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ORIGINAL RESEARCH

End expiratory occlusion test and tidal volume challenge test for assess fluid responsiveness in prone patients

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ABSTRACT:

Background: Assessing fluid responsiveness in patients in the prone position with low tidal volume ventilation presents challenges when utilizing pulse pressure variation (PPV) and the inferior vena cava (IVC) distensibility index. These challenges stem from the use of low tidal volume and the difficulty of conducting IVC assessment in the prone position. Consequently, an alternative method for predicting fluid responsiveness in these patients is imperative.

Method: This study comprises a prospective investigation that was carried out on hypotensive patients positioned in the prone posture and undergoing lung-protective ventilation at Bhumibol Adulyadej Hospital. Prior to the administration of a 500 ml fluid bolus, end-expiratory occlusion (EEO) and tidal volume challenge (TVC) tests were conducted. Initial recordings of cardiac output, cardiac index, and PPV were documented, followed by subsequent recordings after each procedure.

Result: Among the 20 participants in the prone position study, 4 patients developed severe acute respiratory distress syndrome (ARDS) while 16 patients were in that position for surgical reasons. Of these, 7 patients exhibited a positive response to fluid administration, while 13 patients did not. An increase in cardiac index (CI) of more than 5% during EEO is indicative of fluid responsiveness with a sensitivity of 100% and specificity of 92.3%. Moreover, a 3.5% absolute increment in PPV during TVC suggests fluid responsiveness with a sensitivity of 57.1% and specificity of 92.3%. We observed an interrater reliability (kappa) of 0.894 for EEO and 0.529 for PPV.

Conclusion: In the case of hypotensive patients undergoing prone positioning and receiving low tidal volume ventilation, both EEO for 15 seconds and TVC methodologies can be employed to evaluate fluid responsiveness. It is important to note that EEO demonstrates greater reliability in this context.

Keywords: Fluid responsiveness; Tidal volume challenge test; End expiratory occlusion test; Prone position

INTRODUCTION

Fluid management is of paramount importance; excessive fluid administration can adversely affect patient outcomes, while inadequate fluid provision may fail to rectify existing deficits. Several techniques are available for evaluating fluid responsiveness in patients experiencing circulatory shock. These include pulse pressure variation, passive leg raising tests, and the inferior vena cava (IVC) distensibility index [4,5,6], Achieving optimal fluid management becomes increasingly complex due to the limitations inherent in various fluid assessment techniques.

The prone position confers several clinical benefits, particularly in the context of spinal and posterior cranial surgeries, as well as for enhancing gas exchange in the dorsal lung regions of patients suffering from acute respiratory distress syndrome (ARDS). The advantages of employing low tidal volume ventilation are substantiated by robust empirical evidence, which has facilitated its widespread incorporation into contemporary clinical practice.

However, the reliability of the fluid responsiveness technique is constrained when patients are in the prone position with low tidal volume ventilation. Methods such as the tidal volume challenge test (TVC), end-expiratory occlusion test (EEO), and mini-fluid challenge test are showing promise for patients in prone positions [6,7,8,9]. In a recent 2022 study [14], Alvarado Sanchez JL et al. demonstrated that, among low tidal volume ventilated patients, the TVC and EEO methods outperformed other tests in determining fluid responsiveness. A 2022 study by Rui Shi et al. [10] demonstrated the effectiveness of TVC and EEO in predicting fluid responsiveness when compared to an > 8% increase in cardiac index (CI) following the Trendelenburg maneuver. However, the gold standard for a fluid responsiveness test should entail a 15% increase in CI following the administration of a 500 ml fluid bolus over 15 minutes[15]. Invasive and noninvasive methods are available for measuring cardiac output, with the gold standard being invasive pulmonary artery catheterization. However, noninvasive methods like transpulmonary thermodilution and pulse contour analysis are gaining popularity due to their lower risk with comparable reliability [11,12,13].

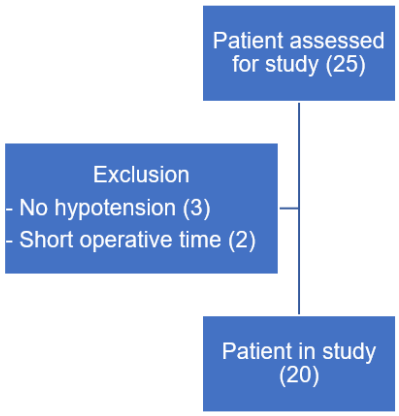
The objective of this study is to evaluate the effectiveness of fluid responsiveness parameters, EEO and TVC, in hypotensive patients undergoing prone positioning and low tidal volume ventilation.

MATERIALS AND METHODS

This study is a non-randomized prospective trial being conducted at Bhumibol Adulyadej Hospital. We are seeking to enroll patients over 18 years of age who are positioned prone and ventilated with a tidal volume of 6 mL/kg predicted body weight. Exclusion criteria include patients without hypotension, abnormal heart rhythms (atrial or ventricular arrhythmias with a heart rate exceeding 120 beats per minute), a history of pneumothorax, patients with mechanical cardiovascular support, patients or relatives who declined to participate, and patients with known allergies to medications used in the study. The researcher is responsible for providing comprehensive explanations of the research procedures, apprising patients or their relatives of potential side effects, and obtaining informed consent.

