Impact of Echocardiography Guided Fluid Resuscitation on Critically Ill Patients' Outcomes

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Objective
To compare echocardiography-guided versus clinically guided fluid resuscitation rgarding mortality of critically ill patients in ICU.

Patients and methods
This randomized controlled trial was carried out on 120 patients with circulatory shock. Demographic, clinical, and routine laboratory data were recorded. Eligible patients were randomly assigned to either echocardiography-guided fluid resuscitation or clinically guided fluid resuscitation. Fluid responsiveness was defined as either left ventricular outflow tract-time velocity integral respiratory variation by 12% or an increase in left ventricular outflow tract-time velocity integral by 12% after 250 ccs of normal saline challenge.

Results
Echocardiography-guided resuscitation cases have significantly lower hospital mortality (30 vs. 43% in controls; P = 0.001), intubation and mechanical ventilation rates (7.87 ± 0.63 vs. 4.48 ± 0.38 days in controls; P = 0.01). Moreover, cases have a significantly lower amount of fluid (26 800 vs. 50502 ml in the control group20), with significantly lower net cost [13.4$ (214 EGP) vs. vs 25.11 $ (401 EGP) in the controls; P = 0.000 in controls; P = 0.00].

Conclusions
Echocardiography-guided fluid resuscitation appears to have lower hospital mortality, hospital morbidities, and ICU cost.

Keywords:
echocardiography, fluid therapy, shock, volume status

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Introduction

Resuscitation of shock patients usually requires the infusion of intravenous fluid to reverse organ dysfunction. Proven harm of inappropriate use of fluid has been established in the literature [1]. In critically ill patients, the gold standard to assess fluid responsiveness is to perform a fluid challenge test. A patient with a positive fluid responsiveness should show an increase of at least 10–15% in stroke volume (SV) in response to a fluid challenge of (250–500 ml) [2].

Fluid responsiveness can be defined as either Left Ventricular Outflow Tract-Time Velocity Integral (LVOT - TVI) respiratory variation by 12% or an increase in LVOT - TVI by 12% after 250 ccs normal saline challenge [3].

The clinical effect of dynamic evaluation of fluid responsiveness (FT-DYN) remains unclear. The clinical impact of dynamic assessment of fluid responsiveness (FT-DYN) remains unclear. This trial aimed to determine whether echocardiography- guided fluid resuscitation impacts relevant outcomes of shock patients admitted to the intensive care unit (ICU) in comparison to standard care.

Patients and methods

The trial is a single centre (NCT03296319), randomised, controlled, sequential trial that randomly allocated eligible patients to either echocardiography guided fluid resuscitation (cases) or clinically guided fluid resuscitation (control) in a 1:1 ratio.

Study population

This trial was carried out on 120 patients with Acute Physiologic Assessment and Chronic Health Evaluation II score more than or equal to 25 in the Critical Care Unit of Internal Medicine Department of Assiut University Hospital in the period between January 2018 and January 2019. Eligible patients were randomized to either echocardiography-guided fluid resuscitation (cases) or clinically guided fluid resuscitation (controls).

Patient allocation

A permuted block randomization method with variable block sizes was used to allocate eligible patients to either echocardiography guided fluid resuscitation (cases) or clinically guided fluid resuscitation (control) in a 1:1 ratio. It was not feasible to blind treatment providers in the ICU. Patient Flow Chart is shown in Fig. 1.

Ethical considerations

Written informed consents were obtained from all the participants or their legal guardians as applicable. The research was approved by the institutional review board, Assiut Faculty of Medicine, Assiut University (IRB No 17101346).

Demographic and clinical data

Patients' demographic data and medical history data, including name, age, sex, and history of chronic diseases, were recorded. Physical examination including arterial blood pressure, respiratory rate, temperature, urine output, and thorough chest, cardiac, and abdominal examination was done and recorded.

Laboratory data

Arterial blood samples were withdrawn for blood gases from the patients at the time of admission, during follow-up at variable intervals according to the patient's clinical conditions, and at discharge. The other laboratory measurements included serum levels of creatinine and blood urea nitrogen, prothrombin time and concentration, and electrolytes including Na and K. Serum samples were withdrawn on admission and discharge from each patient and stored at −20°C until tested.

Echocardiography

All echocardiograms were performed with a Philips Envisor C HD (Philips Medical Systems, Bothell, Washington, USA) equipped with a broadband harmonic transducer. All echocardiograms were carried out at the Critical Care Unit of Assiut University Hospital. The sample box of pulsed wave Doppler was put at the level of the aortic valve or within 1 cm of it within the LVOT. LVOT-TVI change of 12% after 250 ml normal saline challenge in adults foretells fluid responsiveness, and LVOT-TVI variation is also predictive [3].

