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Validation of echocardiography as predictor of fluid responsiveness in critically ill septic patients

Suzy Fawzy[1], Mervat M. Khalaf[2], Alsayed R. Saadah[3], Adel Y. Alsis[4], Sheirf Mokhtar[5]

[1-5] *Critical Care Department, Cairo University, Egypt*
[3] *Ministry of Healthy Hospital, Egypt*

Email: manalmanar@mail.com

ABSTRACT

Background: Dynamic parameters have recently replaced static measures which failed to accurately predict fluid responsiveness (FR) in critically ill patient .Transthoracic echocardiographic (TTE) can be used to non- invasively assess two dynamic parameters to predict fluid responsiveness, subaortic velocity time integral variations (ΔVTI) and respiratory variations of inferior vena-caval diameter (ΔIVCD). The aim of the work is to assess the accuracy of TTE measured variations in aortic blood flow (VTI as a surrogate) and inferior vena-caval diameter with limited bolus colloid infusion in predicting fluid responsiveness in patients with septic shock.
Methods: The study included 40 spontaneously breathing patients with acute circulatory failure secondary to septic shock admitted to ICU over 6 months period.
Results: TTE measures VTI by Doppler on a 5 chamber apical view, and IVCD in subcostal view in M-mode. Then, 500 ml 6% hydroxyethyl starch (HES) were infused via a specific venous line; the first 100 ml were regularly infused over one minute, the remaining 400 ml were infused at a constant rate over 14 minutes. TTE reassessments were performed after the first minute and after completion of infusion. Patients were classified into two groups, responders and non-responders according to FR, there were a significant difference between responders and non- responders concerning mean VTI after 100 ml fluid infusion (P= 0.003).
Conclusion: TTE could accurately predict fluid responsiveness in critically ill septic patient after only 1 minute of colloid infusion by measuring variations of subaortic VTI.

Kew word: Septic shock; Fluid challenge; Fluid responsiveness; TTE

INTRODUCTION

According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016, septic shock has been defined as sepsis with persisting hypotension, despite adequate volume resuscitation, requiring vasopressors to maintain MAP ≥ 65mmHg and having a serum lactate level >2 mmol/L (18mg/dL)[1].Rapid perfusion restoration is the ultimate goal in septic shock treatment which can be achieved mainly by fluid infusion especially in the first 3 hours of presentation [2]. Only about 50% of hemodynamically unstable patients are volume responsive. Also, excessive fluid loading can induce peripheral and pulmonary edema which may compromise microvascular perfusion and oxygen delivery associated with increased mortality [3].

Pulmonary artery occlusion pressure and central venous pressure as static parameters failed to predict fluid responsiveness[4]. The preload dependency dynamic parameters are the transient expression of stroke volume or cardiac output in response to a generally reversible and short-lasting change in cardiac preload (i.e., fluid challenge)(5). In mechanically ventilated patient, dynamic parameters were thought to apply only as breathing frequency, tidal volume and the intrathoracic pressure are controlled. However, in spontaneously breathing patient, recently it has been proven to be applicable as well, as spontaneous breathing also results in stroke volume variation. Contrary to mechanical ventilation, preload of the right ventricle decreases during expiration and increases during inspiration [6].

In response to a fluid challenge, TTE can assess dynamic parameters as variations in aortic blood flow (ΔVTI) and inferior vena-caval diameter (ΔIVCD). We aimed to evaluate the prediction of fluid responsiveness in patients with septic shock by measuring the variation in aortic blood flow and inferior vena-caval diameter with limited bolus of colloid infusion.

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PATIENTS

This prospective cohort study included 40 spontaneously breathing patients with acute circulatory failure secondary to septic shock admitted to critical care department at Cairo University in the period from October 2014 to March 2015. All patients gave informed consent, and the protocol was approved by the institutional review board in March 2014.

Inclusion Criteria

Critically ill septic patients with one or more of the following: Systolic blood pressure < 90mmHg (or decrease >50 mm Hg in previously hypertensive patients) or the need of vasopressor drugs (dopamine 5µg/kg/min or norepinephrine at any dosage). Urine output<0.5 ml/kg/hr for ≥2hrs.

Exclusion Criteria

Patients with one or more of the following: cardiac arrhythmias, rheumatic heart disease, tricuspid insufficiency, cardiomyopathy, cardiogenic pulmonary edema, preexisting renal impairment (including those with obstructive uropathy). Also patients in whom echocardiography could not be performed (e.g. those with severe obesity or COPD).

