	5.00
O2 sat (%)	96.23±3.49	97.00	86.00	100.00
CVP	9.38±3.38	10.00	4.00	17.00

CVP: central venous pressure; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; CRT: capillary refill time; sat: saturation.

Organ system failure was present in 6 (24%) with 1 system failure, 14 (56%) with 2 system failure, 4 (16%) with 3 system failure and only one (4%) has 4 system failure. Of the 25 patients, only 10 (40%) needed mechanical ventilation, 13 (52%) were fluid responsive and 12 patients (48%) were fluid nonresponsive. (Figure 1). Initial blood cultures withdrawn at PICU admission revealed no growth in 15(60%), MRSA in 3 (12%), klebsiella 3(12%), Acinetobacter 3(12%), pseudomonas 1(4%) and CONS 1(4%). Culture did not correlate with FR (r= 0.294, p= 0.153) or with septic shock presentation (r= -0.05, p= 0.79) or outcome whether improved or died (r= 0.225, p= 0.279).

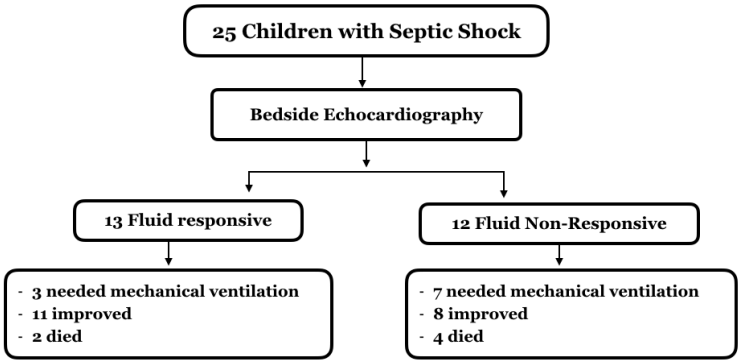

Figure 1. Flowchart of included patients in this study**.**
FR: fluid responsiveness; FNR: fluid non responsiveness.

FR correlated with CVP measurements (p=0.000017) and inotropic support (p=0.0074) but not with main diagnosis of septic shock, mechanical ventilation of patients or not and not with number of system failure. Table 2.

Table 2. Factors affecting outcome in our studied cohort.

	FR		FNR		R	P value
	Number	%	Number	%		
Outcome						
Improved	11	44	8	32	0.209	0.316
Died	2	**8**	4	16		
CVP (mean ± SD)	5.6±2.3		11.58±3.29		0.748	0.000017
Septic shock	13	52	12	48	0.320	0.118
MV						
Yes	3	12	7	28	-0.359	0.07
No	10	40	5	20		
Inotropes						
Yes	2	8	8	32	-0.522	0.0074
No	22	44	4	16		
Number of system failure						
1	3		3		-0.04	0.81
2	8		6			
3	2		2			
4	0		1			
DOS in ICU	8.7±1.8		9±3.02		-0.046	0.41
Weight Z score	-0.58±0.7		1.08±0.51			0.399
MAP (mean ±SD)	85.53±19.18		87.5±18.04			0.401

CVP: central venous pressure; DOS: duration of stay; FR: fluid responsiveness; FNR: fluid non responsiveness; ICU: intensive care unit; MV: Mechanical ventilation.

Table 3. Echocardiographic findings before and after IV fluids.

	Mean ±SD	**Minimum**	**Maximum**
Non ventilated patient			
IVC collapsibility index (Before)%	61.68±23.78	24.00	100.00
IVC collapsibility index (After)%	60.00±23.65	14.00	100.00
Ventilated patient			
IVC distensibility index (Before)%	33.14±22.03	9.50	88.00
IVC distensibility index (After)%	38.56±14.05	15.00	53.00
All patients			
IVC variability index (Before)%	73.97±56.04	3.00	200.00
IVC variability index (After)%	69.84±53.24	6.00	200.00
All patients			
CI (Before)ml/min/m2	3200±1184	1631	6800
CI (After) ml/min/m2	3427±-1184	2029	6950

IVC: inferior vena cava; CI: cardiac index; % : index number expressed by percentage.