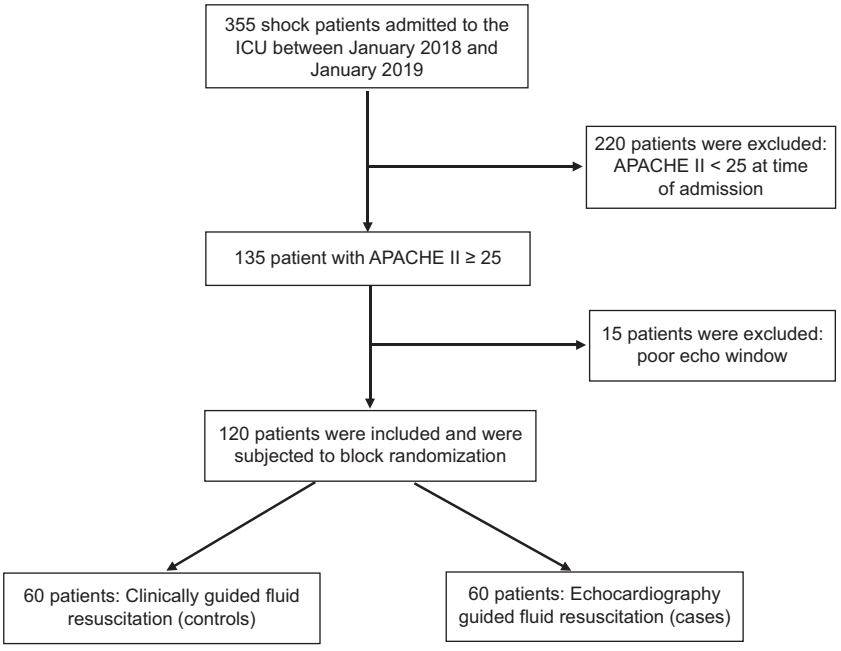
End point

In-hospital mortality was the primary end point. Secondary end points included the duration of hospital stay, time to control various clinical and laboratory abnormalities (mean arterial pressure, lactate, and renal chemistry), and development of complications such as pulmonary edema and the need for mechanical ventilation.

Statistical analysis

Statistical analysis was done using the statistical package for social sciences (SPSS 19). We assumed that the prevalence of responsiveness in shock patients

Figure 1



Patients flow chart.

Table 1: Demographic, Clinical and Lab data of the studied groups

	Mean±SD		*P*
	Cases (*n*=60)	Controls (*n*=60)	
Age (years)	51.93±22.15	46.35±17.00	0.124
Sex *n* (%)			0.361
Male	33 (55.0%)	28 (46.7%)	
Female	27 (45.0%)	32 (53.3%)	
Duration of hospital stay (days)	3.12±2.19	2.77±2.46	0.412
Chronic illness *n* (%)	45 (75.0%)	38 (63.3%)	0.166
Smoking *n* (%)	23 (38.3%)	8 (13.3%)	0.002*
Drug intake *n* (%)	43 (71.7%)	38 (63.3%)	0.330
SOFA score	7.20±5.05	8.60±4.22	0.102
APACHE II score	35.90±16.34	34.48±9.81	0.566
Creatinine* (mg/dl)	177.80±183.06	180.77±145.08	0.922
BUN* (mg/dl)	12.19±8.84	10.15±8.17	0.191
Prothrombin time* (s)	14.31±4.92	13.43±1.92	0.201
Prothrombin concentration* (%)	79.12±18.12	79.07±17.30	0.988
Sodium* (Mmol/l)	137.78±5.40	139.52±6.84	0.126
Potassium* (Mmol/l)	3.86±0.58	3.94±0.88	0.581
pH* on admission	7.34±0.15	7.35±0.11	0.716
Urine output (ml/day)	736±499	578±577	0.120

SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, BUN: blood urea nitrogen. *Admission level

Table 2: CVP measurements of the study groups

CVP	Mean±SD		*P*
	Cases (*n*=60)	Controls (*n*=60)	
H1	12.87*±6.42	10.35±7.49	0.050
H2	16.03±6.45	14.95±8.94	0.448
H3	16.53±5.45	17.22±7.94	0.582
H4	16.62±5.80	16.57±5.74	0.964
D2	15.21±4.33	16.83±6.80	0.166
D3	15.33±2.86	16.29±8.41	0.585
D4	16.11±2.30	17.12±8.72	0.639
D5	14.20±2.04	17.15±7.40	0.236

