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Research Article

Comparing transesophageal Doppler corrected systolic flow time versus central venous pressure as a guide for fluid resuscitation in septic shock

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KEYWORDS

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Abstract *Background:* Aortic corrected flow time (FTc) is easily measured by Doppler techniques. Recent data using transesophageal Doppler suggest that it may predict fluid responsiveness in critical care. This use of FTc has not previously been evaluated in septic shock, and only one preliminary study has incorporated transcutaneously measured FTc, denoting its importance in prediction of fluid responsiveness in septic patient. Furthermore, no comparison has been made between transesophageal FTc and central venous pressure (CVP).

Objective: The aim of our study was to compare the impact of using FTc versus CVP as a guide for fluid resuscitation in septic shock on stroke volume denoting cardiac responsiveness for fluid administration.

Methods: This was a prospective study of 46 consecutive adult septic shock patients (in sinus rhythm). 44 patients were mechanically ventilated, treated with intravenous fluid challenge (500 mL over 15 min), guided with CVP in control group and guided by FTC in Doppler group assessment incorporating transesophageal aortic Doppler (CardioQ®) measurements in a surgical tertiary intensive care unit. Stroke volume (SV), mechanical ventilation days, length of stay and mortality of both groups were recorded.

Results: Fourty one patients demonstrated an increase in stroke volume (SV) by more than 10% (fluid responders) while five patients were non responders. There were statistically significant increases in SV after 1 h post resuscitation in the Doppler group as the values were 63.87 ± 25.87 & 81.39 ± 35.02 in the control group and the Doppler group respectively (p value = 0.034). There were statistically significant differences in FTc values after 1 h [397.00 (390.00–404.00) & 362.00 (351.00–377.00)] between non-responders and responders respectively (p value was 0.003) and after 6 h [377.00 (376.00–378.00) & 330.00 (314.00–353.00)] between non-responders and responders respectively (p value was 0.007).

Conclusion: Transesophageal aortic Doppler is a simple, non-invasive tool of guiding fluid therapy in patients with severe sepsis and septic shock. FTC change was a better predictor of fluid responsiveness than CVP in septic shock. There was higher significant difference in SV after resuscitation when using FTC as guidance.

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1. Introduction

Septic shock is an extremely complex disorder whose deranged hemodynamics results from the interplay of hypovolemia, vasodilatation, peripheral blood pooling, and extravasation of fluid into the interstitial space.

Intravenous fluids remain the cornerstone of treating patients with septic shock. The goal of fluid resuscitation in severe sepsis and septic shock is not merely achieving a predetermined value, but rather optimizing systemic oxygen delivery (cardiac preload, afterload, arterial oxygen content, contractility or stroke volume) [1].

Many factors may contribute to these findings, including physiologic compensatory mechanisms. These mechanisms often mask the true nature of blood flow. For example, whereas a patient may have a significant decrease in cardiac output (CO), the initial compensatory response of reflex vasoconstriction results in increased systemic vascular resistance and a normal blood pressure. The compensatory effects inhibit the clinician's ability to assess decreased blood flow and oxygen delivery accurately [2–4].

Surprisingly, dosing intravenous fluid during resuscitation of shock remains largely empirical. Too little fluid may result in tissue hypoperfusion and worsen organ dysfunction; however, over-prescription of fluid also appears to impede oxygen delivery and compromise patient outcome. Several studies demonstrated that positive fluid balance was associated with increased mortality and the duration of mechanical ventilation [5,6].

In a randomized controlled, single-center study, early quantitative resuscitation improved survival for emergency department patients presented with septic shock [7].

The 2012 Surviving Sepsis Guidelines suggest the infusion of intravenous fluids until achieving a central venous pressure of 8–12 mmHg and raise this target to 12–15 mmHg in patients with mechanical ventilation [8].

However, there are no recommendations as to when it is appropriate to discontinue or to reduce the rate of administration of intravenous fluid.

