RESEARCH PAPER

The Validity of Combined End Expiratory and End Inspiratory Occlusion Test and Tidal Volume Challenge Test for Prediction of Fluid Responsiveness in Immediate Post Cardiac Surgery Patients: A Prospective Randomized Single-Blinded Study

Martina Farag Wahba*, Mostafa Soliman Mohamed, Ghada Fouad El-Baradey, Osama Mahmoud Shalaby, Tarek Abdel-Hay Mostafa

Anesthesiology, Surgical ICU and Pain management Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Received: 04th June, 2026; Revised: 25th June, 2026; Accepted: 20th July, 2026; Available Online: 25th July, 2026

ABSTRACT

Effective fluid expansion constitutes a critical management for patients exhibiting hemodynamic instability. The purpose of this study was to evaluate validity of a combined end-inspiratory occlusion test and end-expiratory, in combination with a tidal volume challenge test, for predicting fluid responsiveness (FR) in immediate postoperative period following cardiac surgery. This prospective randomized single blinded study involved 90 cases scheduled for cardiac surgery in Tanta University Hospitals at surgical intensive care unit. Cases were randomly allocated to one of 2 equal groups: Group A: Tidal volume challenge test and group B: Inspiratory occlusion (EIO) and combined end expiratory occlusion (EEO) test. Cardiac output (CO) with area under curve (AUC) of 0.637 and at cutoff value >5 L/min can significantly predict the fluid responsiveness (P=0.020), with 77.78% sensitivity, 42.22% specificity, 57.4% PPV and 65.5% NPV. The pulse pressure variation with AUC of 0.612 and at cutoff value >11.32 % can significantly predict the fluid responsiveness (P=0.039), with 73.33% sensitivity, 40% specificity, 55.2% PPV and 60% NPV. The pulmonary dead space fraction with AUC of 0.638 and at cutoff value ≤0.24 can significantly predict the fluid responsiveness (P=0.018), with 71.11% sensitivity, 40% specificity, 54.2% PPV and 58.1% NPV. The combined EEO and EIO test can significantly predict the FR through their effect on CO, PPV, pulmonary dead space fraction with significantly higher AUC, sensitivity and specificity compared to the TV challenge test which was insignificant predictor of the FR.

Keywords: Tidal Volume Challenge Test, End Expiratory, End Inspiratory Occlusion Test, Fluid Responsiveness, Post Cardiac Surgery.

How to cite this article: Wahba M.F, Mohamed M.S, El-Baradey G.F, Shalaby O.M, Mostafa T.A, The Validity of Combined End Expiratory and End Inspiratory Occlusion Test and Tidal Volume Challenge Test for Prediction of Fluid Responsiveness in Immediate Post Cardiac Surgery Patients: A Prospective Randomized Single-Blinded Study. 2026;16(72s): 308-319. DOI: 10.25258/ijddt.16.72s.35

Source of support: None

Conflict of interest: None

INTRODUCTION

Hemodynamic management and optimal fluid therapy continue to be significant challenges in critically ill cases. [1, 2] Insufficient cardiac output (CO) and diminished organ perfusion can precipitate compromised microcirculation and multiorgan dysfunction. This has been demonstrated in cases undergoing coronary artery bypass grafting (CABG). [3]

Due to the fluid overload risk, decision to administer fluid cannot be taken lightly. Multiple methods and assessments are available to determine volume responsiveness. The selection of techniques is contingent upon patient's condition and monitoring modalities available. [4] Initiation of fluid administration is recommended as primary therapeutic intervention for hemodynamic management throughout perioperative phase. [5]

Effective fluid administration is a vital intervention for patients experiencing hemodynamic instability. [6, 7] Furthermore, numerous studies demonstrate that dynamic variables arising from heart-lung interactions, including variation and pulse pressure variation (PPV) and stroke volume (SV), reliably predict fluid responsiveness (FR) in mechanically ventilated patients. [8]

End expiratory occlusion (EEO) maneuver is a dynamic assessment predicated on the interplay between cardiovascular and respiratory systems. In FR subjects, cessation of mechanical ventilation at expiration end causes a transient reduction in intrathoracic pressure, resulting in an internal fluid challenge and a brief increase in CO. The incorporation of EEO and EIO modifications has been utilized to enhance diagnostic sensitivity for detecting changes in CO, especially in mechanically ventilated cases characterized by low tidal volumes (< 8 ml/kg). [9]

To reduce the risk of the elevated ventilation-perfusion (V/Q) and reduced CO syndrome following cardiac surgery, noninvasive assessment of alveolar dead space relative to alveolar tidal volume (Vd/Vt) is recommended, also known as pulmonary dead space fraction, measured through capnography, it is increasingly being adopted to guide postoperative management of critically ill patients. Utilizing bedside volumetric

**Author for Correspondence: Martinafarag09@gmail.com*

capnometry in conjunction with PaCO2 measurements Vd/Vt has been demonstrated in both pediatric and adult populations to possess substantial prognostic significance in cases of acute lung injury. [10]

The objective of study was to evaluate validity of combined EEO and EIO tests, in conjunction with a tidal volume challenge test, for predicting FR in immediate postoperative period following cardiac surgery.

PATIENTS AND METHODS

This prospective randomized single blinded study was involved 90 patients scheduled for cardiac surgery in Tanta University Hospitals at surgical intensive care unit in period from August 2023 to September 2025 after approval from institutional ethics committee with Approval code: 3624MD105\6\23. A written informed consent was obtained from patient's relatives. Registration number: NCT05957003.