CVP: central venous pressure, H: hours, D: days. *Measurements by cm H_2O

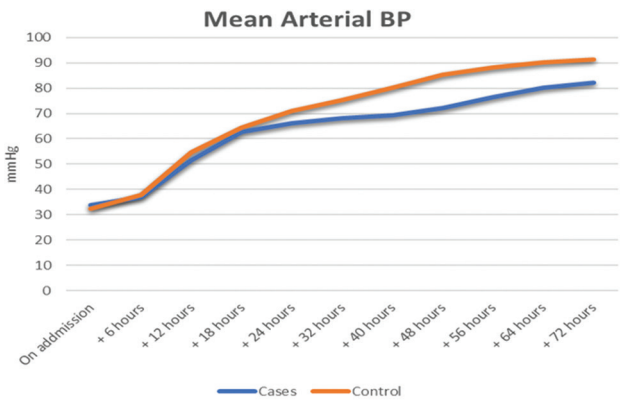
Table 3: Echocardiographic measurements of the study groups

Variable*	Mean±SD		*P*
	Cases (*n*=60)	Controls (*n*=60)	
Peak aortic valve flow (M/S)	0.52±1.12	0.62±1.85	0.257
TVI (M)	12.25±3.54	11.98±4.25	0.254
CO (L/Min)	2.25±1.45	2.54±1.98	0.965

*On admission. TVI: time velocity integral, CO: cardiac output

is 50%, sample sizes of 60 patients in each arm would allow estimation of a two-sided 95% confidence interval for the difference between echocardiography guided fluid resuscitation (cases) and clinically guided fluid resuscitation (control) with a width that is equal to 0.46 (-0.23, 0.23) when the difference in sample proportions is 0. Continuous variables were expressed as mean and SD. Qualitative data were expressed as percentages. Kaplan–Meier curves were used to assess survival, normalization of kidney injury, the incidence of pulmonary edema, and the need for mechanical ventilation. Level of significance was reached if *P* value was less than 0.05.

Figure 2



Mean blood pressure of the study groups.

Results

Demographic, clinical and labortatory data are shown in Table 1. There was no significant difference between the two groups regarding mean blood pressure (Fig. 2) and central venous pressure recordings (Table 2). The average duration of hospital stay for the cases was 3.1 days (3.12 ± 2.19) and 2.7 days for the controls (2.77 ± 2.46), with no significant difference (*P* = 0.412). There was no significant difference between the two groups regarding urine output (736.11 ± 499.38 in the cases and 578.07 ± 577.16 in the controls; *P* = 0.12). Lactate levels were insignificantly different between groups (Fig. 3). There was no significant difference between the two groups regarding urine output with (736.11 ± 499.38 in cases and 578.07 ± 577.16 *P* = 0.12).

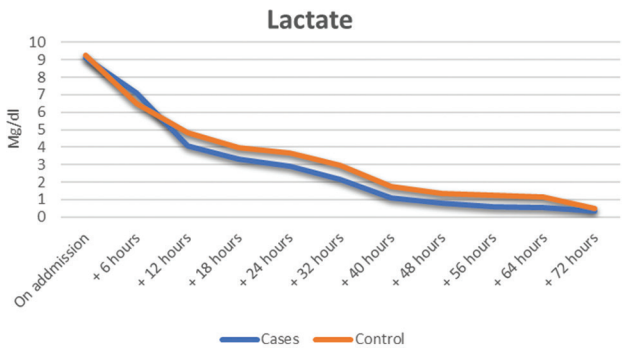
Echocardiographic data

There was no significant difference between the two groups regarding admission echocardiographic data (Table 3).

Amount of fluid, the incidence of pulmonary edema, and risk of intubation

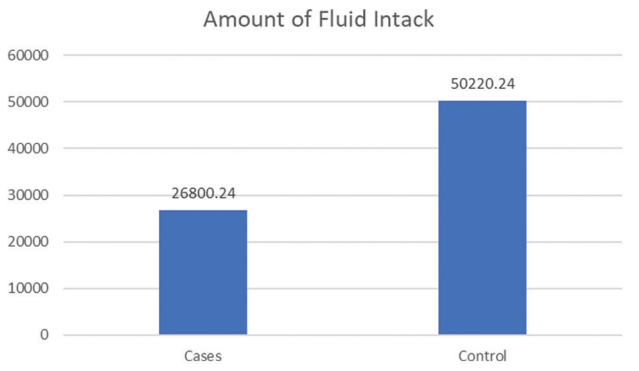
The amount of intravenous fluid was significantly lower in the cases than in the controls. It was 26 800 ml in the cases and 50220 ml in the controls, with a significant reduction in the net amount of cost [13.4$ (214 EGP) in the cases and 25.11$ (401 EGP) in controls (*Egyptian rate at the time of the study*) (Fig. 4). There were no significant differences regarding the incidences of pulmonary edema between the cases and the controls (5.02 ± 0.44 days for pulmonary edema to