The measurement of descending aortic blood flow via an esophageal ultrasound probe offers an alternative method of monitoring circulatory status. Measured parameters include peak velocity (PV) and systolic flow time [FTc, corrected for heart rate (HR)]. PV ($cm\ s^{-1}$) is an index of left ventricular contractility while FTc reflects ventricular preload. Concurrent changes in PV and FTc reflect changes in afterload. The technique has been validated extensively compared with pulmonary artery catheters and is now widely used in adult anesthesia and intensive care units practice [8,9].

To the best of our knowledge there is only one published small study on the use of transcutaneous FTc in patients with septic shock [9].

Optimal fluid loading after cardiac surgery or early in the course of septic shock also may ameliorate morbidity and mortality [10].

Taken together, fluid therapy should aim at physiologically and clinically relevant endpoints, in order to improve outcome, but further refinement of these endpoints seems warranted [1].

We tried to compare the impact of using FTc versus CVP as a guide for fluid resuscitation in septic shock on stroke volume denoting cardiac responsiveness for fluid administration.

2. Patients and methods

This study was conducted in the surgical intensive care unit (SICU), at the faculty of medicine, Cairo University (Egypt), from November 2012 to February 2014.

Out of 350 patients admitted to the surgical intensive care unit (SICU), 46 septic patients met the inclusion criteria and were enrolled in the study.

The study was done after approval by local ethics committee and after obtaining written informed consent from the patients' next of kin.

2.1. Study population

2.1.1. Inclusion criteria

1. Ventilated patients who met the criteria of septic shock [8].
2. Mean arterial pressure $\leqslant$60 mmHg after at least a 1000 mL crystalloid bolus.

2.1.2. Exclusion criteria

1. Age less than 18 years.
2. Cardiac rhythm other than sinus.
3. Moderate to severe valvular heart disease.
4. Pregnant patients.
5. Patients who were on hemodialysis.
6. Relative contraindications to the use of the esophageal Doppler probe, such as orofacial and esophageal injury or other known oropharyngeal and esophageal disease.
7. Late stages of sepsis i.e. hypotension persisted >12 h or received previous fluid resuscitation.

2.1.3. Randomization

Patients who met the inclusion criteria were randomly assigned to the protocol group (Doppler) or the control group using computer generated number. Randomization was concealed using sequentially numbered, sealed opaque envelope technique. There were no restrictions or stratification in the randomization process. The allocation envelope was opened by the attending resident at the time of ICU admission. Data were analyzed on an intention-to-treat basis and included all patients who were randomly assigned.

2.2. Study protocol

2.2.1. Control group

The patients received 500 mL of normal saline every 15 min till the CVP reached 12–15 mmHg with maximum administration of 60 mL/kg.

2.2.2. Doppler group

The patient received 500 mL of normal saline every 15 min till the FTc $\geqslant$350 ms with maximum administration of 60 mL/kg

2.2.3. In both groups

If the mean arterial pressure is less than 65 mmHg, norepinephrine was given in a dose of 0.1–0.7 μg/kg/min to maintain a mean arterial pressure of at least 65 mmHg. If the