Patients on mechanical ventilation (MV), and aged ≥18 years of age, with normal systolic function of the left and right ventricle, schedueled for cardiac surgery, defined as left ventricular ejection fraction (LVEF) > 45 % and right ventricular fractional area change (RV FAC) > 30% requiring invasive arterial monitoring (IBP) through a radial arterial catheter, with MV with protective lung strategy which was a ventilation strategy aiming to reduce pulmonary complications after MV including plateau pressure low tidal volume (Tidal volume = 6 ml/kg of predicted body weight), driving pressure (less than 14 cmH2O) and (less than 30 cmH2O) were included.

Cases with severe peripheral arterial occlusive disease, undergoing emergent cardiac surgery, spontaneously breathing activity, contraindication of PLR, pregnant women, post-operative complications such as uncontrolled bleeding, unstable post-operative course (frequent fatal arrhythmias unstable post-operative arrhythmia that could cause sudden cardiac arrest include ventricular tachycardia and ventricular fibrillation), accidental mechanical complications, severe neurologic impairment, Pao2/Fio2 ≤ 200, presence of residual severe tricuspid or any open chest and valvular regurgitations were excluded.

Randomization:

Cases were randomly allocated to one of 2 groups by an independent data manager who allocated participants based on a computer-generated randomization program. Distribution was provided within sealed, opaque containers.

-Group A (n=45): TV challenge test (transient increase of TV from 6 to 8 mL/kg of predicted body weight (PBW) for 1 minute).

-Group B (n=45): EEO and EIO test. a 15-s EEO separated by a time window of 1 minute to allow hemodynamic parameters to return to baseline followed by a 15-s EIO.

Patients monitoring included (5 lead ECG, pulse oximetry, invasive blood pressure, End tidal CO_2, bispectral index (BIS), urine output and core temperature). The choice to administrate intravenous fluids should be grounded in the identification of at least one clinical indicator of acute circulatory failure, such as hemodynamic instability demonstrated by a mean arterial pressure (MAP) below 65 mmHg, or stability with a MAP of 65 mmHg or higher accompanied by vasopressor support or associated signs of hypoperfusion, including a central venous oxygen saturation ($ScvO_2$) less than 70% or other relevant indicators.

PCO_2 gradient P(cv-a) CO_2 ≥6 mmHg, or a capillary refill time ≥ 4 s together with hyperlactatemia serum lactate level >2 mmol/L) initial volume assisted ventilation: positive end-expiratory pressure 4-6 cmH_2O, tidal volume = 6 mL/kg PBW, respiratory rate 12-16/min.

The predicted body weight formula: PBW = 50 + 0.91 X (centimetres of height - 152.4) for males. PBW = 45.5 + 0.91 X (centimetres of height - 152.4) for females to achieve Etco2 ranging between 35-45 mmhg with PH ranging between 7.35 - 7.45.

FIO_2 was adjusted to achieve $Pao_2/Fio_2 \geq 200$. The sedation with midazolam and fentanyl was utilized to achieve BIS ranging between 60-80. Baseline hemodynamic characteristics was recorded including (mean arterial blood pressure, heart rate, PPV using invasive radial arterial monitoring, central venous pressure (CVP) through internal jugular central line, cardiac output measurement using volumetric capnography). Real time assessment of FR was performed using PLR test with changes of PPV.

Passive leg raising test method:

At baseline, cases occupied a semi-recumbent posture; simultaneously, an initial set of hemodynamic parameters, PPV, and CO measurements was obtained and recorded. Throughout PLR, angle formed among trunk and lower extremities remained constant. Maximum effect of PLR on aortic blood flow was detected within one minute, coinciding with measurement and documentation of second set of hemodynamic data, including PPV and CO. CO variations were determined through volumetric capnography using CARESCAPE B650. FR and unresponsiveness were detected through assessment of alterations in PPV and CO during PLR. FR was specified as an increase ≥ (10%) in PPV after PLR. PPV (%) = 100 × (PPmax − PPmin) / PP mean. PP mean = PPmax + PPmin /2. PPV was automatically measured by GE CARESCAPE B650 monitor.

Dead space equation (Bohr Equation for Physiologic Dead Space) V_D/V_T = ($PaCO_2$ – $PECO_2$)/($PaCO_2$_ Where: V_T = Tidal volume, V_D = Dead space volume, PECO_2 = mixed expired CO_2 partial pressure (mmHg) and PaCO_2 = arterial CO_2 partial pressure (mmHg).

The normal physiologic dead space fraction (V_D /V_T) in healthy adults was usually: 0.20–0.35 (20–35% of each breath). If PPV and CO changes ≥ 10% (volume responder). If PPV and CO changes < 10 % (non-volume responder), non-volume responders were reassessed.

All patients were positioned in a 30° semi-recumbent posture. EEO test was made by pausing MV at end-expiration for a period of 15 seconds using end-expiratory hold function available on GE CARESCAPE R860 ventilator. EIO test was conducted by briefly

suspending MV at conclusion of inspiration for 15 seconds, utilizing end-inspiratory hold function of ventilator. CO and PPV measurements were recorded promptly after each trial. Ventilatory parameters and additional treatment modalities remained consistent throughout study duration.

Measurements:

Demographic data including (gender, age, body surface area (BSA), type of surgery, duration of cardiopulmonary bypass, surgery duration). The hemodynamic characteristics were recorded including (mean arterial blood pressure, heart rate, PPV using invasive radial arterial monitoring, CVP through internal jugular central line, cardiac output measurement using volumetric capnography). Oxygen saturation (SPO_2), pulmonary dead space fraction was measured by volumetric capnography. All previous paramereters were measured before and after each test. The sensitivity and specificity of EEO and EIO tests, as well as the tidal volume challenge test, in predicting FR following cardiac surgery.

