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ORIGINAL ARTICLE

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The use of end-expiratory occlusion test *vs.* inferior vena cava respiratory variation for the prediction of volume responsiveness in mechanically ventilated patients with sepsis: A comparative study

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ABSTRACT

Sepsis being a chief prominent fatal condition in critically ill patients. In septic-shocked patients, the first-line therapeutic intervention is fluid resuscitation in an attempt to improve their cardiac output (COP). However, fluids must be given only if the chance of improving COP exists. So, assessing fluid responsiveness is crucial. To our knowledge, yet no studies comparing the end-expiratory occlusion (EEO) test and the variation of the inferior vena cava (IVC) diameter with respiration (ΔIVC) in hypovolemic cases. So, our aim is to use both tests as indices for responsiveness to fluid in septic mechanically ventilated (MV) patients. The Patients and Method: Thirty-four MV septic patients were enrolled and baseline COP assessment was performed followed by an EEO test applied to each patient, after which, COP was measured to detect the probable responders (defined as an increased COP by ≥ 15%) and non-responders. Then, ΔIVC was assessed for the same patients to predict the probable responders (with ΔIVC >12%) and non-responders. Finally, fluid therapy was initiated as per the guidelines of surviving sepsis campaign (2021) followed by COP re-assessment to determine actual fluid responders\non-responders. Results: 67% of the cases was responding to fluid. Receiver operating characteristic showed areas under curve for EEO and ΔIVC in predicting responsiveness to fluid were 0.597 and 0.925, respectively. EEO (32.4%) was predictive with 47.8% sensitivity and 100% specificity. The ΔIVC (64.7%) was predictive with 91.3% sensitivity and 100% specificity. Conclusion: IVC-respiratory variation showed better values in prediction of response to fluid in MV patients with sepsis than EEO test.

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KEYWORDS
IVC; EEO; fluid responsiveness; ventilated; sepsis

1. Introduction

Septic shocked patients are prevalent among critically ill patients. Reduction of mortality using initial fluid therapy is well established among these patients [1]. Fluid therapy can upsurge the systolic volume (SV) and subsequently improves the cardiac output (COP) [2]. Dynamic parameters as stroke volume (SV) and changes in pulse pressure are sturdy parameters, with several confines [3]; so other approaches such as End-expiratory occlusion (EEO) test have been established [4] and investigated the possibility of predicting responsiveness to fluid therapy. In mechanically ventilated (MV) patients, inspiration raises the intra-thoracic pressure and causes reduction in the venous return. EEO averts any intra-thoracic pressure changes. This causes upsurge per cardiac preload, venous return and SV among responding cases. So, increased cardiac index throughout the EEO foretells response to fluid therapy. Recommendations in previous studies [5,6] recommend that inferior vena cava (IVC) can be estimated to detect the pressure in the patients' right atrium. Ultrasound is utilized in ICU routine to assess various dynamic parameters predicting response to fluid [7,8], example: ΔIVC [9,10].

So, **the goal** of the current study was comparing between EEO test and ultrasound-guided ΔIVC as indices to responsiveness to fluid in MV septic-shocked cases.

2. Patients and method

The current comparative study was performed after receiving the **approval** from the research ethical committee, Faculty of Medicine, Ain Shams University, Cairo, Egypt, number of approval is FMASU M D 251/2020, and Pan African Clinical Trial registration number "**PACTR202306581320725"**, on 34 sedated MV patients. Written informed consents were signed by the patients' legal guardians following clear explanation of the techniques with its probable consequences.

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The study was done over 6 months in the period from September 2021 to March 2022.

