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ORIGINAL ARTICLE

End Tidal Carbon dioxide can track cardiac output changes during fluid challenge in Shocked Mechanically Ventilated Patients

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ABSTRACT

Background: In this study, we investigated the ability of end tidal carbon dioxide pressure ($P_{ET}CO_2$) to monitor the changes in cardiac output (CO) induced by fluid challenge and to predict fluid responsiveness. **Patients and Methods**: We conducted our study upon 38 shocked patients requiring fluid challenge (FC). Hemodynamic variables, central venous pressure (CVP), End-tidal CO_2, arterial and venous blood gas analysis and cardiac output were recorded before and after fluid challenges. Fluid responders were identified when cardiac output increased more than 15% after fluid challenge, cardiac output (CO) was estimated by measuring left ventricular outflow tract velocity-time integral (LVOT VTI) by transthoracic doppler echocardiography. **Results**: Twenty-one (55.3%) patients were fluid responders. Fluid challenge induced increase in CO and $P_{ET}CO_2$ was moderately correlated (r = 0.5; P 0.002). The area under receiver operating characteristic (ROC) curve of Δ $P_{ET}CO_2$ was 0.89±0.05 CI (81- 98) with an increase ≥ 3.13% in $P_{ET}CO_2$ can predict fluid responsiveness with 85.7% sensitivity and 88.3% specificity. No other clinical or hemodynamic variables can predict fluid responsiveness. The area under ROC curve of ΔCVP was 0.48±0.1 CI (32- 64) with an increase ≥ 2cmH_2O in CVP can predict fluid responsiveness with 38% sensitivity and 76.5% specificity**. Conclusions**: Our findings indicate that induced changes in $P_{ET}CO_2$ during fluid challenge could be used to monitor changes in cardiac output (CO) for prediction of fluid responsiveness in mechanically ventilated shocked patients, under stationary minute ventilation and steady CO2 production.

Keywords: fluid responsiveness, cardiac output, VTI, Doppler echocardiography, Partial end tidal CO_2

INTRODUCTION

Fluid management is used to be the first-line treatment of acute circulatory failure in critically ill patients. Mainly, increasing stroke volume is the only target of giving any patient a fluid challenge; if this does not occur, the administration of fluid may lead to harmful effects [(1)]. Moreover, cardiac output increase must be evaluated to be beneficial. [(2)].

The fluid administration -induced change in partial end tidal CO_2 pressure ($\Delta P_{ET}CO_2$) could be an alternate for the fluid administration- induced change in cardiac output. The exhaled carbon dioxide (CO_2) amount depends on the amount of CO_2 produced by the body, its transport by pulmonary blood flow (CO), and its wash by alveolar ventilation**.** [(3)] If alveolar ventilation is kept steady, as during volume control mode, and if CO_2 production is relatively unchanged, then $\Delta P_{ET}CO_2$ would reflect change in cardiac output (ΔCO). [(4), (5)]**.** Cardiac arrhythmia can't limit use of $\Delta P_{ET}CO_2$ in contrast to the indices that use beat-to-beat analysis. Pulse pressure respiratory variation (PPV) was suggested to predict fluid responsiveness rather than to monitor the effects of a fluid challenge. [(6)]

PATIENTS AND METHODS

Site of the study:

This study was carried out in the surgical intensive care unit at Zagazig University hospitals.

Administrative design:

Approval was obtained from the department of anesthesia & surgical intensive care and the Institutional Review Board (IRB) at Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for studies involving humans.

Written Informed consent:

Written informed consents were obtained from all the patients' guardians.

Sample size:

Assuming that mean ± SD of left ventricular outflow tract velocity time integral (VTI) before fluid challenge is (13.2±4.8) cm and after fluid challenge is (18.3±6.2) cm[7] ; using openEpi with power 80% and C.I. 95% so, the total sample size was 38 cases.

We included 38 patients with inclusion criteria.