Outcome:

Primary outcome was the sensitivity and specificity of combined tidal volume challenge test, EEO and EIO test and in FR prediction after cardiac surgery.

Secondary outcome was in PPV and CO changes.

Sample size:

The calculation of sample size and statistical power was conducted utilizing Epi-Info software, a statistical tool developed collaboratively by World Health Organization and the Centers for Disease Control and Prevention in Atlanta, Georgia, USA, version 2002. Parameters employed to calculate the sample size encompassed a 95% confidence level, 80% statistical power, and an anticipated validity of combined end-expiratory and EIO tests, as well as the tidal volume challenge test, for predicting fluid responsiveness in patients immediately following cardiac surgery, estimated at 60%, with a permissible margin of error of 10%. The sample size determined in accordance with criteria mentioned above was established at N=43 for each group. The investigator will augment sample size to 45 subjects per group to account for incomplete data and attrition rate.

Statistical analysis:

For this study, we consulted IBM's SPSS v28 (Armonk, NY, USA). The mean and standard deviations (SD) of quantitative variables were demonstrated using an unpaired t-test. A t-test for students. For purpose of comparing the same subjects across different time intervals, repeated measures ANOVA tests were employed. After analyzing the qualitative variables using either Fisher's exact test or a chi-square test, the results were given as frequencies and percentages (%). Statistical significance was determined by a two-tailed P value that was less than 0.05. Assessment of diagnostic accuracy, including sensitivity and specificity in making diagnoses, as well as PPV and NPV. ROC (Receiver Operating Characteristic) curve is examined: We used ROC curve analysis to compare overall diagnostic accuracy of tests. AUC measures overall performance of test; an AUC more than 50% indicates satisfactory performance, while an AUC close to 100% indicates optimal performance.

RESULTS

In our study, 117 cases were evaluated for eligibility, 18 cases did not satisfy criteria, and 9 cases declined to participate. The remaining 90 cases were randomly allocated to two equal groups, with 45 patients in each. All 90 cases were monitored and thoroughly examined. **Figure 1.**

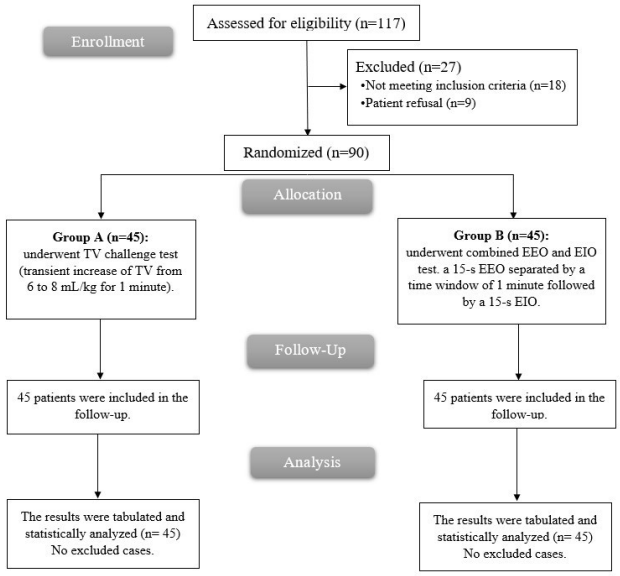

Figure 1: CONSORT flowchart of the enrolled patients

There was an insignificant difference between two groups regarding baseline characteristics (sex , age, BMI and BSA), the type of surgery, surgery duration, duration of cardiopulmonary bypass and the fluid responsiveness according to PLR. **(Table 1)**

Table 1: Baseline characteristics, surgical data and fluid responsiveness according to PLR of the studied groups and fluid responsiveness in group A and group B

			Group A (n=45)	Group B (n=45)	P value
Baseline characteristics	**Age (years)**		63.09± 8.35	63.47±8.48	0.832
	Sex	**Male**	32 (71.11%)	29(64.44%)	0.498
		Female	13 (28.89%)	16(35.56%)	
	BMI (kg/m^2)		28.04± 4.36	28.7± 4.76	0.495
	BSA (m^2)		1.99± 0.12	1.97± 0.14	0.381
Surgical data	**Type of surgery**	**CABG**	20 (44.44%)	25 (55.56%)	0.145
		Combined cardiac surgery	15 (33.33%)	7 (15.56%)	
		Valve replacement	10 (22.22%)	13(28.89%)	
	Surgery duration (min)		225.36±36.33	215.71±40.27	0.236
	Duration of cardiopulmonary bypass (min)		128.49±32.39	114.98±32.47	0.051
Fluid responsiveness	**Responders**		25 (55.56%)	27 (60%)	0.669
	Non-responders		20 (44.44%)	18 (40%)	
Fluid responsiveness					
			TV challenge test		
Group A	**TP**		20		
	TN		13		
	FP		6		
	FN		6		
			Combined EEO and EIO test		
Group B	**TP**		26		
	TN		12		
	FP		5		
	FN		2		

Data are presented as mean ± SD or frequency (%), and numbers. CABG: Coronary artery bypass graft surgery. BSA:Body surface area. EEO: end expiratory occlusion, EIO: end inspiratory occlusion, TP: true positive, TN: true negative, FP: false positive, FN: false negative.