The patients' inclusion criteria were age 21–60 years old, both sexes, septic hypotensive, sedated, and intubated, MV (controlled mode) with no respiratory effort. The involved patients showed sepsis criteria included organ dysfunction which is brought on by an inadequate host reaction to infection, inadequate perfusion, or low blood pressure needed intravenous fluid therapy for resuscitation according to the clinical presentation (mean arterial pressure (MAP) <65 mmHg, systolic arterial blood pressure (BP) <90 mmHg, or a fall of >20 mmHg from the baseline of MAP, or with persistent hypotension necessitating vasopressor to raise MAP above 65 mmHg or showing signs of hypo-perfusion, e.g., oliguria <0.5 ml/kg/h with arterial lactate exceeding 2.5 mmol/L with lactic acidosis in arterial blood gases or including two criteria of systemic inflammatory response syndrome (SIRS) as total leukocytic count > 12000/CU or below 4000/CU or with positive cultures or positive procalcitonin levels with heart rate > 90 beat/min.

The patients' exclusion criteria were poor cardiac echogenicity, spontaneous breathing, cardiac arrhythmia, intracardiac shunt or significant valve lesions, ascites, diastolic dysfunction (ejection fraction below 40%), pregnant female, malignancy besides limitations to fluid resuscitation, e.g., congestive heart failure, and kidney impairment.

3. Procedure and technique

In the ICUs at Ain Shams University Hospitals, patients meeting our inclusion criteria were enrolled in our study. The patients were evaluated with precise history taking and general physical examination. All included patients were connected to five leads ECG with central venous line and arterial line inserted for cardiovascular monitoring. Patients were sedated and MV on GE HealthCare CARESCAPE ^{TM} R860 ventilator (assisted control mode and tidal volume (Vt)) of 8 ml/kg [11,12], time of inspiration to expiration is 1:2, and positive end-expiratory pressure (PEEP) = 5 cm/H_2O, with flow-volume loop and pressure-volume curves used for respiratory monitoring.

Baseline COP assessment for all patients using ECHO Doppler velocity time integral (VTI) was recorded [13] using GE HealthCare, Vivid^{TM} ultrasound equipment by a specialized echo cardiographer then EEO was done for the same patient by interposing the ventilation for 15 s during the end of the expiration in sedated MV patients with no respiratory effort, during positive pressure ventilation [14]. The EEO was applied to predict probable responder and non-responder according to the COP changes where the result of volume expansion was identified as increase by ≥ 15% of COP being a probable responder [15]. Then, the ΔIVC =$(D_{max} - D_{min})/[(D_{max}+D_{min})/2]$ was calculated for the same patients. The ΔIVC exceeding 12% among septic MV individuals was considered to be a positive predictive value to predict probable responders [10,16].

There is a strong recommendation by SSC 2021 guidelines that hypotensive septic patients or with high serum level of lactate are indicated to receive as a minimum 30 mL/kg of crystalloid intravenously over 3 h [17]. Consequently actual responders and non-responders were determined according to the changes in COP using ECHO Doppler VTI.

4. Recorded measurements

4.1. Primary outcome

Predictive value of EEO and ΔIVC to fluid responsiveness among septic MV patients.

4.2. Secondary outcomes

Changes in BP and changes in heart rate in response to fluid therapy.

5. Sample size calculation

The involved sample size was computed by the aid of PASS© version 11 (NCSS©, LLC. Kaysville, Utah, USA. www.ncss.com).

According to previous studies on septic patients responding to fluid therapy [18], accuracy of EEO [19] and ΔIVC [20] in prediction of response to fluid, 34 patients were estimated to be the sample size attaining a power = 91% and revealing statistical significance for a difference of 36.6% between the accuracy of either test using a two-sided McNemar test (statistical significance; $P < 0.05$) assuming a proportion of discordant pairs of 0.46 (based on proportions correctly classified of 0.92 and 0.46 for EEOT and IVC RV, respectively).

6. Statistical analysis

The whole recorded data were reviewed, coded, formulated, and presented to a PC using social sciences statistical package (IBM SPSS 20 for windows) to be analyzed and to statistically compare between the involved groups. Quantitative values were represented by means ± standard deviations, while qualitative parameters have been introduced by percentages and frequency. Chi-square (X^2) test had been adopted for comparing proportions of two qualitative variables. Independent sample t-test had been used for comparing responders with non-responders regarding parametric variables of normal distribution, unlike Mann-Whitney test in case of non-parametric data.