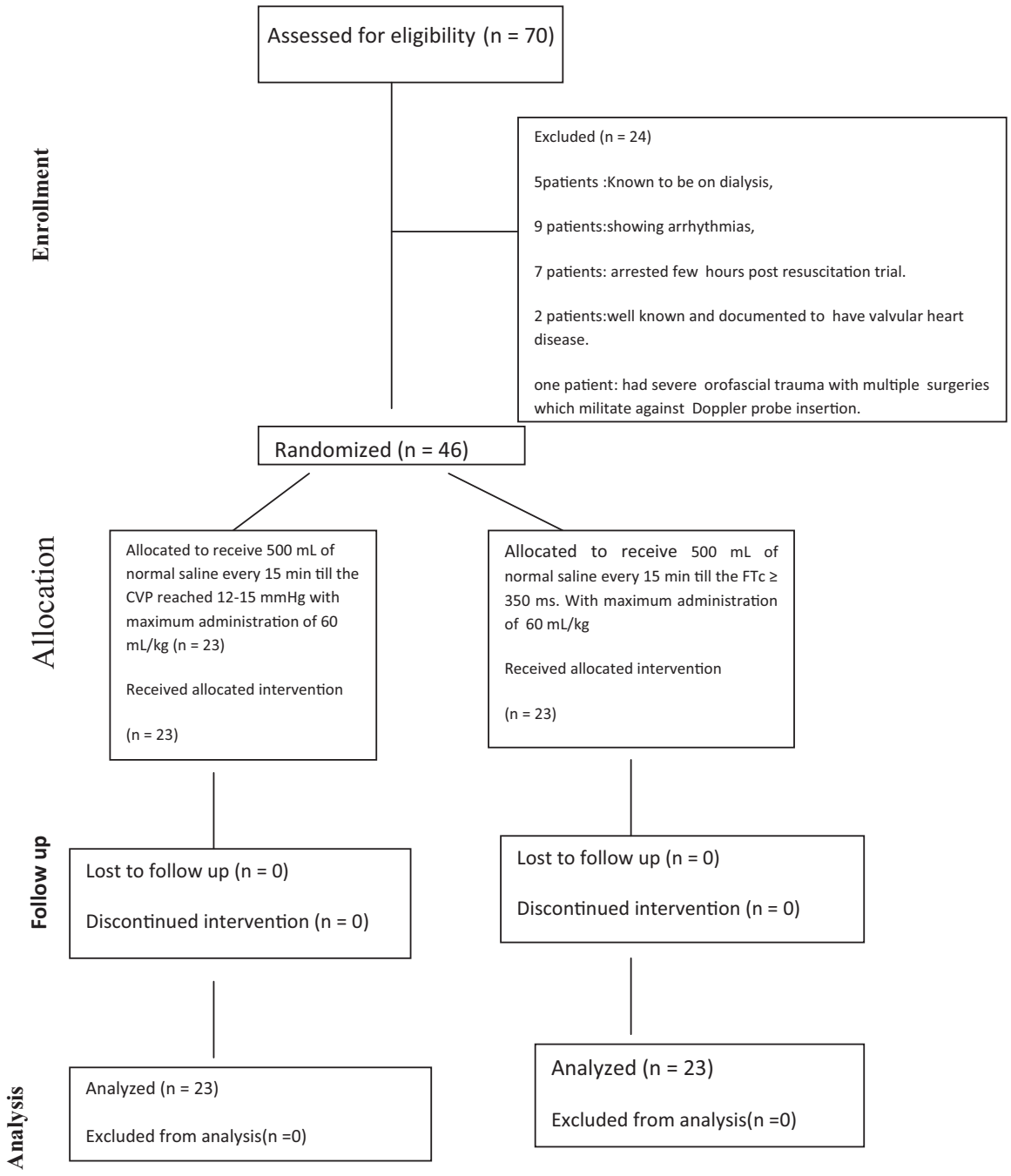

Figure 1 CONSORT diagram showing the flow of participants through each stage.

central venous oxygen saturation (S_cVO_2) is less than 70%, red blood cells were transfused to achieve a hematocrit of at least 30%. After the central venous pressure, mean arterial pressure, and hematocrit were optimized, if $S_cVO_2 < 70\%$, dobutamine administration was started at a dose of 2.5 μg/kg/min., a dose that was increased by 2.5 μg per kilogram per minute every 30 min until the central venous oxygen saturation is 70 percent or higher or until a maximal dose of 20 μg/kg/min. was given.

2.2.4. Transesophageal Doppler

The transesophageal Doppler was inserted by intensivist who had inserted at least 5 transesophageal Doppler's each prior to the study.