**Author for Correspondence: Martinafarag09@gmail.com*

Table 3: Vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in group A (n=26), and vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in group B (n=31)

		Group A (n=26)			
		On admission (n=26)	**After PLR (n=26)**	**After TV challenge test (n=26)**	**P value**
Vital signs	**HR (beat/min)**	91.98± 8	91.96± 8.25	92.04± 8.27	0.876
	MAP (mmHg)	76.62± 6.57	76.8± 6.69	77.02± 6.93	0.916
	SpO_2 (%)	96.02± 2.39	96.16± 2.3	96.36± 2.19	0.225
	CVP (cm/H_2O)	11.76± 1.49	11.98± 1.67	11.78± 1.57	0.238
CO (L/min)		4.8± 0.87	5.47± 1.67	3.60± 1.10	**0.002***
P value		P1=**0.005*, P2=0.001*, P3=0.001***			
PPV (%)		11.51± 0.68	12.61± 0.68	13.09± 0.78	**<0.001***
P value		P1=**0.003***, **P2=0.001*, P3<0.001***			
Pulmonary dead space fraction		0.241± 0.03	0.24± 0.03	0.259± 0.03	**0.026***
P value		P1=0.904, **P2=0.035*, P3=0.035***			

Group B (n=31)						
		On admission (n=31)	**After PLR (n=31)**	**Combined end expiratory and end inspiratory occlusion (n=31)**		**P value**
				After EEO	**After EIO**	
Vital signs	**HR (beat/min)**	91.16± 8.14	90.91± 8.13	91.07± 8.07	91± 8.25	0.554
	MAP (mmHg)	74.2± 7.83	74.27± 7.8	74.38± 7.76	74.31± 8.02	0.689
	SpO_2 (%)	95.53± 2.39	95.38± 2.84	95.47± 2.59	95.42± 2.73	0.736
	CVP (cm/H_2O)	12± 1.45	12.02± 1.54	12.11± 1.75	11.98± 1.73	0.797
CO (L/min)		4.91± 0.9	5.89± 1.8	6.18± 1.59	4.23± 1.33	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*, P4<0.001*, P5<0.001*,** P6**<0.001***				---
PPV (%)		11.32± 0.75	12.33± 0.76	13.68±0.78	14.68± 0. 8	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*,** P4=**0.001*, P5=0.001*, P6=0.004***				--
Pulmonary dead space fraction		0.253±0.03	0.235± 0.03	0.228± 0.03	0.256± 0.03	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*,** P4=0.201, **P5=0.005*, P6=0.001***				--

Data are presented as mean ± SD. HR: heart rate, MAP: mean arterial pressure, SpO2: Oxygen saturation, CVP: central venous pressure, PLR: passive leg raising. CO: cardiac output, PPV: pulse pressure variation, PLR: passive leg raising *: statistically significant as p value <0.05, P1: p value between on admission and after PLR, P2: p value between on admission and after TV challenge test, P3: p value between after PLR and after TV challenge test. EEO: end expiratory occlusion, EIO: end inspiratory occlusion, *: statistically significant as p value <0.05, P1: p value between on admission and after PLR, P2: p value between on admission and after EEO, P3: p value between on admission and after EIO, P4: p value between after PLR and after EEO, P5: p value between after PLR and after EIO, P6: p value between after EEO and after EIO.

Table 4: Vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in the two studied groups

			Group A (n=26)	Group B (n=31)	P value
Vital signs	HR (beat/min)	On admission	91.98± 8	91.16± 8.14	0.630
		After PLR	91.96± 8.25	90.91± 8.13	0.547
	MAP (mmHg)	On admission	76.62± 6.57	74.2± 7.83	0.115
		After PLR	76.8± 6.69	74.27± 7.8	0.102
	SpO_2 (%)	On admission	96.02± 2.39	95.53± 2.39	0.334
		After PLR	96.16± 2.3	95.38± 2.84	0.157
	CVP (cm/H_2O)	On admission	11.76± 1.49	12± 1.45	0.433
		After PLR	11.98± 1.67	12.02± 1.54	0.896
CO (L/min)		On admission	4.8± 0.87	4.91± 0.9	0.553
		After PLR	5.47± 1.67	5.89± 1.8	0.363
PPV (%)		On admission	11.51± 0.68	11.32± 0.75	0.324
		After PLR	12.61± 0.68	12.33± 0.76	0.125
Pulmonary dead space fraction		On admission	0.241± 0.03	0.253±0.03	0.108
		After PLR	0.240± 0.03	0.235± 0.03	0.533

Data are presented as mean ± SD. HR: heart rate, MAP: mean arterial pressure, SpO_2: Oxygen saturation, CVP: central venous pressure, PLR: passive leg raising, EEO: end expiratory occlusion, EIO: end inspiratory occlusion. CO: cardiac output, PPV: pulse pressure variation, PLR: passive leg raising, EEO: end expiratory occlusion, EIO: end inspiratory occlusion, *: statistically significant as p value <0.05. P1: p value between after TV challenge test and after EEO, P2: p value between after TV challenge test and after EIO, P3: p value between after EEO and after EIO.

The TV challenge test was insignificant predictor for the fluid responsiveness in group A. The combined EEO and EIO test with AUC of 0.889 can significantly predict the fluid responsiveness in group B, with 92.86% sensitivity, 70.87% specificity, 83.87% PPV and 85.71% NPV. **(Table 2)**

Table 2: Diagnostic accuracy of TV challenge test for prediction of the fluid responsiveness in group A and the combined EEO and EIO test for prediction of the fluid responsiveness in group B

	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV	AUC	P value
TV challenge test	**76.92%**	53.3-90.2	68.42%	29.8 - 74.3	76.92%	68.42%	0.637	0.104
combined EEO and EIO test	**92.86**	87.2 - 100.0	70.87	52.4 - 93.6	83.87	85.71	0.889	**<0.001***

Data are presented as mean ± SD or frequency (%). EEO: end-expiratory occlusion, EIO: end inspiratory occlusion, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as p value <0.05.