The receiver operating characteristic (ROC) curves and area under the curve (AUC; with 95% confidence intervals [CIs]) for EEO besides ΔIVC had been estimated as well as assessed to evaluate their capability in predicting fluid responsiveness. CI had been adjusted to 95%, and the margin of error allowed had been adjusted to 5%. Therefore, P value < 0.05 had been regarded as significant (S), and a P value ≥ 0.05 had been regarded as non-significant (NS).

7. Results

The eligibility of 50 patients in total was evaluated. Six individuals were disqualified from the research's analysis because of poor echogenicity, while 10 patients failed to comply with the inclusion criteria as represented in the flow chart of the study (Figure 1). 34 patients in septic shock were enrolled and their average age was 51.94 ± 6.1 years as determined by descriptive statistics. The sex distribution revealed that males were more prevalent 20 (58.8%) compared to females 14 (41.2%). Ten patients were of ASA physical status II, 10 patients were ASA III and 14 patients were ASA IV. Mean **Baseline systolic BP** 96.9 ± 10.6 mmHg, **baseline diastolic BP** 63.4 ± 6.7 mmHg, and baseline heart rate 96.6 ± 12.8 beats/min (Table 1).

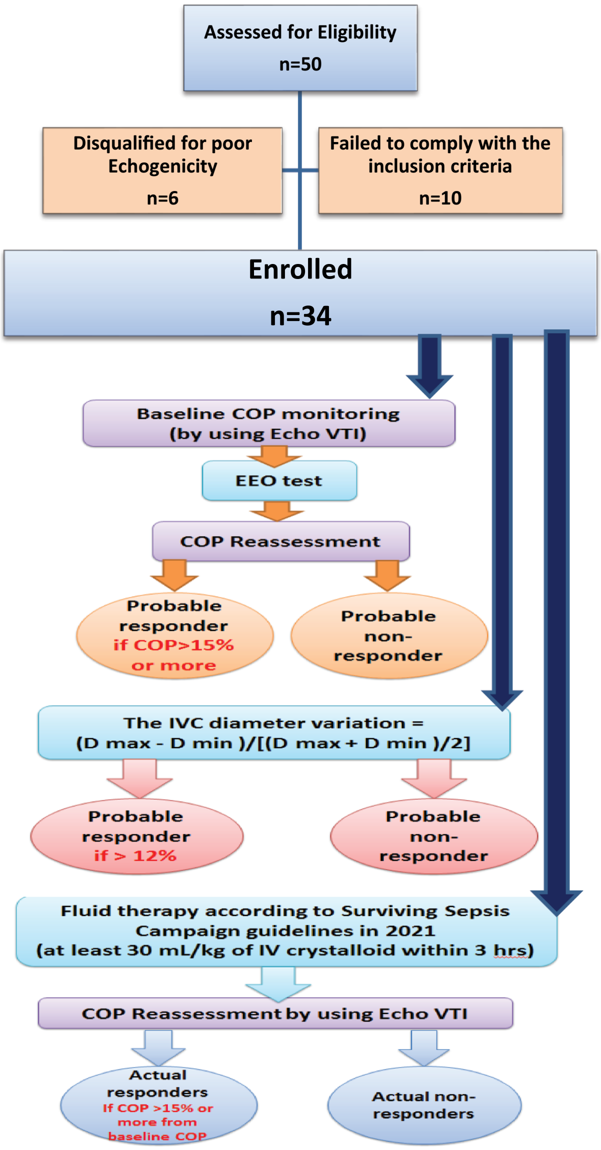

Figure 1. The study flow chart. COP: Cardiac output; VTI; velocity time integral; Dmax: maximum diameter; Dmin: minimal diameter; EEO: End expiratory occlusion test; N: number of patients; IVC: inferior vena cava

Table 1. Demographic data, baseline BP readings besides HR.

