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Validity Of End Tidal Carbon Dioxide Gradient As An Indicator Of Volume Response In Spontaneous Breathing Shocked Patients

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Background: When metabolic and ventilator conditions are constant, acute changes in ET-CO2 is well correlated with cardiac output changes in experimental and clinical. Changes in Peak aortic flow velocity and velocity time integral of left ventricle (VTI LVOT) after the effect of passive leg rise (PLR) are good predictors of fluid response in critically ill.
Aim and objectives: evaluation of the ability of expired CO2 gradient (ΔET-CO2) after a PLR maneuver to predict response to fluid loading in those breathing spontaneously shocked patients.
Subjects and methods: This study was a prospective observational study that was conducted on 40 shocked spontaneously breathing patients who were admitted to the critical care department in Beni-Suef university hospital.
Results: there was a statistically significant difference between the studied groups regarding type of shock, need of vasopressors, Comparison between responders and non-responders to PLR regarding their baseline end-tidal CO2 with its follow up and percent of increase, Comparison between hypovolemic and septic shock in response to PLR regarding their baseline VTI with its follow up and percent of increase, Comparison between hypovolemic and septic shock in response to PLR regarding their baseline cardiac output with its follow up and percent of increase.
Conclusion: Percent of change in COP after passive leg rising test did not correlate with percent of changes in ETCO2 (r=0.069, P=0.76) in spontaneous breathing patients. Area under the ROC curve (AUC) for percent of increase of ETCO2 showed a little utility in discrimination of responders and non-responders (AUC = 0.775)

Keywords: carbon dioxide gradient, spontaneous breathing, shocked patients.

INTRODUCTION

Maintaining good and adequate DO2 is the main goal of resuscitation in critical care patients. DO2 depends on cardiac output (CO). Increasing LV preload and LV stroke volume (SV) is challenging issue as not all patients will be good responders to fluid administration. Close

monitoring is mandatory as dehydration and volume overload can lead to delirious outcome. [1, 2]

For this purpose, it is challenging to Find if the patient will be volume responder or not. Another reason is that guiding fluid therapy in spontaneous breathing patients is very difficult due to rare methods, most of them need invasive maneuvers. [3]

Most of these maneuvers are out of reach especially in emergency department. Detecting change in peak velocity of aortic flow and velocity time integral of left ventricle (VTI LVOT) by transthoracic echocardiography (TTE) after a passive leg rise (PLR) maneuver predicts fluid response in critically ill patients as a promising and non-invasive tool with (sensitivity77% and 100% specificity) [4, 5]; however, more advanced training is needed due to poor acoustic windows to keep adequate angle between Echo probe and the Aortic outflow tract in both positions, and finally, these measurements are time consuming. The relationship between expired CO2 (ET-CO2) and CO has been studied well in the last decades. [6, 7]

ET-CO2 is depending mainly on carbon dioxide (CO2) produced by tissues, alveolar ventilation and CO [8], sudden changes in ET-CO2 have strong correlation with changes CO in experimentally [9–11] and clinically with keeping metabolic and alveolar ventilation factors constant. [12, 13]

So we can use Delta or change in ET-CO2 as a predictor of volume responsiveness after a PLR maneuver in patient on mechanical ventilation . [14]

This work aimed to test the accuracy of end-tidal CO2 (ET-CO2) gradient to predict volume response in shocked spontaneous breathing patients. Using passive leg rise (PLR) maneuver to predict volume response.

PATIENTS AND METHODS

This study was a prospective observational study that was conducted on 40 shocked spontaneously breathing patients who were admitted to the critical care department in Beni-Suef university hospital.

The study protocol was approved by the ethical committee of the faculty of medicine in Beni-Suef university ethical committee DW00034

Inclusion Criteria

Randomized sample of 40 critically ill patients "Hypovolemic or septic shock" indicated to fluid challenge for hemodynamic optimization, fulfilling the following criteria: Adult patients ≥ 18 years old, Spontaneous breathing patients, Non cardiogenic shocked (hypovolemic & Septic) patients with lactic acidosis in the form of lactate ≥2mmol/L, sepsis is defined as patient who had 2or more of qSOFA score: (Respiratory rate > 22 breath /min, disturbed consciousness and SBP <100 mmHg

Septic shock is a subset of severe sepsis with persistent hypotension requiring vasopressor to maintain MAP ≥ 65 mmHg with a serum lactate level ≥ 2 mmol/L despite adequate fluid resuscitation. [15]

Hypovolemic shock is a life-threatening condition that occurs after losing more than 30 percent of body's blood or fluid supply.