The combined EEO and EIO test had significantly higher AUC compared to the TV challenge test in prediction of the fluid responsiveness (P<0.001), with also higher sensitivity (92.86% vs. 76.92% respectively) and specificity (70.87% vs. 68.42% respectively). **(Figure 2A),** There was insignificant difference among CO, PPV and the pulmonary dead space fraction in prediction of the fluid responsiveness. **(Figure 2B)**

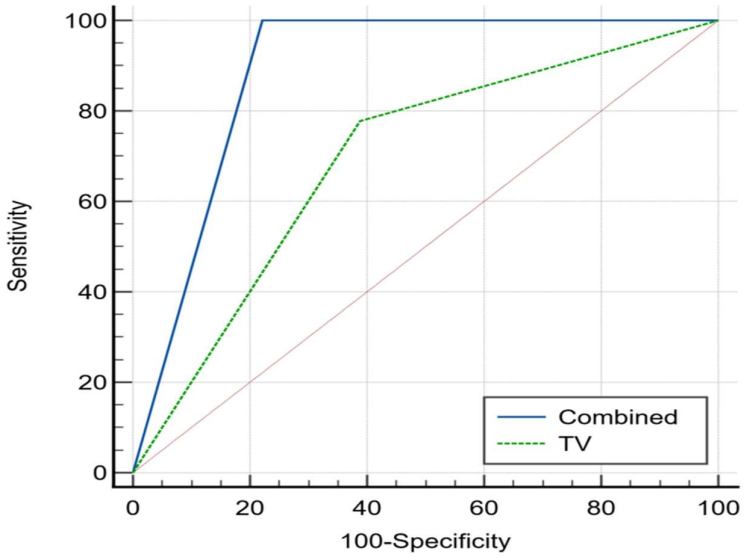

Figure 2: Comparison of ROC curve analysis of TV challenge test and the combined EEO and EIO test for prediction of the fluid responsiveness

In group A, vital signs including heart rate (HR), MAP, SpO_2, and CVP were insignificantly different among the various measurements. CO was significantly increased after PLR and significantly decreased after TV challenge test compared to CO on admission (P=0.005, 0.001), and was significantly decreased after TV challenge test compared to CO after PLR (P=0.001). In group A, PPV was significantly increased after PLR test and after TV challenge test compared to PPV on admission (P=0.001, <0.001), and significantly increased after TV challenge test compared to after PLR. The pulmonary dead space fraction significantly increased after TV challenge test compared to after PLR and after its value on admission. With insignificant difference between pulmonary dead space value after PLR compared to on admission. **(Table 3)**

In group B, the vital signs including HR, MAP, SpO_2, and CVP were insignificantly different among the various measurements. CO was significantly increased after PLR, after EEO and significantly decreased after EIO compared to CO on admission (P<0.05), CO was significantly increased after EEO compared to CO after PLR (P<0.001, <0.001), CO significantly decrease after EIO compared to PLR. PPV and was significantly increased after PLR, after EEO and after EIO compared to their values on admission (P<0.05) and was significantly higher after EIO and EEO compared to their values after PLR. The pulmonary dead space fraction significantly decreased after PLR and after EEO challenge test compared to after EIO and compared to its value on admission**. (Table 3)**

Table 3: Vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in group A (n=26), and vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in group B (n=31)

		Group A (n=26)			
		On admission (n=26)	**After PLR (n=26)**	**After TV challenge test (n=26)**	**P value**
Vital signs	**HR (beat/min)**	91.98± 8	91.96± 8.25	92.04± 8.27	0.876
	MAP (mmHg)	76.62± 6.57	76.8± 6.69	77.02± 6.93	0.916
	SpO_2 (%)	96.02± 2.39	96.16± 2.3	96.36± 2.19	0.225
	CVP (cm/H_2O)	11.76± 1.49	11.98± 1.67	11.78± 1.57	0.238
CO (L/min)		4.8± 0.87	5.47± 1.67	3.60± 1.10	**0.002***
P value		P1=**0.005***, **P2=0.001***, **P3=0.001***			
PPV (%)		11.51± 0.68	12.61± 0.68	13.09± 0.78	**<0.001***
P value		P1=**0.003***, **P2=0.001***, **P3<0.001***			

Pulmonary dead space fraction		0.241± 0.03	0.24± 0.03	0.259± 0.03		**0.026***
P value		P1=0.904, **P2=0.035*, P3=0.035***				
Group B (n=31)						
		On admission (n=31)	**After PLR (n=31)**	**Combined end expiratory and end inspiratory occlusion (n=31)**		**P value**
				After EEO	**After EIO**	
Vital signs	**HR (beat/min)**	91.16± 8.14	90.91± 8.13	91.07± 8.07	91± 8.25	0.554
	MAP (mmHg)	74.2± 7.83	74.27± 7.8	74.38± 7.76	74.31± 8.02	0.689
	SpO_2 (%)	95.53± 2.39	95.38± 2.84	95.47± 2.59	95.42± 2.73	0.736
	CVP (cm/H_2O)	12± 1.45	12.02± 1.54	12.11± 1.75	11.98± 1.73	0.797
CO (L/min)		4.91± 0.9	5.89± 1.8	6.18± 1.59	4.23± 1.33	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*, P4<0.001*, P5<0.001*,** P6**<0.001***				---
PPV (%)		11.32± 0.75	12.33± 0.76	13.68±0.78	14.68± 0. 8	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*,** P4=**0.001*, P5=0.001*, P6=0.004***				--
Pulmonary dead space fraction		0.253±0.03	0.235± 0.03	0.228± 0.03	0.256± 0.03	**<0.001***
P value		**P1<0.001*, P2<0.001*, P3<0.001*,** P4=0.201, **P5=0.005*, P6=0.001***				--