Figure 3



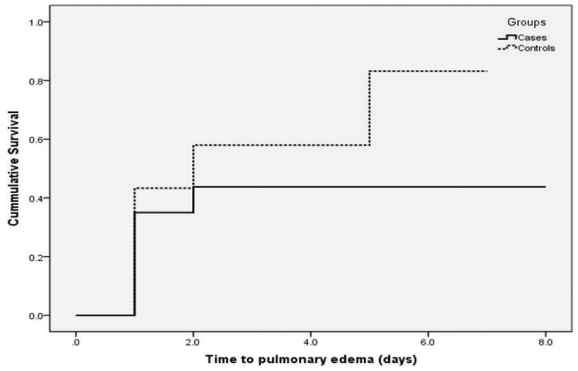
Lactic acid levels of the study groups.

Figure 4



Comparison between total amount of IV fluids between cases and controls.

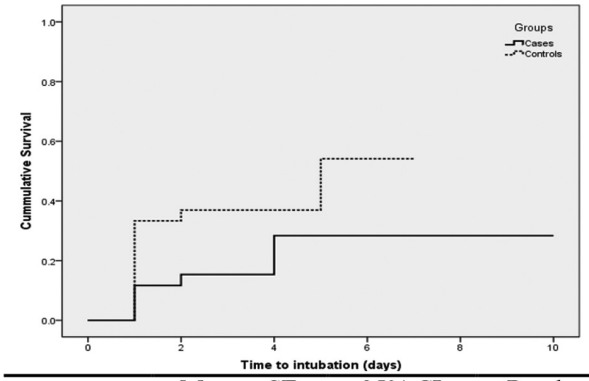
Figure 5



	Mean ± SE	95% CI	P-value
Cases	5.02 ± 0.44	4.16-5.89	
Control	3.16 ± 0.35	2.48-3.85	0.067

Kaplan-Meier analysis for pulmonary edema.

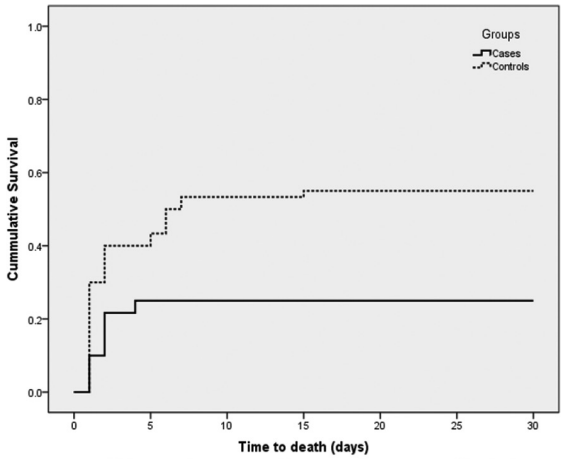
Figure 6



	Mean ± SE	95% CI	P-value
Cases	7.87 ± 0.63	6.64-9.11	
Control	4.48 ± 0.38	3.74-5.21	0.010*

Kaplan-Meier analysis for the need for mechanical ventilation.

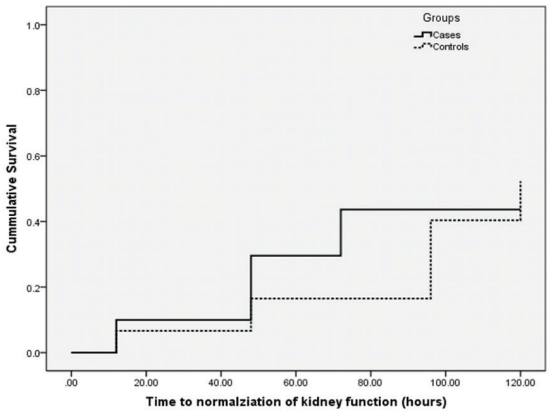
Figure 7



	Mean ± SE	95% CI	P-value
Cases	22.97 ± 1.57	19.88-26.05	0.001
Control	15.05 ± 1.77	11.58-18.52	

Kaplan-Meier analysis for overall survival.