Exclusion Criteria

Cardiogenic shocked patients & overloaded one either right sided systemic congestion or left sided pulmonary congestion, Patients with cardiac dysrhythmias, amputated lower limbs, difficult imaging acquisition, patients intolerant to stay in supine position or rise their legs like pregnant female patients and who refused to participate in our study had been excluded.

All patients included in the study subjected to the following:

1-Consent:

A written informed consent obtained from patients or patients' close relatives for the agreement for inclusion in the study.

2-History taking:

Full history taken from patients or patients' close relatives including personal data and a detailed medical history

3-Full clinical assessment:

All patients subjected to full clinical examination

4-Investigations:

Laboratory: ABG, lactate level, CBC, (CRP, PCT, blood, urine, sputum, wound culture and sensitivities), Liver profile: SGPT, SGOT, Bilirubin, Serum albumin, Coagulation profile, Kidney functions: Urea, Creatinine and Electrolytes: Na, K, Ca, Po4, Mg.

ALL 40 patients included in our thesis were subjected to standard study protocol consists of: baseline evaluation, Passive leg raising (PLR) involves raising a patient's legs (to at least 45 degrees) for 90 seconds and Collecting the same data after passive leg raising.

Passive leg raising (PLR)

Patient is put at 45 degrees' head up semi-recumbent position then lower patient's upper body is lowered to horizontal and passively raised legs at 45 degrees up maximal effect occurs at 90 seconds to induce a gravitational transfer of venous blood from the legs into the right ventricle, resulting in transient increase in cardiac preload of ~150-300 ml to predict whether cardiac output will increase with volume expansion or not. [16]

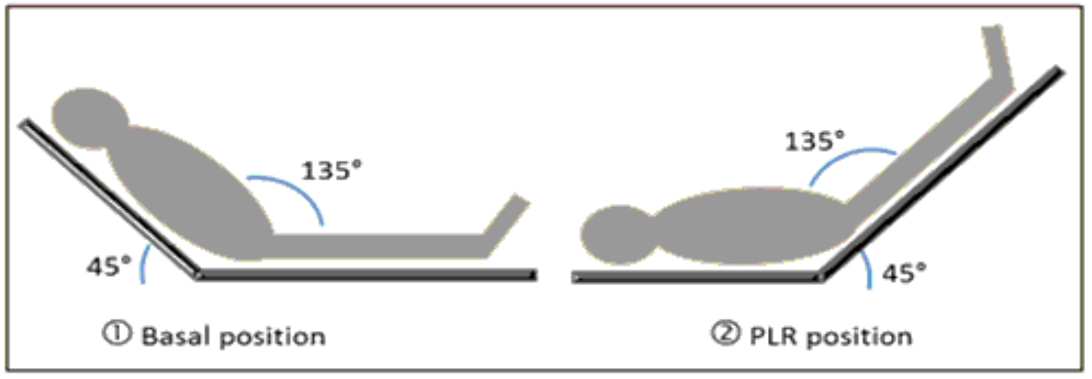

Figure (1) showing passive leg rising maneuver

RESULTS

Table (1) Age and sex distribution of the studied patients

Items	Responders group (no=22)	Non-responders (no=18)	P-value
Age (mean± SD)	46.9±15.5	50.1±15.6	0.528
Sex Males Females	 12(54.5%) 10(45.5%)	 8(44.4%) 10(55.6%)	0.525

This table showed that there was no significant difference between responders and non-responders to fluids regarding their age and sex distribution (P-value>0.05).

Table (2) type of shock, need of vasopressors, among the studied patients

Items	Responders group (no=22)	Non-responders (no=18)	P-value
Shock Hypovolemic Septic	 12(54.5%) 10(45.5%)	 2(11.1%) 16(88.9%)	 0.004* 0.03*
Need of VP *No need *Low dose 0.05 to.15mcg/kg/min *Maximum dose 1 to 3 mcg/kg/min	 13(59.1%) 5(22.7%) 4(18.2%)	 0(0.0%) 5(27.8%) 13(72.2%)	 <0.001*
Lactate level	4.6±1	5.2±1.4	0.092

Regarding the distribution of the type of shock, prevalence of shock was significantly associated with non-responders (P-value=0.004). The need to the maximum dose of vasopressors was significantly higher among non-responders.

Table (3) Comparison between responders and non-responders to PLR regarding their baseline end-tidal CO2 with its follow up and percent of increase.

ET CO_2	Responders group (no=22)	Non-responders (no=18)	P-value between groups
Baseline	28.4±4.6	25.6±4.9	0.072
Post PLR	32±4.9	27.4±5.7	0.011*
P-value (pre-post)	<0.001*	<0.001*	
Percent of increase (%)	13.1±6.4	7.34±5.9	<0.001*

This table showed that there was a significantly higher ETCO2 among responders than non-responders to fluids only after PLR. The ETCO2 increased significantly in responders and non-responders, but the percent of increase was significantly higher in responders than non-responders.