A 5-MHz, continuous-wave ED transducer (Deltex TM) connected to a spectral analyser (CardioQ, Deltex Medical, Chichester, UK) was inserted and orientated. Following oral introduction, the probe was advanced gently until its tip was located in the mid-esophagus and then manipulated until the

Table 1 Demographics data presented as mean, standard deviation and frequency.

Characteristics	Control group ($N = 23$)	Doppler group ($N = 23$)	PV
Age (years)	50.13 ± 16.81	45.52 ± 14.04	0.275
Male sex – no. (%)	14 (60.9%)	13 (56.5%)	0.765
APACHE II score	27.22 ± 7.48	22.87 ± 5.93	0.039
SOFA day 2	8.70 ± 3.52	6.87 ± 2.16	0.050
SOFA day 3	9.00 ± 3.83	7.13 ± 2.63	0.125
Total LOS (days)	6.70 ± 4.49	15.61 ± 25.10	0.273
Mortality outcome	19 (82.6%)	16 (69.6%)	0.300

Plus–minus values are means ± standard deviation. There were significant differences in baseline characteristics across groups, PV (p value) < 0.05 is considered statistically significant. APACHE II (Acute Physiology and Chronic Health Evaluation). SOFA (Sequential Organ Failure Assessment), MV (mechanical ventilation), LOS (length of stay).

Table 2 Fluid resuscitation volumes, data are presented as mean and standard deviation.

Type of fluid	Control group	Doppler group	p value
Crystalloid (mL)			
T1	2021.74 ± 1030.54	2391.30 ± 664.98	0.051
T12	2955.00 ± 1109.30*	3619.57 ± 719.02	0.001
Colloids (mL)			
T1	250.00 ± 370.01	431.82 ± 495.11	0.203
T12	282.61 ± 363.88	478.26 ± 488.00	0.168
Blood units	3.33 ± 1.78*	1.92 ± .86	0.015
FFP units	4.00 ± .00	2.67 ± 1.15	0.182
Total fluid T1	2913.04 ± 871.29*	2336.96 ± 685.10	0.013
Total fluid in T12	4412.39 ± 1486.57	3652.17 ± 906.10	0.054

p value < 0.05 considered statistically significant. T0 (measurement on enrollment), T1 (measurement after 1 h post resuscitation), T12 (measurement after 12 h post resuscitation), FFP (fresh frozen plasma).

* Denotes statistical significant difference relative to the other group.

Table 3 Responder's main parameters.

	Non-responder Median; (IQR)	Responder Median; (IQR)	p-value
CVP			
T0	5.00 (3.00–5.00)	6.00 (3.00–7.00)	0.294
T1	13.00 (12.00–14.00)	14.00 (12.00–16.00)	0.568
T6	11.00 (11.00–13.00)	8.00 (6.00–12.00)	0.145
T12	10.00 (8.00–12.00)	8.00 (5.00–10.00)	0.288
FTC			
T0	380.00 (344.00–384.00)[a]	293.00 (271.00–319.00)	0.000
T1	397.00 (390.00–404.00)[a]	362.00 (351.00–377.00)	0.003
T6	377.00 (376.00–378.00)[a]	330.00 (314.00–353.00)	0.007
T12	325.00 (313.00–351.00)	315.00 (300.00–332.00)	0.158
Total fluid T1	3000.00 (3000.00–3500.00)[a]	2500.00 (2000.00–3000.00)	0.049
Total fluid in T12	4100.00 (4080.00–4200.00)	3700.00 (3100.00–4700.00)	0.298

Data presented with median and inter quartile range (IQR), p value < 0.05 considered statistically significant. T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

[a] Data are presented as median and range.

transducer obtained the characteristic blood flow signal. Gain setting was adjusted to obtain the best outline of the aortic velocity waveform within 30 s. The average of 5 consecutive readings was taken. Prior to each measurement, probe position was verified to ensure optimal acquisition of the maximal velocity signal. Both cardiac output and flow time constant (FTc) were measured for each patient.