Data are presented as mean ± SD. HR: heart rate, MAP: mean arterial pressure, SpO2: Oxygen saturation, CVP: central venous pressure, PLR: passive leg raising. CO: cardiac output, PPV: pulse pressure variation, PLR: passive leg raising *: statistically significant as p value <0.05, P1: p value between on admission and after PLR, P2: p value between on admission and after TV challenge test, P3: p value between after PLR and after TV challenge test. EEO: end expiratory occlusion, EIO: end inspiratory occlusion, *: statistically significant as p value <0.05, P1: p value between on admission and after PLR, P2: p value between on admission and after EEO, P3: p value between on admission and after EIO, P4: p value between after PLR and after EEO, P5: p value between after PLR and after EIO, P6: p value between after EEO and after EIO.

The vital signs including (HR, MAP, SpO_2 and CVP) and CO, PPV and pulmonary dead space fraction on admission and after PLR were insignificantly different among 2 groups. **(Table 4)**

Table 4: Vital signs, cardiac output, pulse pressure variation and pulmonary dead space fraction of the volume responders in the two studied groups

			Group A (n=26)	**Group B (n=31)**	**P value**
Vital signs	**HR (beat/min)**	**On admission**	91.98± 8	91.16± 8.14	0.630
		After PLR	91.96± 8.25	90.91± 8.13	0.547
	MAP (mmHg)	**On admission**	76.62± 6.57	74.2± 7.83	0.115
		After PLR	76.8± 6.69	74.27± 7.8	0.102
	SpO_2 (%)	**On admission**	96.02± 2.39	95.53± 2.39	0.334
		After PLR	96.16± 2.3	95.38± 2.84	0.157
	CVP (cm/H_2O)	**On admission**	11.76± 1.49	12± 1.45	0.433
		After PLR	11.98± 1.67	12.02± 1.54	0.896
CO (L/min)		**On admission**	4.8± 0.87	4.91± 0.9	0.553
		After PLR	5.47± 1.67	5.89± 1.8	0.363
PPV (%)		**On admission**	11.51± 0.68	11.32± 0.75	0.324
		After PLR	12.61± 0.68	12.33± 0.76	0.125
Pulmonary dead space fraction		**On admission**	0.241± 0.03	0.253±0.03	0.108
		After PLR	0.240± 0.03	0.235± 0.03	0.533

Data are presented as mean ± SD. HR: heart rate, MAP: mean arterial pressure, SpO_2: Oxygen saturation, CVP: central venous pressure, PLR: passive leg raising, EEO: end expiratory occlusion, EIO: end inspiratory occlusion. CO: cardiac output, PPV: pulse pressure variation, PLR: passive leg raising, EEO: end expiratory occlusion, EIO: end

inspiratory occlusion, *: statistically significant as p value <0.05. P1: p value between after TV challenge test and after EEO, P2: p value between after TV challenge test and after EIO, P3: p value between after EEO and after EIO.

In non-responders, there was insignificant difference among measurements (after PLR, TV challenge test, EEO and EIO) regarding HR, MAP, CVP, SpO_2, CO, PPV and pulmonary dead space fraction. (**Table 5)**

Table 5: Comparison of the vital signs in the non-responders

	After PLR (n=38)	After TV challenge test (n=19)	Combined end expiratory and end inspiratory occlusion (n=14)		P value
			After EEO	After EEO	
HR (beat/min)	93.8± 7.84	93.8± 8.15	91.2± 7.65	91.4± 8.27	0.350
MAP (mmHg)	79.1± 5.29	79.6± 6.16	75.9± 7.01	76.1± 6.87	0.090
SpO_2 (%)	95.9± 2.4	96± 2.5	95.3± 2.95	95.3± 2.97	0.489
CVP (cm/H_2O)	11.94± 1.55	11.67± 1.64	11.78± 1.77	11.89± 1.91	0.839
CO (L/min)	4.44± 1.25	4.06± 1.06	4.78± 1.06	4.5± 0.92	0.180
PPV (%)	7.74± 0.91	7.70± 0.91	7.76± 1.26	7.74± 1.25	0.898
Pulmonary dead space fraction	0.25± 0.03	0.26± 0.04	0.25± 0.02	0.25± 0.02	0.524

Data are presented as mean ± SD. HR: heart rate, MAP: mean arterial pressure, SpO2: Oxygen saturation, CVP: central venous pressure, CO: cardiac output, PPV: pulse pressure variation.