Table (4) Comparison between hypovolemic and septic shock in response to PLR regarding their baseline VTI with its follow up and percent of increase

VTI	Hypovolemic (no=22)	Septic (no=26)	P-value between groups
Baseline	**22.6±1.7**	**22.8±3.5**	**0.788**
Post PLR	**26.1±2.1**	**24.6±4.3**	**0.240**
P-value (pre-post)	**<0.001***	**<0.001***	
Percent of increase (%)	**15.8±9.7**	**7.4±5.9**	**0.002***

This table showed that there was insignificantly difference of VTI in hypovolemic and septic shock in response to fluids before and after PLR. The VTI increased significantly in both shocks, but the percent of increase was significantly higher in hypovolemic than septic shock.

Table (5) Comparison between hypovolemic and septic shock in response to PLR regarding their baseline cardiac output with its follow up and percent of increase:

COP	Hypovolemic (no=22)	Septic (no=26)	P-value between groups
Baseline	9.9±2.6	11.3±2.2	0.100
Post PLR	12±2.5	12.5±2.7	0.598
P-value (pre-post)	<0.001*	<0.001*	
Percent of increase (%)	23.6±14.8	10.9±7.9	0.001*

This table showed that there was insignificantly difference of COP in hypovolemic and septic shock in response to fluids before and after PLR. The COP increased significantly in both shocks, but the percent of increase was significantly higher in hypovolemic than septic shock.

Table (6) Correlation between the rate of increase of ETCO2, ETCO2 at baseline and after PLR with different parameters among responders.

response responders		ETCO21	ETCO22	rate of increase of ETCO
VTI 1	**R**	.343	.299	-.148
	P-value	.118	.176	.511
VTI 2	**R**	.370	.289	-.235

	P-value	.090	.193	.292
SV1	**R**	.185	.148	-.116
	P-value	.409	.512	.607
SV2	**R**	.197	.145	-.145
	P-value	.381	.519	.520
COP1	**R**	.019	-.049	-.188
	P-value	.932	.827	.402
COP2	**R**	.067	.008	-.164
	P-value	.768	.974	.466
VTI % of increase	**R**	.010	-.048	-.129
	P-value	.966	.831	.567
SV % of increase	**R**	.009	-.048	-.123
	P-value	.968	.834	.584
COP % of increase	**R**	.152	.181	.069
	P-value	.501	.421	.760

This table showed that, among responders, there was no significant positive linear correlation between the ETCO2 at baseline, after PLR and its rate of increase with any of other independent parameters.

Table (7) Sensitivity, specificity and cut off baseline, post PLR CO2, rate of increase and absolute difference of CO2, in prediction of response to fluid after PLR:

Items	**Rate of increase of ET CO2**	**Baseline ET CO2**	**Post PLR ET CO2**	**Absolute difference**
AUC (95%CI)	0.775 (.563-.860)	0.684 (.580-.790)	0.737 (.541-.823)	0.830 (.790-.910)
Cut off	8.01%	28.5	29.5	2.5
P-value	**0.003***	**0.047***	**0.011***	**<0.001***
Sensitivity (95%CI)	81.8% (75-90)	68.2%(60-79)	72.7%(67-83)	81.8%(78-90)
Specificity (95%CI)	72.2% (67-81)	67.7%(60-78)	61.1%(57-75)	77.8%(71-90)
PPV (95%CI)	80%(69-83)	67%(59-80)	70%(50-80)	80%(75-90)
NPV (95%CI)	71%(69-78)	66%(60-79)	60%(55-70)	75%(70-89)

This table showed that baseline ET CO_2, post PLR, in addition to the rate of increase of ET CO_2, had a significant role in prediction of the response to fluids. At a cut off 28.5 or more of

baseline ET CO_2, it can predict the response to fluids after PLR with 68.2% sensitivity and 67.7% specificity. At a cut off 29.5 or more of ET CO2 after PLR, it can predict the response to fluids after PLR with 72.7% sensitivity and 61.1% specificity. At a cut off 8.01% percent of change from baseline to after PLR or of baseline ET CO2, it can predict the response to fluids after PLR with 81.8% sensitivity and 72.2% specificity. The absolute difference in end tidal CO2 ≥ 2.5mmHg has a significant role in prediction of responsiveness (P-value<0.001).