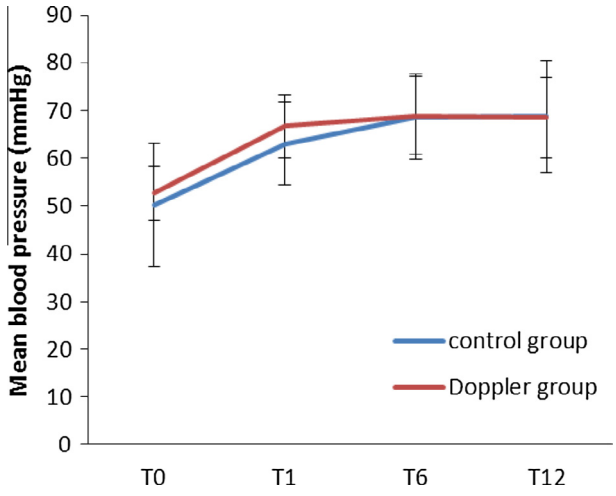

Figure 2 Mean arterial blood pressure pre- and post resuscitation in both groups. T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

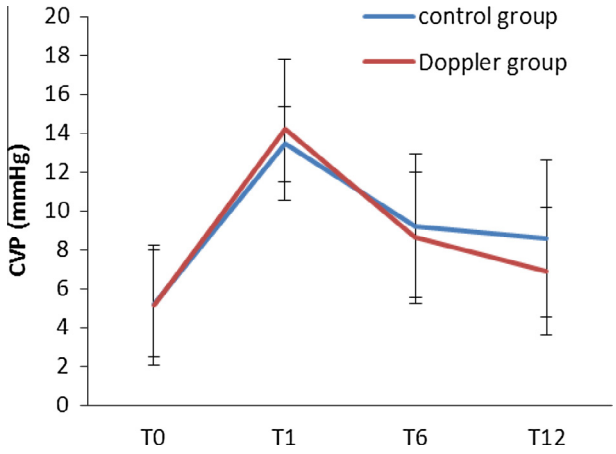

Figure 3 CVP pre- and post resuscitation in both groups. CVP = central venous pressure, T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

2.3. Measured variables

2.3.1. Hemodynamic variables

In both groups, CVP, SV, FTc, hemodynamic data were recorded at baseline before volume replacement and at 1, 6, and 12 h after protocol initiation.

2.3.2. Other variables

Acute Physiology and Chronic Health Evaluation II (APACHE II) score had been calculated after admission to the ICU. Sequential Organ Failure Assessment (SOFA) score was measured at 0, 24, 48 h after ICU admission.

According to the degree of fluid responsiveness, patients were divided into 2 groups:

1. Responders were defined as patients who had an increase in SV $\geqslant$10% of baseline measurements by trans-esophageal Doppler.
2. Non-responders were defined as patients who had an increase in SV $<$10% of baseline measurements by trans-esophageal Doppler.

2.4. Statistical analysis

Data were coded and entered using the statistical package SPSS version 21. Data were summarized using mean, standard deviation, median, minimum and maximum. Comparisons between variables over time were done using repeated measure analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametrical Friedman test and Wilcoxon test were used for non-normally distributed variables. Correlation was done to test for linear relations between quantitative variables by spearman correlation coefficient. *p*-values less than 0.05 were considered as statistically significant.

3. Results

From January 2012 through February 2014, we enrolled 70 patients. Twenty-four patients were excluded from the study [(5 patients) Known to be on dialysis, (9 patients) showing arrhythmias, (7 patients) arrested few hours post resuscitation trial, (2 patients) well known and documented to have valvular heart disease and one patient had severe orofacial trauma with multiple surgeries which militate against Doppler probe insertion)] leaving a final cohort of 46 patients for the analysis: 23 in the control group and 23 in Doppler group (see Fig. 1).

Patient characteristics and demographic data are presented in Table 1. There were no statistically significant differences between the two groups at baseline, except for lower APACHE II score in the Doppler group than in the control group with *p* value 0.039 (see Table 2).