Inclusion criteria:

The inclusion criteria were as follows:

- Age 18-60 years.
- Continuous sedation and mechanical ventilation.
- Instrumentation with central venous catheter through the internal jugular vein or subclavian vein.
- A clinical requirement for a fluid challenge; patients who had signs of shock

Exclusion criteria:

- Spontaneous breathing activity
- Active bleeding,
- Pregnancy.
- An inadequate echocardiographic window

Study protocol:

The baseline characteristics and severity scores (APACHE II & SOFA) were collected at the patient's inclusion in the study. The selected patients were mechanically ventilated; the tidal volume was adjusted to 8 -9ml/kg, (based on the patient's predicted body weight), PEEP (5-8cmH_2O). We gave muscle relaxant to prevent spontaneous breathing activity

We recorded/collected ventilation data and hemodynamic variables, such as the arterial pressure, heart rate, central venous pressure and oxygen saturation. Also, arterial and central venous blood samples were obtained for blood gases. End tidal carbon dioxide pressure ($P_{ET}CO_2$) was continuously measured at the tip of the endotracheal tube using a mainstream infrared gas analyzer, readings were averaged and recorded before and after fluid challenge.

We also used the reference standard, the change in the cardiac output, measured by echocardiography, by measuring the left ventricular outflow tract velocity-time integral (LVOT VTI) with a pulsed doppler and left ventricular outflow tract (LVOT) area. "Responders" had a cardiac output increase of at least 15%, whereas "non-responders" had a cardiac output increase of <15% after fluid challenge. All measurements and calculations were performed before and after fluid challenge, using 500 ml of crystalloid (Ringer) infused over 15 minutes.

Stroke Volume = left ventricular outflow tract (LVOT) area x LVOT velocity-time integral VTI.

Cardiac output = stroke volume x heart rate

Statistical analysis

We used **Kolmogorov-Smirnov normality test** to test the normality of distribution. Data are expressed as numbers (%), means ± standard deviation (SD) for continuous variables tested to be a normal distribution. The comparisons of hemodynamic data before and after fluid challenge were assessed using **the paired Student's t-test** and the comparisons between responders and non-responders were assessed using the **independent Student's t-test** for normally distributed variables. The linear correlation between the changes in $P_{ET}CO_2$, and changes in cardiac output were tested using the Pearson correlation test.

We constructed the receiver operating characteristic (ROC) curves with 95% confidence interval to evaluate the capacity of $\Delta P_{ET}CO_2$ and ΔCVP to predict fluid responsiveness. The best cut-off values that yielded the greatest sensitivity and specificity, were also calculated (Youden method).

RESULTS

Forty-three patients were eligible for this study and 38 patients were included. We excluded 5 patients (three patients had poor an echocardiographic window, two patients had become unstable leading to changes in dose of vasoactive drugs) as shown in the consort flow chart of the study (figure 1).

After fluid challenge, patients were divided into;

- Responders (N=21) (55.3 %) who had an increase in cardiac output of ≥15%
- Non-responders (N=17) (44.7%) who had an increase in cardiac output of <15%.

This study reported a total of 31 patients (81.5%) with septic shock and only 7 patients (18.5%) with hypovolemic shock

There is no statistical significance between the two groups as regarding gender, age and type of shock (p=0.31,0.09 and 0.07 respectively).

APACHE II score and SOFA score were higher in the non-responders than the

In the two groups, the mean blood pressure and CVP were significantly higher after the fluid challenge, for both responders and Non-responders. Regarding the end tidal CO2, we reported a statistically significant increase after the fluid challenge in the responders only (28.68±6.64 before vs 30.47±6.6 after, P=0.001) as shown in table 2.

Arterial HCO3 and venous PH increased significantly after fluid challenge in the responders only (p=0.003 and 0.02 respectively). PvO2 and central venous oxygen saturation ($ScVO_2$) in the non-responder group decreased significantly after fluid challenge, (p=0.01 and 0.005 respectively) as shown in table 3.

responders significantly (P=0.04, P=0.01 respectively) as shown in table 1.