Demographic data		
Age in years (mean ± SD)		51.94 ± 6.1
SEX (number, %)	Male	20 (58.8%)
	Female	14 (41.2%)
ASA physical status (number, %)	II	10 (29.4%)
	III	10 (29.4%)
	IV	14 (41.2%)
Baseline systolic BP(mmHg) (mean ± SD)		96.9 ± 10.6
Baseline diastolic BP(mmHg) (mean ± SD)		63.4 ± 6.7
Baseline HR (beats/minute) (mean ± SD)		96.6 ± 12.8

ASA=American society of Anaesthesia, BP=blood pressure, HR=heart rate, SD= standard deviation.

Table 2. Probable and actual VTI and IVC responders.

	Responders	Non-responders
Probable VTI responsiveness	11 (32.4%)	23 (67.6%)
Probable IVC responsiveness	22 (64.7)	12 (35.3%)
Actual responsiveness	23 (67.6%)	11 (32.4%)

IVC= inferior vena cava, VTI= velocity time integral. Data (numbers in %).

As demonstrated (Table 2), probability of VTI responsiveness showed that there was only 32.4% probable responders and 67.6% were probable non-responders. While there was 64.7% of the patients were probable responders while 35.3% of the patients were probable non-responders according to the IVC test. Finally, fluid therapy was initiated according to the SSC guidelines followed by COP re-assessment to determine actual responders and non-responders for fluid therapy. The results showed that 67.6% of the patients were actual responders while only 32.4% were actual non-responders.

Comparing demographic data of actual volume responder and non-responders. No statistically significant difference was present (Table 3).

ROC values for VTI and IVC are mentioned in Table 4 (A and B, respectively). ROC analysis for IVC and VTI probability to responsiveness showed that the probable VTI responsiveness was insignificant with AUC equivalent to 0.597 at P-value = 0.33 while for the probable IVC, responsiveness was significant with AUC = 0.925 at $p < 0.001$ and sensitivity 91.3% and 100% specificity (Table 5). Upon comparing between both curves of probable VTI (Figure 2) and IVC responsiveness (Figure 3), the difference in AUC reached 0.328 and found to be of significance at $P = 0.002$ (Table 6 and Figure 4).

8. Discussion

The circulatory failure in septic shock patient is most probably due to either severe vasodilatation,

Table 3. A comparison of volume responders vs. volume non-responders in regards to demographic data.

Demographic data		Actual volume Responders (*n*=23)	Actual volume Non-responders (*n*=11)	P-value
Age in years (mean±SD)		51.22 ± 6.8	53.5 ± 4.4	0.3
SEX (n, %)	Male	13 (56.5%)	7 (63.6%)	0.69
	Female	10 (43.5%)	4 (36.4%)	
ASA physical status (n, %)	II	6 (26.1%)	4 (36.4%)	0.83
	III	7 (30.4%)	3 (27.3%)	
	IV	10 (43.5%)	4 (36.4%)	

ASA=American Society of Anaesthesia, *n* = number of patients.

Table 4. Criterion values and coordinates of the ROC curve for (A) probable VTI responsiveness and (B) probable IVC responsiveness.

Criterion	Sensitivity	Specificity	+LR	-LR
(A) Criterion values and coordinates of the ROC curve for probable VTI responsiveness				
≥5.47	100.00	0.00	1.00	
>5.47	95.65	0.00	0.96	
>5.5	95.65	9.09	1.05	0.48
>6.4	82.61	9.09	0.91	1.91
>6.6	82.61	18.18	1.01	0.96
>6.89	78.26	18.18	0.96	1.20
>7	78.26	27.27	1.08	0.80
>9.7	52.17	27.27	0.72	1.75
>10.5	52.17	63.64	1.43	0.75
>11.05	47.83	63.64	1.32	0.82
>14.4	47.83	100.00		0.52
>41	0.00	100.00		1.00
(B) Criterion values and coordinates of the ROC curve for probable IVC responsiveness				
≥6.06	100.00	0.00	1.00	
>6.06	95.65	0.00	0.96	
>6.9	95.65	18.18	1.17	0.24
>10	91.30	36.36	1.43	0.24
>13.33	91.30	100.00		0.087
>73.6	0.00	100.00		1.00

ROC = receiver operating characteristic, VTI = velocity time integral, + LR = positive likelihood ratio, - LR = negative likelihood ratio.