KEY MESSAGES:

- Assessing fluid responsiveness in prone-positioned patients is challenging, conventional methods are less reliable in this setting.
- This study evaluates two alternatives methods: end-expiratory occlusion (EEO) test and tidal volume challenge (TVC) test in prone patient ventilated with low tidal volume.
- An increase in CI > 5% during EEO and an increase in PPV > 3.5 during TVC can be used to assess fluid responsiveness in prone patients.
- EEO higher reliability than TVC in this study.



Hemodynamic monitoring

The radial arterial catheter and central venous catheter were both linked to a pulse contour analysis cardiac output monitoring transducer (FloTrac sensor®, HemoSphere® Advance monitor, Edwards Lifesciences). This configuration facilitated recording parameters such as blood pressure, cardiac output, cardiac index, pulse pressure variation, and central venous pressure.

Procedure:

1. All patients were adequately sedated and paralyzed to facilitate respiratory control, consistent with standard medical procedures, except for fluid administration.
2. Each patient underwent an EEO procedure for 15 seconds to record cardiac output measurements before and after the occlusion.
3. Five minutes later, a TVC was administered with a fluid volume ranging from 6 mL/kg to 8 mL/kg, and measurements of pulse pressure variation and cardiac output were conducted.
4. Following a five-minute interval, patients received isotonic crystalloid solution (500 mL) over a 15-minute period, and subsequent measurements were taken to assess changes in cardiac output.

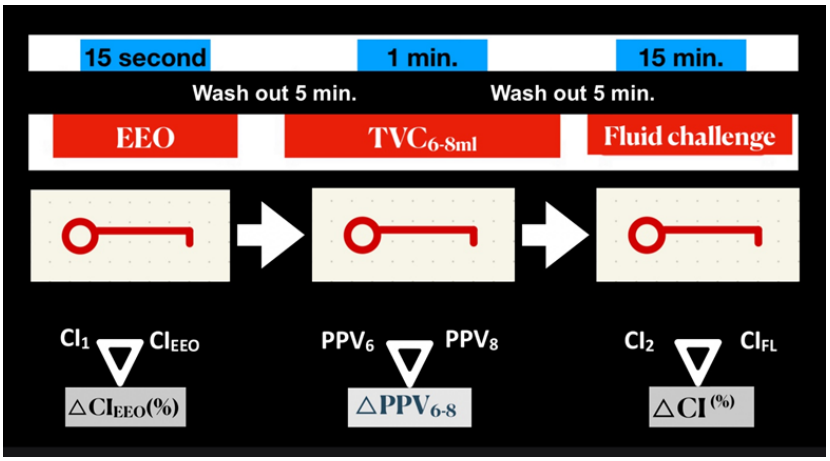


Figure 1. Study procedure.

Statistical analysis

The primary objective of this study was to evaluate whether changes in PPV (ΔPPV6–8) during TVC and alterations in cardiac index during EEO (ΔCIEEO) could effectively ascertain preload responsiveness in the prone position, with the area under the receiver operating characteristic (AUROC) of at least 0.9. We posited the null hypothesis at 0.75, as an AUROC between 0.5 and 0.75 would yield inadequate sensitivity and specificity for drawing significant conclusions. The required sample size, factoring in a 5% α risk and a 20% β risk, and assuming a 50% prevalence of preload responsiveness as indicated by Shi R. et al., was calculated to be 38 participants for each group. Quantitative and categorical variables were expressed as frequency (percentage) and mean±SD. Data distribution was verified utilizing histograms. The ROC curve data were reported as the AUROC value±standard error (with a 95% confidence interval), sensitivity (with a 95% confidence interval), and specificity (with a 95% confidence interval). Additionally, p-values were computed for the interaction effects among different time points, between baseline and maximal values, and between responsive and non-responsive cases.

Ethics approval

The Bhumibol Adulyadej Hospital Ethics Committee approved this study on November 30, 2023 (IRB No.95/66), and it has been registered with the Clinical Trial Registry. NCT06254456).

RESULTS

Patient characteristics

Among the 20 participants in the prone position, 4 patients developed severe ARDS while in the prone position, while 16 patients adopted the prone position during surgical procedures. Out of the participants, 7 were identified as fluid responders, with the remaining 13 categorized as non-responders. The average age of the participants was 61 years, with hypertension being the most prevalent co-existing condition. (Table 1, 2 and 3)

End expiratory occlusion test

An increase in the cardiac index exceeding 5% serves as a significant discriminator between fluid responders and non-responders (p = 0.012). This discrimination achieves

Table 1. Demographic data.