There was no statistically significant difference between the study groups in term of basal recordings of mean blood pressure, heart rate, SPO2, end tidal CO2, CVP, data of ventilation and data of arterial and venous blood gas analysis as shown in table 2 and table 3.

We considered responsiveness as increase of cardiac output equal to or more than 15 % after fluid challenge

There was a moderate correlation between fluid challenge induced increase in cardiac output and ΔPETCO2 (r = 0.5; P 0.002).

The area under ROC curve of ΔPETCO2 (figure.2) was 0.89±0.05 CI (81- 98) with an increase ≥ 3.13% in PETCO2 can predict fluid responsiveness with 85.7% sensitivity and 88.3% specificity (P<0.001) .The area under ROC curve of ΔCVP (figure.3) was 0.48±0.1 CI (32- 64) with an increase ≥ 2cmH2Oin CVP can predict fluid responsiveness with 38% sensitivity and 76.5% specificity (P=0.8) as shown in table 5.

Table (1): Baseline characteristics and ventilation data of included patients:

Variables		Responders (N=21)	Non-responders (N=17)	Total (N=38)	P value
Gender	**Female**	6 (28.7%)	7 (41.17%)	13 (34.2%)	0.31
	Male	15 (71.3%)	10 (58.8%)	25 (65.8%)	
Age (Year)		42±13	44±11	43±12	0.09
Weight (kg)		80.5±10.3	84.1±11.3	82.1±10.8	0.3
Height (cm)		172.43±6.5	171±8.1	172.1±7.2	0.76
Type of shock	**Septic**	15 (71.4%)	16 (94%)	31(81.5%)	0.07
	hypovolemic	6 (28.6%)	1 (6%)	7(18.5%)	
APACHE II		24.6 ±10.3	31.17 ±8.7	27.55 ±10.1	**0.04***
SOFA		9.95 ±3.35	12.8 ±3.3	11.24 ±3.6	**0.01***
Predicted Body Weight (kg)		67 ±7.2	65.7 ±9.4	66 ±8.3	0.41
Tidal Volume (ml)		561.4±40.2	548 ±52.3	555.5 ±45.8	0.33

Tidal volume /PBW (ml/kg)	8.4±0.4	8.4±0.5	8.4±0.4	0.96
Peak pressure (cmH_2O)	27.48±5.35	26.65 ±5.1	27.11 ±5.2	0.69
Plateau pressure (cmH_2O)	19.7 ±3.5	20.17 ±3.9	19.94 ±3.7	0.78
PEEP (cmH_2O)	5.9±1	5.8±0.9	5.86±0.99	0.8
Driving pressure (cmH_2O)	14.8±4	15.29±4.6	15±4.26	0.73
Static compliance (ml/cmH2O)	42.2± 11.3	40.16± 10.7	41.26± 11.1	0.58
Noradrenaline(µg/kg/min)	0.32 ± 0.12	0.33 ± 0.11	0.32±0.11	0.59

APACHE II: Acute Physiology and Chronic Health, SOFA: Sequential Organ Failure Assessment, PBW: Predicted Body Weight, PEEP: Positive End Expiratory Pressure. The data are expressed as mean ± standard deviation or number (%).
* value of P <0.05: statistically significant difference between responders and non-responders

Table (2): Hemodynamics, CVP and End-tidal CO2 For Each group Before and After fluid challenge (FC)