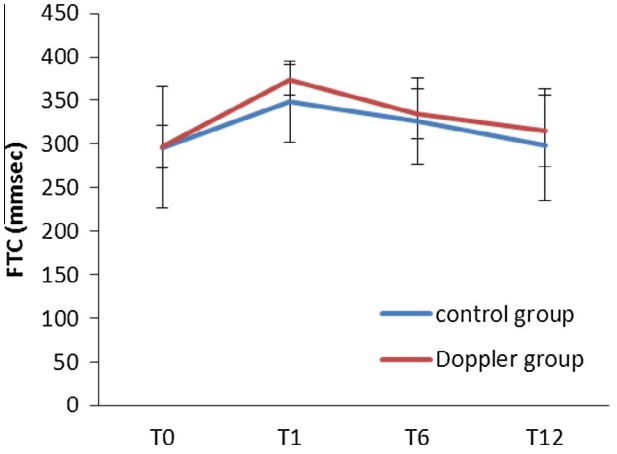

Figure 4 FTC pre- and post resuscitation in both groups. T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

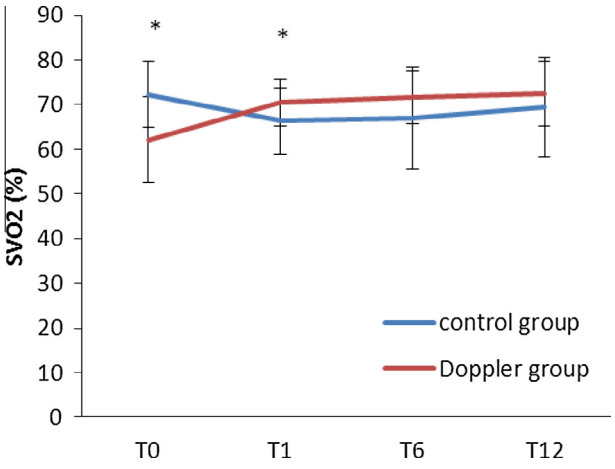

Figure 5 S_cVO_2 pre- and post resuscitation in both groups. S_cVO_2 = central venous oxygen saturation * significant p value between control and Doppler groups. p value <0.05. T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

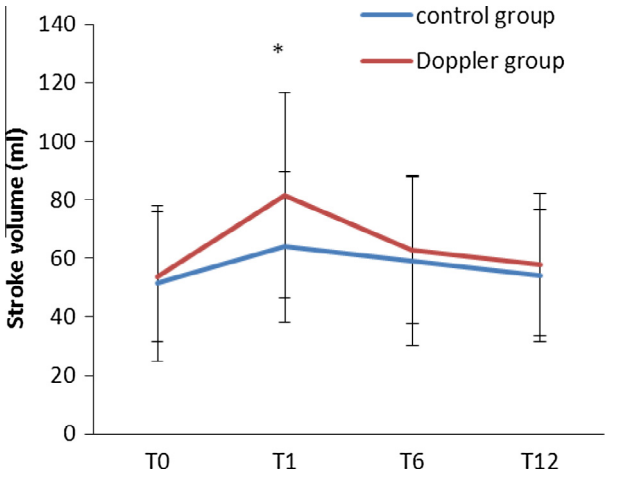

Figure 6 SV pre- and post resuscitation in both groups. SV (stroke volume), * (significant p value between control and Doppler groups, p-value <0.05), T0 = measurement on enrollment, T1 measurement after 1 h post resuscitation, T6 measurement after 6 h post resuscitation, T12 = measurement after 12 h post resuscitation.