Echocardiography findings revealed decrease in IVC collapsibility index measured by % after IV fluids in non-ventilated patients and increase in IVC distensibility index measured by % after IV fluids in ventilated patients. Both groups had decrease in IVC variability index measured by % and increase in VTIAA measurements. (Table 3). There was a significant difference between ventilated patients and non-ventilated patients as regards IVC variability % before and after IV fluids with ($p < 0.001$) and ($p=0.001$) respectively being lower in ventilated patients. There was a significant difference between ventilated patients and non-ventilated patients as regards SV and CO after IV fluids ($p=0.033$) and ($p=0.001$) respectively being higher in ventilated children. There was a significant increase in SV, CI, and VTI AA sign after IV fluid administration to ventilated and non-ventilated patients. (Table 4). There was a significant difference as regards SV, CI, VTIAA ($p= 0.002$), ($p=0.021$), ($p<0.001$) respectively being increased after fluid therapy in all pediatric septic patients included in our study. VTIAA correlated positively with SV, CO, CI before IV fluids ($p <0.001$), ($p=0.001$), ($p=0.003$) respectively, and after IV fluids ($p= 0.001$), ($p=0.001$) and ($p= 0.007$) respectively. IVC variability index correlated positively with IVC collapsibility % before and after IV fluids ($p <0.001$) and ($p <0.001$) respectively, and IVC distensibility % before and after IV fluids ($p <0.001$) and ($p <0.001$) respectively. (Table 4).

Table 4. Echocardiographic Fluid Responsiveness Parameters between ventilated and non-ventilated.

	Ventilation		t	P value
	On mechanical ventilation	No mechanical ventilation		
	Mean ±SD	Mean ±SD		
IVC variability %(Before)	31.50±17.48	93.27±57.06	-4.623	< 0.001
IVC variability % (After)	36.10±18.60	85.18±56.98	-3.636	0.001
SV (Before)	15.60±10.92	10.08±5.20	1.596	0.136
SV (After)	15.9±7.89	10.72±5.43	2.232	0.033
CO (Before)	2236.55±1427.67	1371.46±645.13	1.922	0.079
CO (After)	2292.30±971.73	1373.04±500.73	3.658	0.001
CI (Before)	3349.27±1125.06	3190.12±1361.60	0.338	0.738
CI (After)	3878.00±1033.17	3273.08±1113.79	1.472	0.151
HR (Before)	146.55±28.26	139.17±20.78	0.870	0.391
HR (After)	146.20±23.33	134.33±23.81	1.332	0.192
LVOT diameter	1.21±0.32	0.99±0.18	2.088	0.057
VTI AA sign (Before)	12.15±2.49	12.35±2.01	-0.254	0.801
VTI AA sign (After)	14.39±1.87	13.38±2.51	1.150	0.259

IVC: inferior vena cava; SV: Stroke volume; CO: Cardiac output; CI: Cardiac index; HR: Heart rate; LVOT: Left ventricular outflow tract; VTI AA: velocity time integral across aortic valve.

Table 5. Predictors of outcome of our studied cohort.

	Outcome	
	R	**P value**
FR FNR	0.209	0.316
Inotropes	-0.335	0.101
Cultures	0.225	0.279
CRT	-0.226	0.282
HR	0.223	0.282
CVP	0.08	0.6862
Septic shock	0.166	0.427
MV	0.076	0.71
System failure	-0.15	0.47
DOS	0.36	0.071
Weight z score for age		0.129
MAP (mean±SD)		0.1237

FR: fluid responsiveness; FNR: fluid non responsiveness; CVP: central venous pressure; MV: Mechanical ventilation; DOS: duration of stay.

Outcome of the included patients in this study (whether improved or died), did not correlate with the FR whether or not, CVP measurements inotropic support, culture results, heart rate, septic shock , mechanically ventilated or not, number of system failure and duration of stay in intensive care unit (ICU). Table 5.

Discussion

Pediatric septic shock is associated with a high rate of mortality and morbidity. In hospitalized pediatric patients, the prevalence of severe sepsis and septic shock ranges from 1% to 26%, with a 5-percent mortality rate in developed countries while in developing countries it reaches up to 35% (*13*). Septic shock presents as a clinical syndrome complicating severe infection with systemic inflammation, immune dysregulation, microcirculatory derangements, and end-organ dysfunction. The continuum for an individual patient may be clinically impossible to distinguish the transitions from sepsis to severe sepsis and septic shock with reduction of preload, distributive and cardiogenic phase of the shock (*14*). Each hour of delay in initiation of appropriate resuscitation or persistence of hemodynamic abnormalities is associated with a clinically significant increased risk of death.

Fluid resuscitation is the mainstay of management in the warm phase of sepsis and septic shock. But, some patients and types of shock may be harmed by aggressive fluid resuscitation that leads to severe tissue edema, compromises organ function, increased morbidity and mortality (*15*). In the present study, clinical signs such as a hypotension, tachycardia, narrow pulse pressure, poor skin perfusion, and slow capillary refill, were helpful in identifying adequacy of perfusion, but these signs were unable to determine volume status or fluid responsiveness. CVP as one of static preload parameters was found to be indicative of fluid responsiveness ($p= 0.00007$), as well as the echocardiography parameters of 10-15 % increase in SV, CI, and VTIAA sign after fluid therapy.