HR, MAP, SPO_2 and CVP were insignificant predictors of fluid responsiveness. The CO with AUC of 0.637 and at cutoff value >5 L/min can significantly predict the fluid responsiveness (P=0.020), with 77.78% sensitivity, 42.22% specificity, 57.4% PPV and 65.5% NPV. The PPV with AUC of 0.612 and at cutoff value >11.32 % can significantly predict the fluid responsiveness (P=0.039), with 73.33% sensitivity, 40% specificity, 55.2% PPV and 60% NPV. The pulmonary dead space fraction with AUC of 0.638 and at cutoff value ≤0.24 can significantly predict the fluid responsiveness (P=0.018), with 71.11% sensitivity, 40% specificity, 54.2% PPV and 58.1% NPV. **(Table 6)**

Table 6: Diagnostic accuracy of the vital signs, the cardiac output, pulse pressure variation and pulmonary dead space fraction for prediction of fluid responsiveness

		Cutoff	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV	AUC	P value
Vital signs	**HR (beat/min)**	≤89	42.22	27.7 - 57.8	57.78	42.2 - 72.3	50.0	50.0	0.534	0.574
	MAP (mmHg)	≤71	46.67	31.7 - 62.1	66.67	51.0 - 80.0	58.3	55.6	0.602	0.090
	SPO_2 (%)	≤95	51.11	35.8 - 66.3	57.78	42.2 - 72.3	54.8	54.2	0.588	0.144
	CVP (cm/H_2O)	>11	60.00	44.3 - 74.3	48.89	33.7 - 64.2	54.0	55.0	0.514	**0.825**
CO (L/min)		>5	77.78	44.3 - 74.3	42.22	48.8 - 78.1	54.2	57.6	0.637	**0.020***
PPV (%)		>11.32	73.33	55.7 - 83.6	40	25.7 - 55.7	55.2	60	0.621	**0.039***
Pulmonary dead space fraction		≤0.24	71.11	55.7 - 83.6	40.00	25.7 - 55.7	54.2	58.1	0.638	**0.018***

Data are presented as numbers. HR: heart rate, MAP: mean arterial pressure, SpO2: Oxygen saturation, CVP: central venous pressure, PPV: pulse pressure variation, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve. CO: cardiac output, PPV: pulse pressure variation, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, *: statistically significant as p value <0.05.

DISCUSSION

Intravenous fluids are frequently administered to cases experiencing acute circulatory failure in order to enhance CO and tissue perfusion. Only about 50% of cases showed a significant increase in CO, so-called fluid responders. [11] Fluids significantly influence clinical outcomes, encompassing mortality, morbidity, and duration of hospitalization, particularly when administered inadequately or excessively. The limitations of static parameters in assessing FR, including CVP and pulmonary artery wedge pressure, have spurred development of dynamic assessment techniques, which offer improved precision in distinguishing fluid responders from non-responders. Due to their respective limitations, clinicians

require multiple dynamic assessments to accurately predict FR across different scenarios. [7]

In our study, there was an insignificant difference between two groups regarding baseline characteristics (sex, age, BMI and BSA) and type of surgery, surgery duration and duration of cardiopulmonary bypass. There was insignificant difference between both groups regarding FR according to PLR.

Our findings demonstrated that the combined EEO + EIO test exhibited superior diagnostic accuracy over the TV challenge test. The EEO + EIO test achieved a PPV of 83.87%, sensitivity of 92.86%, specificity of 70.87%, and NPV of 85.71%, with an AUC of 0.889 ($p<0.001$). In contrast, the TV challenge test had a lower sensitivity of 76.92%, specificity of 68.42%, and an AUC of 0.637, which was insignificant.

Furthermore, in our study hemodynamic analysis further revealed that in responders, cardiac output was most augmented by EEO, PPV peaked after EIO, and pulmonary dead space fraction was reduced after EEO, suggesting that the combined test not only predicts FR but also reflects dynamic cardiopulmonary interactions. By contrast, non-responders showed no significant variations across maneuvers, supporting the reliability of these indices in identifying true responders.

These results support the growing evidence that transient occlusion maneuvers, especially when combined (EEO + EIO), can provide a more robust and reproducible evaluation of preload responsiveness in mechanically ventilated cases. Significantly higher AUC of combined test ($p<0.001$) underscores its enhanced predictive value compared to the tidal volume challenge.

In accordance with these studies that affirm which combining inspiratory and expiratory occlusion provides additive information by integrating physiological changes at both ends of respiratory cycle. These maneuvers transiently increase venous return (EEO) and impede cardiac output (EIO), allowing a better prediction of preload reserve. [7, 12]

Interestingly, while the TV challenge test showed moderate sensitivity in some studies, its diagnostic performance was limited by overlapping hemodynamic changes and variable ventilatory mechanics post-cardiac surgery. Such results are consistent with studies suggesting limited accuracy of TV challenge in patients with low lung compliance or altered chest mechanics, often present after cardiothoracic procedures. [13, 14]

Regarding secondary outcomes, CO, PPV, and pulmonary dead space fraction showed significant changes with each maneuver. In fluid responders, CO peaked after EEO, PPV was highest after EIO, and pulmonary dead space fraction was lowest after EEO—all supporting the dynamic preload responsiveness induced by these tests, in contrast to non-responders

Up to date there is no available trials demonstrates validity of combined end-expiratory and EIO test, as well as the tidal volume challenge test, for predicting FR in patients immediately following cardiac surgery.

Our result were agreed with a prospective study revealed that fluid challenge significantly higher velocity time integral (VTI) by over 15% in 36 patients (48% of the cohort), who were classified as responders. A rise in VTI surpassing 5% during EEO assessment predicted FR with a specificity of 93% and a sensitivity of 81%. [15] Area beneath receiver operating characteristic curve (AUROC) for ΔVTI-EEO was 0.90. ΔVmax-EEO demonstrated limited predictive capability for FR, with an AUC of 0.75. They determined that alterations in VTI caused by a 20-second EEO can serve as a reliable predictor of FR in cardiac surgical cases within operating room, whereas variations in Vmax are not predictive.