METHODS

All included patients were subjected to detailed history taking and physical examination with laboratory tests including CBC, creatinine, lactate, bilirubin, transaminases and albumin. Patient characteristics including age, gender, height, weight and Acute Physiology and Chronic Health Evaluation (APACHE) II score were recorded. Baseline heart rate (HR), mean arterial blood pressure (MAP) and central venous pressure (CVP) were recorded. The inotropic and/or vasopressor support (epinephrine, norepinephrine, dobutamine and dopamine, expressed as µg/kg/min) and the number of organ dysfunction and source of infection were recorded. A portable digital color Doppler ultrasound system; Sonoscape S6 machine with phased array 2-4 MHz probe was used to assess aortic blood flow (ABF) and inferior vena-caval diameter (IVCD) via transthoracic approach. By transthoracic echocardiography (TTE), velocity time integral (VTI) measurement were recorded by pulse wave doppler on a 5 chamber apical view [7]. IVCD was measured by TTE in subcostal view, in M-mode coupled to two-dimensional mode just upstream of the junction of the hepatic veins, maximum IVCD and minimum IVCD were measured. Measurements were validated when the M-mode tracing was perpendicular to the IVC [8].

Echocardiographic assessment of ABF and IVCD was performed by experienced operator at the baseline followed by infusion of 500 ml 6% HES (voluven)[9] via a specific venous line. The first 100 ml were regularly infused over 1 minute followed by echocardiographic assessment, the remaining 400 ml were infused at a constant rate over 14 minutes followed by reassessment by echocardiography.

Then, measurements of variations of VTI and IVCD were taken as follows:

$\Delta VTI_{100} = (VTI_{100} - VTI_0)/VTI_0 X100$ &

$\Delta VTI_{500} = (VTI_{500} - VTI_0)/VTI_0 X100$,

$\Delta IVCD = (IVCDmax - IVCDmin)/IVCDmax X100$.

These calculations were measured at baseline ($\Delta IVCD_0$), after100 ml fluid infusion ($\Delta IVCD_{100}$) and after completion of 500 ml fluid infusion ($\Delta IVCD_{500}$). Percentage difference between $\Delta IVCD_{100}$ and $\Delta IVCD_0$ indicates variability of inferior vena-caval diameter after 100 ml fluid infusion while its variability after 500 ml fluid infusion was obtained by subtracting $\Delta IVCD_0$ from $\Delta IVCD_{500}$. HR, MAP and CVP are reassessed after 100ml and 500ml fluid infusions.

Patients were classified into two groups, responders and non-responders according to fluid responsiveness, the threshold for responsiveness was ≥ 15% increase in cardiac output after 500 ml of fluid infusion (reflected as ≥ 15% an increase in ABF). Cardiac output is the product of stroke volume and heart rate. The stroke volume is calculated by the product of the subaortic VTI recorded with pulse wave doppler in the left ventricular outflow chamber on an apical 5-chamber view and the subaortic left ventricular area (SV=VTI x LVOT area), LVOT area can be measured through the following the formula: subaortic left ventricular area (LVOT)=πR^2 where R is radius of the left ventricular outflow tract which equals half its diameter measured at 2-dimensional imaging. Assuming that the diameter of the left ventricle outflow chamber is constant in a given patient and that variations of heart rate are low (as patients with arrhythmia were excluded), the variations in cardiac output are related to VTI variations. Thus, the measurement of VTI and its variations are directly correlated with variations in cardiac output, avoiding the potential error in the measurement of the left ventricle outflow diameter chamber, so an increase of ≥ 15% VTI can be used as a surrogate of ≥ 15% cardiac output, i.e. fluid responsiveness, which always corresponds to ≥10% an increase ABF after 100ml fluid infusion [10].

Statistical Analysis

All obtained data were analyzed statistically by SPSS (Statistical Package for Social Science) program version 17.0 to obtain: Descriptive statistics were calculated in form od mean±standard deviation (SD), minimum and maximum, and frequency (number-percent). Analytical statistics using one of the following tests to compare between the different groups: Student's T-test (compare between mean of 2 groups numerical data and chi square test for inter group comparison. Pearson correlation coefficient to correlate different parameters. Sensitivity and specificity using ROC curve for analysis to determine the best cutoff point. P (probability) valve <0.05 was considered statistically significant.