Variables		Responders	P*	Non-responders	P*	P¶ value
		Mean ±SD		Mean ±SD		
Mean blood Pressure	**Before FC**	69.54±6.2	**<0.001***	71.65 ±10.24	**<0.001***	0.44
	After FC	81.67±8.5		79 ±10.93		0.4
Heart Rate	**Before FC**	94.46±18.3	0.31	90.18 ±19.53	0.33	0.48
	After FC	94.95±17.6		89.88 ±19.09		0.4
SPO_2	**Before FC**	97.38 ±1.70	0.71	96.25 ±1.44	0.71	0.07
	After FC	97.13 ±1.79		96.35 ±1.27		0.13
$PETCO_2$ (mmHg)	**Before FC**	28.68 ±6.64	**0.001***	30.12 ±8.23	0.84	0.6
	After FC	30. 47 ±6.6		30.05 ±7.9		0.86
CVP (cmH_2O)	**Before FC**	7.33 ±3.48	**0.001***	7.94 ±2.96	**0.04***	0.57
	After FC	8.42 ±3.27		9.18 ±3.45		0.49

SPO_2: Oxygen saturation, $PETCO_2$: Partial pressure of end tidal carbon dioxide, CVP: central venous pressure**.** Data are presented as mean ± SD.
P¶ value of independent t-test comparing the variables between the two groups.
P* value of paired t-test comparing the variables before and after FC in each *group.*
* value of P <0.05: statistically significant difference

Table (3): Arterial and central venous blood gas analysis for each group before and after fluid challenge (FC):

Variables	Responders		P* Value	Non-responders	P* value	P¶ value
	Mean ±SD			Mean ±SD		
Arterial PH	Basal	7.33±0.08	0.15	7.32±0.11	0.94	0.65
	After FC	7.34±0.07		7.32±0.09		0.47
$PaCO_2$ (mmHg)	Basal	34.7±5.76	0.89	35.8±8.21	0.91	0.62
	After FC	34.6±5.75		35.8±6.89		0.57
Arterial HCO3 (mmol/L)	Basal	18.5±5.11	**0.003**	19.2±6.91	0.46	0.71
	After FC	19.4±4.9		18.87±5.33		0.73
Arterial BE	Basal	-6.15±5.98	0.16	-6.21±7.29	0.23	0.97
	After FC	-5.77±5.95		-6.84±6.24		0.6
PaO_2(mmHg)	Basal	107.1 ±29.8	0.22	103.1 ±25.95	0.18	0.53
	After FC	104.4 ±29.7		97.2 ±17.94		0.25
Venous PH	Basal	7.32±0.07	**0.024**	7.31±0.09	0.78	0.48
	After FC	7.33±0.07		7.30±0.08		0.24
PvCO2 (mmHg)	Basal	39.2±5.5	0.16	39.72±5.84	0.19	0.78
	After FC	38±5.1		41.01±5.67		0.09
Venous HCO3 (mmol/L)	Basal	20.42±5.1	0.06	19.78±5.56	0.34	0.71
	After FC	21±4.9		20.34±5.02		0.7
Venous BE	Basal	-4.9±5.6	0.41	-6.48±7.05	0.58	0.46
	After FC	-4.7±5.9		-6.04±6.41		0.51
PvO_2 (mmHg)	Basal	44.2 ±8.4	0.86	45.15 ±8.39	**0.01**	0.74
	After FC	44.1 ±7.9		42.68 ±6.11		0.54
ScVO2 %	Basal	73.2±7.5	0.51	74.34±7.34	**0.005**	0.65
	After FC	73.586±7.46		72.76±5.8		0.71

PaCO2: Partial pressure of arterial carbon dioxide, Arterial BE: arterial base excess or deficit (+/-), Arterial HCO3: Arterial Bicarbonate, PaO2: Partial pressure of arterial oxygen, PvCO2: Partial pressure of venous carbon dioxide, Venous BE: venous base excess or deficit (+/-), Venous HCO3: venous Bicarbonate, PvO2: Partial pressure of central venous oxygen, ScVO2:central venous oxygen saturation. Data are presented as mean ± SD.