Table 5. ROC analysis for IVC and VTI probability to responsiveness.

	AUC	p-value	Cut off value	Sensitivity	Specificity
Probable VTI responsiveness	0.597	0.33	>14.4%	47.8%	100%
Probable IVC responsiveness	0.925	<0.001	>13.3%	91.3%	100%

AUC = Area under the curve, IVC = inferior vena cava, VTI = velocity time integral.

hypovolemia, or both. Hence, volume expansion is crucial in enhancing perfusion of tissues. Consequently, prediction of fluid responsiveness is crucial [21]. So, "Filling or not", this is the struggle. Markers predicting responsiveness to fluid include static markers (as central venous pressure) plus dynamic markers (as EEO) [22]. To successfully anticipate responsiveness to fluid, two requirements should be fulfilled: a change in preload must be generated while measuring the subsequent changes in SV or its derivatives. Therefore, static markers are considered weak giving superiority to dynamic markers as promising predictive factors [23,24].

A simple bedside test to successfully adjust preload is the EEO. Insufflation raises the intra-thoracic pressure which hinders venous return. As ventilation is disrupted for a couple of seconds, at level of PEEP, the right cardiac preload reaches its maximum. This indicates preload responsiveness of both ventricles [14]. Response to fluid is anticipated by increases in COP during EEO test. Doctors are capable of prevention and treatment of tissue hypoperfusion when EEO is combined to direct measure that track SV and/or its products continuously, preventing avoidable and possibly hazardous fluid over load and inotropes [25].

In our study, the EEO test was performed to all patients to detect probable responders if there was an increase of COP by ≥ 15% from baseline readings. To diagnose and treat acute circulatory collapse among ICU patients, echocardiography enables quick evaluation of the changes in COP and SV in addition to measuring the effectiveness and tolerance of a fluid challenge [26]. SV is

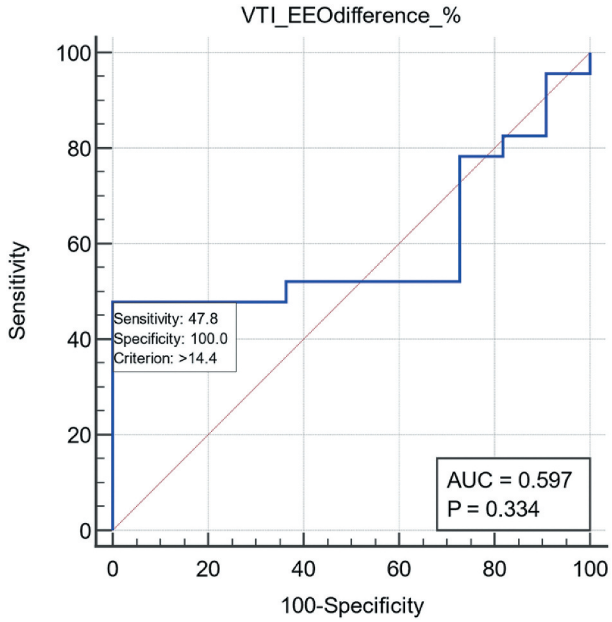

Figure 2. VTI-EEO difference %. AUC: Area under the curve; EEO: End expiratory occlusion, VTI: velocity time integral.