Moreover, a prospective study found that at baseline, MAP, HR, CO, VTI and peak velocity was comparable between responders and non-responders. EEO maneuver elicited a notable higher in SV index among both responders and nonresponders, whereas a significant elevation in peak velocity was observed exclusively in responders. [16] A 9% augmentation in VTI caused by an EEO maneuver precisely anticipated FR, exhibiting a sensitivity of 89% and a specificity of 95%. An 8.5% rise in peak velocity resulting from EEO maneuver accurately forecasted ER, exhibiting a sensitivity of 64% and a specificity of 77%. AUC calculated for variations in VTI was markedly greater than that obtained for alterations in peak velocity ($P = 0.0004$ for both). The indeterminate range encompassed 6 to 10% (affecting 20% of the patient cohort) for variations in VTI, and 1 to 13% (observed in 62% of the patient cohort) for alterations in peak velocity. They concluded that in mechanically ventilated and sedated patients within the neuro-intensive care unit, changes in VTI during a 12-second EEO maneuver could predict FR and surpassed the predictive value of alterations in peak velocity.

Moreover, A systematic review and meta-analysis demonstrated aggregated sensitivity and specificity for EEXPO test-induced changes in CO of 85% and 88%, respectively. The AUSROC curve achieved a value of 0.91, with optimal threshold for CO increase identified at $5.1 \pm 0.2\%$. The test's accuracy remained unchanged when variations in CO were monitored via pulse contour analysis in comparison to alternative methodologies [17]. Furthermore, no distinction was observed in studies where TV was less than or equal to 7 mL/kg than others. Subgroup analyses revealed a potential source contributing to heterogeneity. They concluded that EEXPO testing-induced alterations in CO reliably identify preload responsiveness. Diagnostic accuracy is unaffected by approach employed to monitor EEXPO test-induced alterations in CO.

In contrast, a previous study defined FR as an elevation in cardiac index by 15%. They concluded that neither EIO, EEO, nor their combination reliably predicted FR throughout their investigation. Following an integrated EEO and EIO assessment, a CI variation threshold of 16.7% predicted FR, exhibiting a sensitivity of 61.8%, specificity of 69.6%, and an area under ROC curve of 0.593. [9] They established that in patients subjected to elective cardiac surgery with protective ventilation, respiratory occlusion

experiments failed to accurately forecast FR when employing uncalibrated pulse contour analysis.

Furthermore, Another study found THAT preload responsiveness was observed in forty-two cases. An absolute variation in PPV exceeding 3.5% during TVC assessment of preload responsiveness, accompanied by an AUROC of 0.94 ± 0.03 (sensitivity: 98%, specificity: 86%), exhibited superior diagnostic accuracy relative to baseline PPV (0.85 ± 0.05; p=0.047). In the 56 cases where baseline PPV was inconclusive (ranging from 4% to less than 11%), a ΔPPV TVC6–8 ≥ 3.5% consistently enabled a dependable evaluation of preload responsiveness (AUROC: 0.91 ± 0.05, specificity: 81%, sensitivity: 97%; $p < 0.01$ when compared to baseline PPV). [18]

In addition, A study was reported that ROC curves for the percentage reduction in SV, VTI, and MAP by VTC were generated to estimate their effectiveness in differentiating fluid responders from non-responders. Of 58 cases assessed, 32 (55%) were categorized as responders, while 26 (45%) were classified as non-responders. AUC values for ΔSV-VTC, ΔVTI-VTC, and ΔMAP-VTC in differentiating responders from non-responders were 0.79 (95% CI: 0.66–0.89), 0.81 (95% CI: 0.68–0.90), and 0.56 (95% CI: 0.42–0.69), respectively. [19]

The optimal threshold for ΔSV-VTC was determined to be -16.1%, yielding a specificity of 84.6% and a sensitivity of 78.1%, while optimal threshold for ΔVTI-VTC was identified as -14.5%, with a specificity of 80.8% and a sensitivity of 78.1%. They demonstrated that relative changes in stroke volume and VTI, induced by tidal volume challenge, can serve as predictors of FR in patients undergoing one-lung ventilation.

Also, The AUC metrics for the predictors of FR were as follows: Δ-IVC = 0.86, PLR = 0.84, SVV = 0.90, m-FC = 0.84, PPV = 0.82, EEOT = 0.92, and VtC = 0.92. Based on subgroup analyses, variations in methodologies employed to measure CO and subsequently categorize cases as responders or non-responders markedly influence the precision of PPV and SVV. The operative efficacy of PPV was also markedly affected by respiratory system compliance, whereas patient type and the thresholds employed to assess responsiveness notably impacted the predictability of SVV. Additionally, volume of fluids administered to assess changes in CO markedly affected accuracy of SVV and PLR. Sensitivity analysis revealed no deviations in operational performance of SVV, PPV, and EEOT. [20]

The study's limitations involved a limited sample size and findings of this study do not establish ineffectiveness of TV in predicting FR among patients with impaired left ventricular function.

CONCLUSIONS

The combined EEO and EIO test can significantly predict the FR through their effect on CO, PPV, pulmonary dead space fraction with significantly higher AUC, sensitivity and specificity compared to the TV challenge test which was insignificant predictor of the FR. Therefore, further studies with larger patient populations and more precise measurement methods are warranted to better elucidate the effect of tidal volume challenge test on hemodynamic and is recommended to optimize fluid management strategies in cases with impaired cardiac reserve function.

Acknowledgment: None.
Source of support: Nil.
Conflict of interest: None

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