P¶ value of independent t-test comparing the variables between the two groups. P* value of paired t-test comparing the variables before and after FC in each group. * value of P <0.05: statistically significant difference

Table (4): LVOT VTI, Cardiac output For Each group Before and After fluid challenge

Variables		Responders	P*	Non-responders	P*	P¶ value
		Mean ±SD		Mean ±SD		
LVOT VTI (cm)	**Before FC**	16.08 ±2.8	**<0.001***	17.4±2.9	**0.016***	0.17
	After FC	19.77±3.3		18.25±3.12		0.16
Cardiac output (ml/min)	**Before FC**	4278±857	**<0.001***	4673.2±1065	**0.04***	0.21
	After FC	5302±1153		4871.7±1048		0.24
increase in cardiac output%		(23.85%) ± (6.54%)		(6.56%) ± (3.25%)		**<0.001***

LVOT VTI: Left ventricular outflow track velocity time integral, Data are presented as mean ± SD. P¶ value of independent t-test comparing the variables between the two groups. P* value of paired t-test comparing the variables before and after FC in each group. * value of P <0.05: statistically significant difference. we consider responsiveness increase in cardiac output ≥15 % after fluid challenge

Table (5): Characteristic performance of ΔPETCO2 and ΔCVP with their best cut off to determine the fluid responsiveness

Variables	Best cut off	Sensitivity	Specificity	+PV	-PV	Area ± SE	95% CI	P value
ΔPETCO2	≥ 3.13%	85.7	88.3	90	83	0.89±0.05	81- 98	**<0.001***
ΔCVP	≥ 2cmH_2O	38	76.5	66	50	0.48±0.1	32- 64	0.8

ΔPETCO2: change in Partial pressure of end tidal carbon dioxide, ΔCVP: change in central venous pressure, +PV: Positive predictive value, -PV: Negative predictive value, SE: standard error, CI: confidence interval. * value of P<0.05: statistically significant