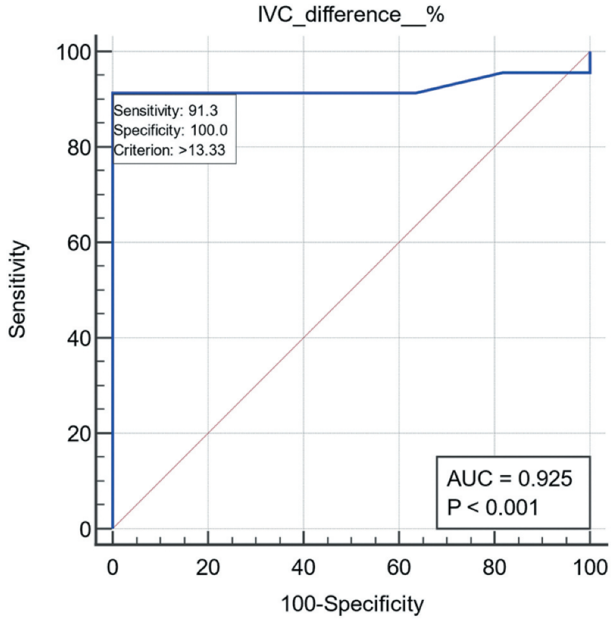

Figure 3. IVC difference %. AUC: Area under the curve; EEO: End expiratory occlusion, IVC: inferior vena cava.

Table 6. Pairwise comparison between the two curves.

	AUC difference	p-value
Probable VTI responsiveness – probable IVC responsiveness	0.328	0.002

AUC = Area under the curve, IVC = inferior vena cava, VTI = velocity time integral.

computed involving area of the aortic valve multiplied by VTI. Assuming constancy of the aortic valve area, variations in VTI can be implemented as a substitute for variations in SV [27,28].

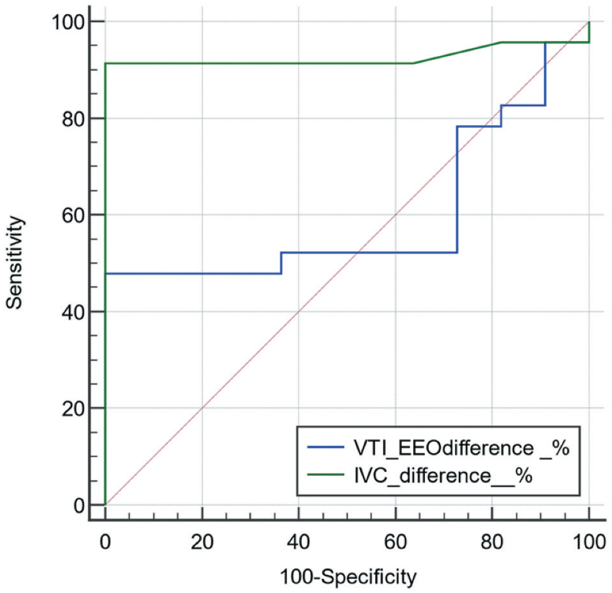

Figure 4. VTI-EEO difference % and IVC difference %. AUC: Area under the curve; EEO: End expiratory occlusion, VTI: velocity time integral.

Ultrasound is routinely practiced in ICU evaluating various dynamic parameters of response to fluid, such as ΔIVC [7–10]

Included patients were considered probable responders if the ΔIVC was > 12%. Following the recommended fluid therapy according to SSC 2021 guidelines, 30 ml/kg of intravenous crystalloid over 3 h, actual responders (COP of ≥ 15%) and non-responders were determined using ECHO Doppler VTI [17]. The responders were 67.6% of the patients.

In the current experiment, we concluded that the usage of ΔIVC was a good predictor assessing responsiveness to fluid among adult septic conditions with acute circulatory collapse where ΔIVC showed higher sensitivity than EEO test.

ROC analysis, done for IVC and VTI probability to responsiveness, showed that the probable VTI responsiveness was insignificant with AUC equivalent to 0.597 at P-value = 0.33 while for the probable IVC responsiveness, it was significant with AUC = 0.925 at $p < 0.001$ and sensitivity 91.3% and 100% specificity. Comparing both curves of probable VTI and IVC responsiveness, the difference in AUC reached 0.328 and found to be of significance at $P = 0.002$.