Regarding fluid responsiveness the total number of responders was 41 patients (89.01%) and 5 patients (10.09%) were non-responders; there were statistically significant differences regarding FTc on enrollment [380.00 (344.00–384.00) & 293.00 (271.00–319.00)] between non-responders and responders respectively, p value was (0.000), in FTc after 1 h [397.00 (390.00–404.00) & 362.00 (351.00–377.00)] between non-responders and responders respectively, p value was (0.003) and in FTc after 6 h [377.00 (376.00–378.00) & 330.00 (314.00–353.00)] between non-responders and responders respectively, and p value was (0.007) (Table 3).

Also, there were statistically significant differences regarding the total fluids administrated after 1 h [3000.00 (3000.00–3500.00) & 2500.00 (2000.00–3000.00)] between non-responders and responders respectively, and p value was 0.049 (Table 3).

There were no statistically significant differences at baseline and after 1, 6 and 12 h post resuscitation regarding mean ABP, FTC and CVP between the two groups as shown in Figs. 2–4.

Baseline S_cVO_2 was higher in control group than in Doppler group (72.3 ± 7.43, 62.1 ± 9.71) respectively $p = <0.001$, however one hour after fluid challenge S_cVO_2 significantly increased in Doppler group more than in control group (70.48 ± 5.24, 66.35 ± 7.34) with p value of 0.043 (Fig. 5).

Regarding stroke volume (SV), there was only statistically significant increase in SV after 1 h post resuscitation in the Doppler group as the values were 63.87 ± 25.87 & 81.39 ± 35.02 in control group and Doppler group respectively (p value = 0.034) (Fig. 6).

4. Discussion

Using trans-esophageal aortic Doppler is a simple, non-invasive tool of guiding fluid therapy in patients with severe sepsis and septic shock. FT changes were a better predictor of change in Doppler derived stroke volume following fluid challenge (fluid responsiveness) than CVP.

In the current study, 41 patients demonstrated an increase in stroke volume ⩾10% (responders) while 5 patients were non-responders To initial fluid resuscitation, the best cut-off value of FTc was 332 m sec, below this value patients were considered responders and above this value they were non-responders.

These results were in line with Sturgess et al. [9] who compared FTc, BNP and central venous pressure as predictors of fluid responsiveness in septic shock patients without cardiac dysrhythmia in a prospective study of 10 consecutive adult septic shock patients treated with intravenous fluid challenge (4% albumin 250 mL over 15 min) in a tertiary intensive care unit and concluded that transcutaneous FTc was a better predictor of fluid responsiveness than either Brain Natriuretic peptide (BNP) nor CVP in septic shock.

Lee et al. [11] who evaluated the ability of FTc to predict fluid responsiveness and compared this with the abilities of other preload indices, such as pulse pressure variation (PPV), central venous pressure (CVP), and left ventricular end-diastolic area index (LVEDAI), demonstrated that FTc and PPV before fluid loading differed between responders (n = 11) and non-responders (n = 9), and correlated with changes in stroke volume index and concluded that FTc predicted fluid responsiveness. However, FTc should be used in conjunction with other clinical information.

On the other hand our results showed that static values of CVP did not predict hemodynamic response to fluid challenge, as the magnitude of the change in SV was (<10%) which were in line with Marik et al. [12] who conducted a systematic review and demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/DeltaCVP to predict the hemodynamic response to fluid challenge and recommended that CVP should not be used to make clinical decisions regarding fluid management.

De Waal et al. [13] demonstrated that the correlation coefficient for the relationship between percent of increase in SVI (stroke volume index) and CVP prior to the volume load was poor for CVP.

5. Limitations

We could not estimate total amount of fluids given to the patients before admission to ICU.

6. Conclusion

Transesophageal aortic Doppler is a simple, non-invasive tool of guiding fluid therapy in patients with severe sepsis and septic shock. FTc change was a better predictor of fluid responsiveness than CVP in septic. Regarding SV, there was higher significant difference in SV after 1 h post resuscitation when using FTC as a guidance. However further randomized trials are required to validate these results.

Conflict of interest

Dr. Waleed Hamimy is an author and is the chief editor of the Egyptian Journal Of Anesthesia.

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