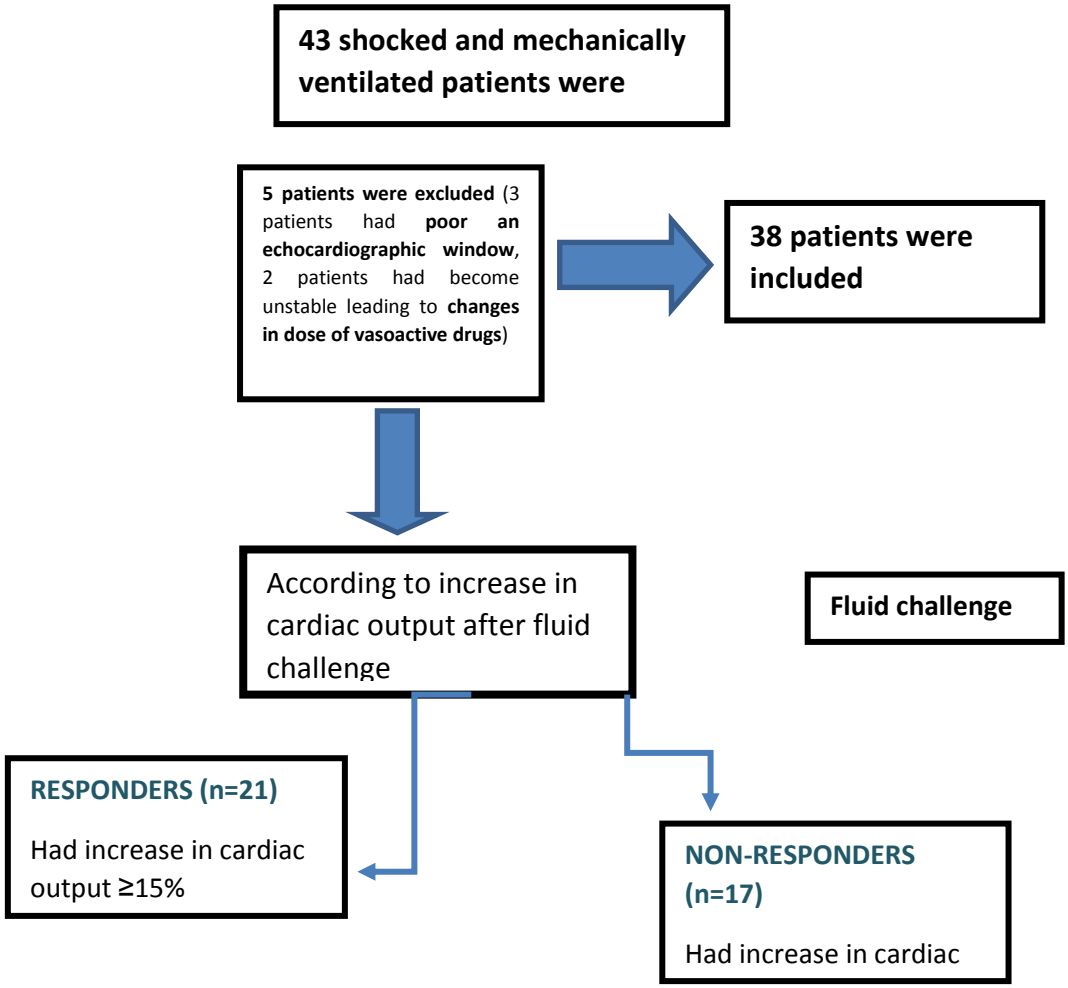

Figure 1: consort flow chart of the study

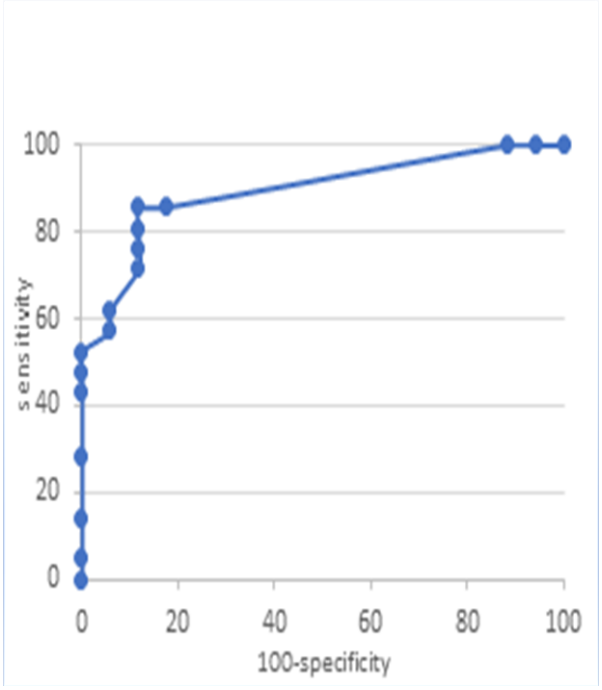

Figure 2: The receiver operating characteristic (ROC) curve of change in End tidal carbon dioxide pressure ($\Delta P_{ET}CO_2$) after fluid challenge for prediction of fluid responsiveness