RESULTS

The mean age of all study population was 65.05 ± 11.61 years. Out Of the forty patients enrolled in the study, 23 (57.5%) were males and 17 (42.5%) were female. Other study population characteristics are summarized in table-1.

Table-1. Study population characteristics.

	Mean	±SD
Weight(kg)	79.0	8.3
Height(cm)	169.4	4.9
HR(bpm)	105.9	14.0
Apache2	21.8	3.0
MAP0	74.1	9.5
MAP100	75.8	8.7
MAP500	81.4	7.7
CVP0	9.2	3.1
CVP100	9.5	3.0
CVP500	11.0	3.1
VTI_0(cm)	18.9	5.8
VTI_{100} (cm)	20.2	5.5
VTI_{500} (cm)	7.7	4.3
ΔVTI_{100} (cm)	21.3	5.5
ΔVTI_{500} (cm)	14.1	6.4
$\Delta IVCD_0$ (%)	38.4	14.8
$\Delta IVCD_{100}$ (%)	34.3	11.6
$\Delta IVCD_{500}$ (%)	27.3	8.4

Patients were classified into two groups, responders and non-responders according to fluid responsiveness, the threshold for responsiveness was ≥ 15% increase in cardiac output after 500 ml of fluid infusion (reflected as ≥ 15% an increase in ABF).

Out of 40 patients included in our study, there were 22 responders representing 55% of study population and 18 (45%) were non responders. There was no significant difference between responders & non-responders regarding age, gender, height, weight, mean heart rate and mean APACHE 2 score (Table-2).

There was no significant difference between both groups regarding MAP at baseline (P=0.08), and after 100ml fluid infusion (P=0.07) but the difference was significant after 500ml fluid infusion (P=0.01) (Table 2). There was no significant difference between responders & non-responders concerning baseline mean CVP (P=0.09), mean CVP following 100ml fluid infusion (P=0.06) & mean CVP after infusion of 500 ml of fluid (P=0.6) (Table-2).

As shown in table-3, there was a significant difference between responders and non-responders regarding mean VTI at the baseline (P<0.0001), after 100 ml fluid infusion (P=0.003).

Table-2. Study population characteristics among Responders and Non-responders

	Non-Responders		Responders		
	Mean	±SD	Mean	±SD	P
Age(y)	64.78	10.76	65.27	12.50	0.89
Weight(kg)	79.0	8.2	78.9	8.6	0.97
Height(cm)	170.6	3.6	168.4	5.6	0.16
HR(bpm)	101.6	19.0	109.5	6.3	0.075
Apache2	23.3	2.7	20.6	2.6	0.062
MAP0	71.7	7.3	67.9	5.8	0.08
MAP100	71.9	7.1	68.1	5.7	0.07
MAP500	72.6	7.3	78.0	5.9	0.01
CVP0	12.1	1.4	11.27	1.6	0.09
CVP100	12.3	1.6	11.5	0.9	0.06
CVP500	13.8	1.6	13.5	0.6	0.6
Gender	Male	Female	Male	Female	P
	13 (72.2%)	5 (27.8%)	10 (45.5%)	12 (54.5%)	0.088

DISCUSSION

During the initial three hours of presentation, early goal-directed therapy (EGDT) in septic patients emphasized on aggressive fluid resuscitation [2]. Many measures have been investigated to predict fluid responsiveness to avoid volume overload hazards in hemodynamically unstable patient. Dynamic parameters have been proved to be more accurate predictors of fluid responsiveness than static ones [4].

In the current study, we used TTE to assess two dynamic parameters, aortic velocity time integral variations and respiratory variations of inferior vena-caval diameter in response to a mini-fluid challenge test. A positive response to volume expansion is usually defined as a 15% increase in cardiac output (CO). Increased CO is reflected as increase in aortic blood flow (ABF) which equals VTI multiplied by left ventricular outflow tract (LVOT) area, assuming that LVOT area is constant. Thus, VTI can be considered a surrogate for ABF. Fluid responsiveness is associated with an increase in VTI by ≥15%, after 500 ml fluid infusion

(which correlates with VTI increase ≥10% after 100ml fluid infusion) [4-7].

About 55% of our study populations were fluid responders while 45% were non-responders. There was a significant variation between responders and non-responders regarding VTI after 100 ml fluid infusion (P = 0.003) and after 500ml fluid infusion (P<0.0001). On the other hand,, the difference was significant between both groups regarding IVCD variation only after 500 fluid infusions (P< 0.0001) but was not significant after the first 100 ml infusion (P value 0.14).