Parallelly, **Alvarado- Sánchez et al**. stated ΔIVC as a predictor of weight for responsiveness to fluid therapy [29]. In the same context, ***Pereira et al.*** highlighted the robust predictive value of the IVC collapsibility index [30].

Furthermore, another study confirmed that ΔIVC is a preferred dynamic measure of responsiveness to fluid in ICU being non-invasive, cheap, easy, reproducible besides, it needs no high training level [31,32].

An earlier study [10] applied the following equation $(D_{max}-D_{min})/[(D_{max}+D_{min})/2]$ stated that values of more than 12% was of negative predictive value = 92% with positive predictive value = 93%. Alike **Barbier et al**. showed that IVC variation is a good predictive test [9].

On the other hand, **Güney Pınar et al**. concluded that ΔIVC displayed no significant difference among fluid responders besides non-responders [33].

Also, **Yao et al**. found weak correlation between ΔIVC and response to fluid [34]. Moreover, **Long et al**. reported that its clinical convenience is limited, predominantly among non-ventilated patients [35]. The importance of IVC relies on patient's clinical situation that must be regarded upon evaluation.

However, another study stated that the usage of IVC as regard the decision of fluid administration must be regarded only in particular clinical and technical conditions [24]. If not, the results are lacking homogeneity and couldn't be generalized.

9. Regarding the EEO test

Monnet and his colleagues revealed that EEO is a predictive tool for response to fluids showing acceptable specificity and sensitivity even for patients breathing spontaneously or showing cardiac arrhythmia [14].

Parallel to our study, **Guinot et al**. highlighted that EEO doesn't precisely predict responsiveness to fluid in the operating room [36]. While, on the other hand, earlier studies conducted on MV patients (Vt ≤8 mL/kg) even below 7 mL/kg clearly stated the validity of EEO test [29,37,38]. Accordingly, low Vt prospectively doesn't limit the EEO test.

10. Limitations

The duration of the EEO must exceed 12 s [37], to allow the transmission of the increased preload between both sides of the heart representing the pulmonary transit time and giving chance for the devices that requires several seconds to calculate the average COP values displaying it's increase. Therefore, EEO is non-practicable among patients disrupting the pause at end of expiration owing to the noticeable respiratory activity, and evidently, EEO is inappropriate for spontaneously breathing patients.

Echocardiography affords valuable information to the clinician in addition to being non-invasive. Nevertheless, some constraints must be underlined. Firstly, parameters gained through echocardiography are reliant on the echogenicity of the patient [15]. Second, echocardiography requires specific training. Third, parameters are considered to be operator-dependent.

One of the limitations that may face the usage of ΔIVC is that the IVC is exposed to intra-abdominal as well as thoracic pressure. Consequently, individuals having high intra-abdominal pressure show poor compliance of IVCs that may result in errors in MV patients. In addition, various mechanical factors are to be taken in consideration, for example thrombosis or extrinsic IVC compression. Finally, the usage of ΔIVC is better avoided in patients with obesity, abdominal surgery, or having a poor echogenicity [39].

11. Conclusion

In conclusion, the IVC respiratory variation is a predictive tool for fluid responsiveness that shows superiority having a higher sensitivity in detecting probable responding patients to fluid therapy compared to the EEO test in mechanically ventilated septic-shocked patients.

Disclosure statement

The author(s) who participated in the study declare that there is no disclosure concerning financial affiliation or conflict of concern regarding this work.

Authors' contribution

Gamal Eldin Mohammad Ahmad Elewa, Mayar Hassan Sayed Ahmed El Sersi, Dalia Fahmy Emam Ali Nawar, Ahmed Monier Ahmed Youssef Eldemerdash contributed substantially in the designing of the research; creating the ideas; editing and reviewing the paper. **Nevein Fawzy El Sayed Abdelmaksoud**: contributed mainly in performing the procedures of the experiment; analyzing and interpreting the data; as well as writing the paper.

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