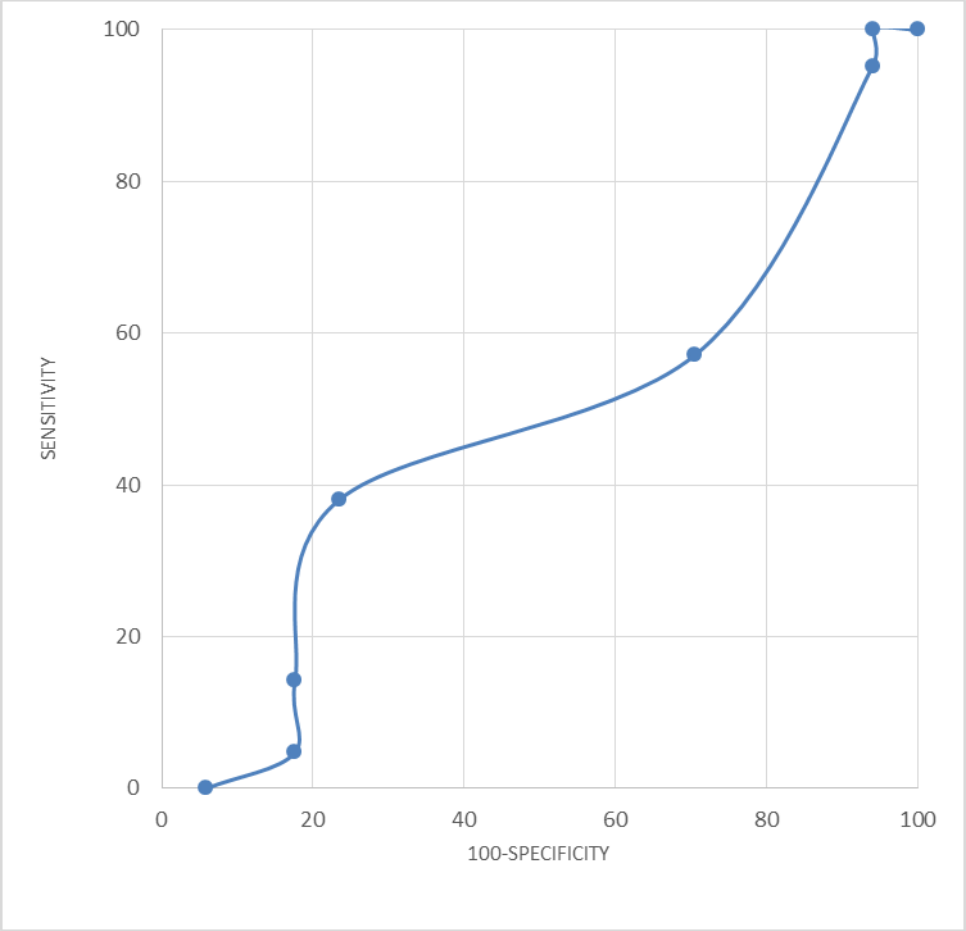

Figure 3: The receiver operating characteristic (ROC) curve of change in central venous pressure (ΔCVP) after fluid challenge for prediction of fluid responsiveness

DISCUSSION

In this study, we found that APACHE II score and SOFA score were higher in the non-responders than the responders significantly, while in a study of Theerawit P, et al., there was no significant difference regarding APACHE score and SOFA score between the responders and non-responders, it might be explained by inclusion of patients with septic shock only in their study without inclusion of patients with hypovolemic shock as we did. [8]

In our study, the mean blood pressure increased significantly after the first fluid challenge in responders and non-responders. Our results are in agreement with previous studies which proved that clinical signs such as tachycardia and blood pressure are neither sensitive nor reliable predictors of fluid responsiveness [9], [10].

In our study, the CVP increased significantly after the first fluid challenge, for responders and Non-responders. The AUROC curve of ΔCVP was 0.48±0.1 CI (32- 64) with an increase ≥ 2cmH_2O in CVP can predict fluid responsiveness with 38% sensitivity and 76.5% specificity. Our results regarding CVP are in agreement with a systematic review that integrated 24 studies, as the authors demonstrated no correlation between baseline CVP nor ΔCVP and fluid responsiveness. [11]

The main finding of this study is that, in volume-controlled ventilation, ΔPETCO2 performed better than ΔCVP in evaluating fluid responsiveness, The AUROC curve of ΔPETCO2 was 0.89±0.05 CI (81- 98) with an increase ≥ 3.13% in PETCO2 can predict fluid responsiveness with 85.7% sensitivity and 88.3% specificity.