Moreover, variation in VTI after initial fluid bolus (100 ml fluid infusion) could predict fluid responsiveness with a sensitivity and specificity of 90.9% and 88.9% respectively.

Our findings are in concordance with the findings of Monnet et al. [10] who tested whether fluid responsiveness could be predicted by the respiratory variation in aortic blood flow before and after fluid infusion (500 ml NaCl 0.9% over 10 min) using an esophageal Doppler monitoring device . They concluded that the respiratory variation in aortic blood flow could be a reliable predictor of fluid responsiveness in mechanically ventilated patients without breathing activity in sinus rhythm [10].

In further agreement with our study, Muller et al.[11], in 39 critically ill sedated ventilated patients with acute circulatory failure assessed aortic blood flow variation in response to rapid fluid infusion . Subaortic VTI was measured by transthoracic echocardiography before fluid infusion (baseline), after 100 ml HES infusion over 1 min, and after an additional infusion of 400 ml HES over 14 min. They concluded that VTI variation after 100 ml could predict fluid responsiveness with a sensitivity and specificity of 95% and 78%, respectively [11].

Our study is in accordance with a study performed by Wu et al. [12]. who prospectively studied 55 mechanically ventilated patients and performed echocardiography after a 50ml infusion of crystalloid solution over 10 seconds and a further 450 ml over 15 minutes. Patients were classified as responders if CO increased by at least 15% following the 500ml volume expansion or non-responders if CO increased by less than 15%. Area under the receiver operating characteristic curves (AUC) compared CO variations after 50 ml over 10 seconds (ΔCO_{50}) and 500 ml over 15 minutes (ΔCO_{500}) and the variation of VTI after infusion of 50 ml of fluid over 10 seconds (ΔVTI_{50}).Results revealed out of 50 patients enrolled 27 (54%) of them were responders. The best cutoff value for ΔCO_{50} was 6% (sensitivity 93%; specificity, 91%) with strong correlation between ΔCO_{50} and ΔCO_{500}.The best cutoff value for ΔVTI_{50} was 9% (sensitivity 74%; specificity 95%). ΔVTI_{50} and ΔCO_{500} were positively correlated (P <0.01) [12].

Regarding the role of respiratory changes in inferior vena-caval diameter (IVCD),our study had revealed high sensitivity and specificity(95.5% and 88.9% respectively)after 500 ml fluid infusion, but low sensitivity and specificity after 100ml fluid infusion (63.5% and 50.0% respectively).This was in accordance with a study performed by Barbier et al.[13] on twenty-three mechanically ventilated patients with acute circulatory failure related to sepsis . Measurements were performed at baseline and after a 7 ml/kg volume expansion using a plasma expander. Patients were separated into

Table-3. Velocity Time Integral (VTI) among Responders and Non-responders

	Non-Responders			Responders			P
	Mean	±SD	Range	Mean	±SD	Range	
VTI (cm)0	24.4	3.7	16-28.0	14.4	2.0	12.0-19.0	<0.0001
VTI (cm)100	25.2	3.8	16.8-29.0	16.0	2.2	13.4-20.9	<0.0001
VTI (cm) Δ100	3.2	1.1	1.0-5.0	11.5	1.2	10.0-14.3	<0.0001
VTI (cm)500	26.3	3.9	17.4-30.1	17.2	2.2	14.2-22.1	<0.0001
VTI (cm) Δ500	7.6	1.7	4.6-10.0	19.5	2.5	16.3-24.5	<0.0001

Table-4. Inferior vena cava diameter (ΔIVCD) among Responders and Non-responders

	Non-Responders				Responders				P
	Mean	±SD	Min.	Max.	Mean	±SD	Min.	Max.	
IVCD%Δ0	23.1	5.4	17.0	33.0	24.9	4.0	18.0	34.0	0.15
IVCD%Δ100	42.38	2.72	38.0	49.0	43.9	3.5	38.0	51.0	0.14
IVCD%Δ500	19.1	4.6	13.0	29.0	33.9	3.4	26.0	40.0	<0.0001

responders (increase in CI≥15%) and non-responders (increase in CI <15%). Using a threshold dIVC of 18%, responders and non-responders were discriminated with 90% sensitivity and 90% specificity [13].

CONCLUSION

Using Transthoracic Echocardiography, fluid responsiveness could be accurately, quickly and safely predicted in a critically ill septic patient, just after one minute of a mini-fluid challenge test.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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