DISCUSSION

Oxygen delivery (DO2) depends on cardiac output (CO) so physicians consider giving intravenous fluid loading to optimize left ventricular preload to enhance stroke volume (SV). Not all patients respond to fluid volume challenge with an increase in CO. Not only Volume deficit worsen the prognosis but also volume overload, so fluid administration should be carefully monitored. [17, 18] Hence, estimation of fluid responders is a difficult challenge. Guiding tools used in fluid therapy in non- invasive ventilated patients or patients with spontaneous breathing are rare, and patients may need invasive methods of monitoring. [19] These tools may be limited in emergency department or may be out of reach in treatment scenarios.

In our study ET-CO2 the percent of increase was significantly higher in responders than non-responders 13.1±6.4 versus 7.34±5.9, respectively (P<0.001).

According to this study percent of Change in COP due to Passive leg rising test did not correlate with percent of changes in ETCO2(r=0.069, P=0,76) in spontaneous breathing patients. Area under the ROC curve (AUC) for percent of increase of ETCO2showed a little utility in discrimination of responders and non-responders (AUC = 0.775) However, at a cut off 8.01% percent of change from baseline to after passive leg rising for 90 seconds, could predict the response to fluids with 81.8% sensitivity and 72.2 %specificity.

We also found, an absolute difference from baseline to after passive leg Rising equal or more than 2.5mmHG, could predict the response with 81.8% sensitivity and 77.8% specificity.

Similar to our study Guiney Pınar et al 2016, conducted a study on 31patients 15 patients were volume responsive. The difference in the ΔETCO2 was 4 mm Hg in the volume responsive and 2 mm Hg in the nonresponsive group ($p = 0.02$). A moderate correlation was detected between the difference in ΔETCO2 and CO ($r=0.585$; $p = 0.001$). According to this study ΔETCO2 can be suggested as an alternative method in predicting volume responsiveness in spontaneously breathing patients with hypovolemia. [20]

According to A meta-analysis published in 2010 for ultra- sonographic methods to determine COP after PLR test, there were different thresholds of fluid responsiveness varied from 8 to 15% according to heterogeneity in type of patients ventilated or not, using standard methods to determine cardiac output or others like cardiac index, stroke volume, VTI LVOT and using TTE, TOE or pulmonary catheter. [21]

In Maizel et al., an increase in cardiac output > 5% after a PLR discriminated responders with a good sensitivity and specificity of (94% and 83%, respectively), positive predictive value of 83%, and negative predictive value of 94%. It was found that an increase in SV > 8% predicted fluid responders with a good sensitivity and specificity (88% and 83%, respectively), positive predictive value 82%, and negative predictive value 88%. [22]

In Lamia et al study an increase in the VTILVOT > 12.5% discriminated responders with a sensitivity of 70% and specificity of 100%. [23]
In Bias et al, an increase in stroke volume > 13% measured by echocardiography after PLR predicted fluid response with sensitivity 100% and specificity 80%. [24]
Préau et al. conducted a study on patients having severe pancreatitis or sepsis, an increase in SV > 10% discriminated fluid responsiveness from non -responsiveness with a sensitivity 86%, specificity 90%, positive predictive value 86%, and negative predictive 90%. [25]
Regarding other findings in our study, there was no significant difference between responders and non-responders to fluids regarding their age and sex distribution (P-value>0.05).
There was no significant difference between responders and non- responders to fluids regarding their co-morbidities distribution (P-value>0.05) except presence of bed sores, it was significantly associated with non- responders (P-value=0.033)
Regarding the distribution of the type of shock, prevalence of septic shock was significantly associated with non-responders (P-value=0.004). The need to the maximum dose of vasopressors was significantly higher among non-responders.
Regarding hemodynamics, the percent of increase of Heart rate was significantly higher in responders than non-responders6.5±5.1 versus 1.7±0.9 respectively with P<0.001.
Regarding respiratory rate, the percent of increase didn't differ significantly between responders and non-responders5.6±4.6 versus4.1±3.8 respectively with P=0.287.
Regarding mean arterial pressure, the percent of increase was significantly higher in responders than non-responders7.5±4.9 versus3.8±2.6with P=0.007.
Regarding ET-CO2 the percent of increase was significantly higher in responders than non-responders13.1±6.4 versus7.34±5.9 with P<0.001.
Our study had some limitations. We have excluded cardiac patients who have different characteristics, we did not use any invasive hemodynamic monitoring for estimation of cardiac output like pulmonary artery catheter which is the gold standard in cardiac output estimation, however many studies showed no difference in mortality and patient outcome when using pulmonary artery catheter with many complications

CONCLUSION

Percent of change in COP after passive leg rising test did not correlate with percent of changes in ETCO2 (r=0.069, P=0.76) in spontaneous breathing patients. Area under the ROC curve (AUC) for percent of increase of ETCO2 showed a little utility in discrimination of responders and non-responders (AUC = 0.775).

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