Cardiac index is a standard parameter in resuscitation of septic shock. The therapeutic goal of CI between 3.3-6.0 L/m² may lead to survival improvement in septic shock patients (*16*). In contrast to our study, CI increased after fluid resuscitation despite signs of myocardial dysfunction, which may be related to, early stage of septic shock in distributive phase and use of inotropic support but it has no significant relation to outcome.

CI is the product of CO divided by the body surface area, so it reflects the changes in CO, which is determined by SV and HR, but it is also affected by cardiac contractility, preload, and afterload (*17*). The cardiac index's strength is that it is a number that includes a more detailed picture of how the heart is functioning relative to the body, and not independently. It decreases in cardiogenic, obstructive, and hypovolemic, in contrast, it is usually a normal to increase in septic and anaphylactic shock (*18*).

The IVC diameter predicted central venous pressure in our spontaneously breathing and mechanically ventilated patients, essentially a very small collapsing IVC in shocked patients suggests fluid tolerance as opposed to a dilated fixed IVC which could be a sign of fluid intolerance (*19*). The IVC collapsibility and distensibility indices were valuable, yet were affected by many factors as the positive pressure in the mechanically ventilated child limiting its value. Another challenge is the need for an experienced physician clinically and echocardiographically to assess the measurements of the different parameters.

Yet, despite the accurate ability to define fluid responsiveness by the static CVP and the dynamic parameters, the fluid responsiveness was not found predictive of outcome. Outcome of the included patients in this study, did not correlate with the fluid responsiveness whether (FR or not), CVP measurements, inotropic support, culture results, sepsis or septic shock, mechanically ventilated or not, number of system failure and duration of stay in intensive care unit (ICU).

In the present study, the presentation of patients was late; after the golden hour. The PICU is the second step after emergency room where the patients receive initial treatment whether fluids or antibiotics, thus only the patient who is in need of further intervention is admitted to PICU, and who might be past the distributive phase of the sepsis- septic shock continuum. The late presentation to PICU might be a factor that explains why FR was not the only determinant of outcome of the enrolled children. It seems that type of infection, FR, myocardial dysfunction, system failure contributed equivocally to the outcome. Our work supports that treatment of septic shock depends on many variables; proper time management, fluid resuscitation, static and dynamic measurements, inotropes, antibiotics, mechanical ventilation and treatment of underlying disease. It was not clear why the culture results in about 15 out of 25 had no growth, it might be related to previous antibiotics taken prior to PICU admission. Also the type of bacteria in the culture did not predict the outcome of our studied children. It might be due to the small sample size, or the each patient individual mounted immune response.

More insight is needed to define the value of bedside echocardiography in the emergency unit as a simple non-invasive procedure for initial assessment and evaluation of fluid response in critically ill septic children. Again the tissue perfusion is a crucial step, to prevent organ failure,

yet all the indices whether static or dynamic assess the FR and not actually the tissue perfusion. Hence the importance of inotropes in the management of septic shock (*20*, *21*). Bedside echocardiography is a simple non-invasive procedure for evaluation of fluid response in critically ill septic children through assessment of CO and CI and for follow up.

Our study was limited by many points, it was single center study with a relatively small sample size, assessment of the patient was late (in PICU not in emergency room), tissue perfusion was not detected to determine real need for fluids, and the fact that mechanically ventilated patients have positive pressure which affect measurements of IVC.

Further studies are needed to follow up all patients with septic shock to record the outcome whether deteriorated or improved especially nonresponsive to fluids for deciding their need to more fluids and inotropes. All measurements whether static or dynamic must be done very early in emergency room to apply proper treatment, all ICU physicians need to be trained on echocardiography to assess patients easily and quickly.

Conclusion

Septic shock must be carefully managed through prompt thorough assessment and timely management through different lines whether IV fluids, inotropes, antibiotics and treatment of the cause if possible to improve the outcome. It is important to stress that the decision of fluid administration should not be based solely on the presence of preload responsiveness, but also on the presence of hemodynamics instability (or peripheral hypoperfusion). Although CVP is a static parameter which may be affected by many factors but still it is helpful and accessible by doctors or nurses in detecting fluid responsiveness. Bedside echocardiography can be a useful non-invasive method for follow up but needs time and professional operator. FR was not found t be a reliable predictor of outcome in our study. Non-invasive bedside contractility, preload, and afterload assessment provide a rational guide to the fluid therapy as they are interventions that must be carefully tailored to the needs of the patient and for selection of appropriate cardiovascular medications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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