Figure 8



	Mean ± SE	95% CI	P-value
Cases	88.35 ± 5.62	77.33-99.37	0.349
Control	100.00 ± 5.11	89.99-110.01	

Kaplan-Meier analysis for normalization of kidney function.

occur in the cases and 3.16 ± 0.35 days in the controls) (Fig. 5).

The need for mechanical ventilation was significantly lower in the cases than in the controls, where the mean

duration of mechanical ventilation was 7.87 ± 0.63 days in the cases versus 4.48 ± 0.38 days in the controls, with a significant *P* value of 0.01 (Fig. 6).

Survival rate

Regarding the overall survival, there was a significantly higher survival rate in the cases, with a mean ± SE of 22.97 ± 1.57 (43%), than in the controls, with a mean ± SE of 15.05 ± 1.77 (30%) (Fig. 7).

There was no significant difference regarding time to normalize kidney function (88.35 ± 5.62 hours in cases and 100.00 ± 5.11 hours in controls and *P*-value 0.3) (Fig. 8).

Discussion

The main findings of the current study were [1] overall survival in echocardiography-guided fluid resuscitation of patients with shock was significantly higher compared with resuscitation by conventional methods [2], The incidence of intubation and the need for mechanical ventilation were significantly lower in the cases than the controls [3], lactate levels were significantly and rapidly reduced in the cases compared with the controls [4], and the amount of fluid and the cost burden were significantly higher in the controls than the cases in our study.

Fluid resuscitation has the capability to restore tissue perfusion to vital organs in critically ill patients with hypotension and shock [4,5].

Even though three large trials of central venous pressure-based fluid loading have failed to show any clinical benefit compared with usual care, many questions have been asked about goal-directed therapy incorporating fluid therapy using dynamic methods (FT-DYN) [6–9]. This approach evaluates changes in SV or surrogate dynamic variables (e.g., SV variation and pulse pressure variation) during changes in cardiac preload initiated by ventilation, passive leg raise, or fluid challenge [10].

The current study shows that the overall survival in fluid resuscitation guided by echocardiography was significantly higher than the use of conventional methods. This finding was in agreement with a large meta-analysis study published in 2017 that found fluid therapy guided by FT-DYN was associated with decreased mortality compared with the standard care [11]. These findings could be owing to the amount of fluid, which was significantly lower in cases than in control, and the consequent volume overload that could result in tissue and interstitial edema.This in turn leads to poor diffusion of oxygen and metabolites, distortion of tissue architecture, obstruction of capillary blood flow and lymphatic drainage, and disorder of the interaction between cells. All these factors could contribute to progressive organ dysfunction.

In the current study, there was no significant difference regarding the duration of hospital stay between the two groups of patients. Conflicting data have been shown regarding the effect of FT-DYN-assisted resuscitation on the duration of hospital stay. Two trials have examined the ICU length of stay and have reported a reduced ICU length of stay in patients receiving FT-DYN [12,13], whereas another two trials found no difference [14,15].

The current study shows that the incidence of intubation and the need for mechanical ventilation were significantly lower in the cases than the controls, which also has been demonstrated in the meta-analysis by Buettner *et al.* [16].

Two studies [12,17] have examined the incidence of acute pulmonary edema in FT-DYN-guided and conventionally guided resuscitate and have found that two cases developed pulmonary edema in the control group, whereas no patient developed pulmonary edema in the case group. Our results show the incidence of pulmonary edema was significantly lower in the cases than the controls from the second day to the end of hospital admission, but regarding the overall duration of hospital stay, there was no significant difference.

The current work shows no significant difference regarding the time of normalization of kidney function, which is in agreement with the meta-analysis study by Goepfert *et al.* [18], which found that FT-DYN was not associated with a significant difference in the frequency of renal complications.

Up to our current knowledge, there is no published study that compares between the amount of fluid in the echocardiographic guided fluid therapy and the standard fluid therapy and the associated cost burden in these therapies. Moreover, both the amount of fluid and the cost were significantly higher in the controls than the cases.

Conclusion

The use of fluid replacement guided by echocardiography appears to be associated with decreased in-hospital mortality, incidence of pulmonary edema, risk of intubation, risk of mechanical ventilation, and both the amount of fluid and the cost of ICU. So, we do recommend that any patient who presents with

shock should be resuscitated with fluid guided by dynamic methods, and echocardiographic guided fluid administration is a useful guide.

Study limitations

Despite the blinding policy of the study, the main limitation was the inherited operator dependency of the ultrasound technique and the risk of observer expectation bias. We recommend the use of other objective methods to guide fluid resuscitation to avoid this inherited characteristic of ultrasound techniques.

Acknowledgments

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Nil.

Conflicts of interest

There are no conflicts of interest.

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