The total of exhaled CO2 depends on the amount produced by the tissues of body, pulmonary blood flow (i.e. CO), and alveolar ventilation. [3] Hence, ΔPETCO2 matches ΔCO if alveolar ventilation is steady, as in patients with volume-controlled mode, and if

tissue metabolism is unchanged (i.e. not changed by the fluid administration itself).

We found, as demonstrated by other studies, [4], [5] that ΔPETCO2and ΔCO are significantly correlated ($r^2$0.25; P<0.002). But they have reported the capability of changes in End tidal CO2 during a passive leg raising maneuver or a mini-fluid challenge to predict fluid responsiveness, not during a fluid challenge. [4], [5], [12].

In a study by Toupin et al., $PETCO_2$ was measured before, during and after a leg-raise maneuver and compared to cardiac output by thermodilution in paralyzed cardiac surgery patients [13]. The authors noted that an increase in $PETCO_2 \geq 2$ mm Hg by a leg-raise maneuver was associated with volume responsiveness (sensitivity 75%) and had a high negative predictive value of 86%.

Arango-Granados et al. found that passive leg raising induced ΔCO was not correlated with $\Delta P_{ET}CO_2$ (R^2 = 0.13; p=0.36) in adults with spontaneous breathing. The area under ROC of $\Delta P_{ET}CO_2$ to predict fluid responsiveness was of 0.67 ± 0.09 (95% CI 0.498–0.853). The best cutoff of $\Delta P_{ET}CO_2$ was ≥ 2 mmHg sensitivity and specificity of 50% and 97.06% respectively, positive predictive value of 88.9%, and negative predictive value of 80.5% for the prediction of fluid responsiveness. [14]

The different methodology may explain the conflicting results; as Arango-Granados et al. conducted their study on healthy adults with spontaneous breathing and used passive leg raising maneuver.

There are three studies that have tested the ability of ΔPETCO2 to predict responsiveness to fluid challenge. The first one reported lower predictive power of ΔPETCO2 in predicting fluid responsiveness in contrast to our results (The AUROC of 0.67 [0.48–0.80])) [15]. That study measured the cardiac output by bioreactance method which has questioned reliability [16]; and that may be the cause of conflicting results.

Our findings are in agreement with the results of the other studies which tested the ability of ΔPETCO2 to predict responsiveness to fluid challenge, [17], [18] The AUROC of ΔPETCO2 was 0.80 [0.65–0.96], 0.82 [0.73–0.90]) respectively.

We found that arterial $HCO3^-$ and central venous PH increased significantly in the responders after first fluid challenge, which means that metabolic acidosis was improved as it has been proved that serum pH, base deficit, lactate and bicarbonate, all are metabolic markers of the severity of shock, and enable to determine the adequacy of resuscitation. [19]

We found that after first fluid challenge, PvO2 and ScvO2 decreased significantly in the non-responders. Central or mixed venous oxygen saturation indicates the balance between oxygen supply and consumption, so reflects tissue perfusion [20], so, it means that fluid administration became harmful and reduced tissue perfusion in the non-responders. However, normal or high mixed and /or central venous oxygen saturation (S(c)VO2) does not exclude hypoperfusion nor the need for fluid administration in the case of septic shock [21]

Limitations of the study:

First; the small sample size

Second; we did not measure basal end tidal CO2 variability

Third; measurement of CO by transthoracic echocardiography is not the gold standard method.

Fourth; the cut-off of 15% for ΔCO to distinguish responders from non-responders may be inappropriate (too high) in some patients.

Fifth; we investigated the ΔPETCO2 during mechanical ventilation only. So, our results may not be applicable to spontaneously breathing patients.

Conflict of interest: there are not any financial or personal relationships with other people or organizations that could inappropriately influence (bias) the authors' actions.

Financial Disclosures: all financial resources needed for that study are related to the equipments that are already available in ICU units in zagazig university hospitals e.g. echocardiogaphy, monitors and ABG analyzer

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