	Total (n=20)	Response (n=7)	Non response (n=13)	p-value
Male	11 (55%)	4 (57.1%)	7 (53.8%)	0.888
Co-morbidities	11 (55%)	5 (71.4%)	6 (46.2%)	0.279
Hypertension	10 (50%)	5 (71.4%)	5 (38.5%)	0.160
Diabetes mellitus	3 (15%)	1 (14.3%)	2 (15.4%)	0.948
Systolic blood pressure	91.95 ± 6.79	95.43 ± 8.72	90.08 ± 4.92	0.093
Diastolic blood pressure	50.6 ± 5.1	51.14 ± 6.69	50.31 ± 4.31	0.737
Pulse	74.4 ± 18.8	75 ± 18.77	74.08 ± 19.58	0.920
Weight	64.4 ± 10.04	64 ± 12.75	64.62 ± 8.85	0.900
Height	160.9 ± 8.61	164 ± 10.95	159.23 ± 6.98	0.248
Body surface area	1.69 ± 0.15	1.7 ± 0.18	1.69 ± 0.13	0.847
Age	60.9 ± 17.83	64.29 ± 14.35	59.08 ± 19.75	0.548
ARDS	4 (20%)	3 (42.8%)	1 (7.7%)	0.120

Table 2. Individual data records.

Case	Wt	Ht	BP	Pulse	CVP	CO_1 (baseline)	CO (EEO)	BP	Pulse	PPV (6)	PPV (8)	BP	Pulse	CO_2 (before loading)	CO (after loading)
1	62	165	92/60	88	8	3.7	4	90/56	88	5	12	90/55	88	3.7	4.5
2	70	150	91/62	100	10	4.6	4.7	88/61	99	5	6	87/60	99	4.4	4.7
3	53	150	90/48	52	8	3	3.1	86/40	54	9	9	87/42	55	3.2	3.6
4	56	165	92/47	70	9	4.7	4.8	96/50	71	6	6	96/50	70	4.5	4.7
5	90	165	100/60	88	4	5.4	5.7	97/62	89	15	22	96/62	89	5.1	5.7
6	60	160	90/49	104	6	6.8	7	95/50	100	9	11	95/50	100	7	7.5
7	61	162	100/47	98	5	4.5	5.2	100/50	96	9	13	101/50	96	4.5	6.7
8	57	158	86/50	70	2	3.9	4	92/55	73	9	11	94/54	72	4	4.3
9	67	165	88/48	110	10	4	4.1	87/50	108	9	10	89/51	108	3.9	4.3
10	57	183	90/52	84	2	3.9	4.4	92/54	82	16	21	92/55	83	3.7	4.5
11	70	170	93/50	61	2	3.5	4.1	88/50	65	6	9	88/50	65	3.4	4.2
12	80	168	92/52	55	15	3.6	3.7	89/55	58	10	12	90/55	60	3.6	3.7
13	68	170	89/53	80	9	4.9	5.1	84/50	84	10	14	87/50	86	4.7	5.2
14	53	150	83/43	54	2	3.8	3.9	85/44	55	4	7	87/46	55	3.8	4.4
15	72	152	79/48	66	11	3.5	3.7	82/50	66	7	10	82/50	67	3.4	3.9
16	60	159	96/50	60	5	3	3.1	96/50	61	6	7	94/51	60	3	3.3
17	55	153	110/46	52	4	3.9	4.1	100/55	55	4	5	98/54	55	3.8	4.5
18	78	160	90/48	60	9	4	4.1	91/48	60	7	9	91/50	60	4	4.4
19	65	163	88/45	80	7	4.3	4.4	90/48	79	6	9	91/48	80	4.2	4.7
20	54	150	100/54	56	9	3.4	3.5	98/57	57	6	9	98/57	57	3.3	3.6

Abbreviations: Wt: Weight; Ht: Height; BP: Blood pressure; CVP: Central venous pressure; CO_1 (baseline): Cardiac output baseline before EEO; CO(EEO): Cardiac output after EEO; CO_2 (before loading): Cardiac output baseline before loading fluid; CO (after loading): Cardiac output after loading fluid

Table 3. Mean difference between groups.

	Response (n=7)	Non response (n=13)	Mean difference (95%CI)	p-value
CO_1 (baseline before EEO)	4.1 ± 0.65	4.13 ± 1.01	-0.03 (-0.92, 0.86)	0.943
CI_1 (baseline before EEO)	2.41 ± 0.29	2.46 ± 0.62	-0.04 (-0.56, 0.48)	0.866
CO EEO	4.5 ± 0.68	4.25 ± 1.03	0.25 (-0.67, 1.16)	0.578
CI EEO	2.65 ± 0.29	2.53 ± 0.63	0.12 (-0.41, 0.65)	0.647
ΔCIEEO%	9.94 ± 5.15	3.02 ± 0.97	6.91 (2.15, 11.68)	0.012*
PPV_6	8.43 ± 5.13	7.62 ± 1.76	0.81 (-3.94, 5.57)	0.697
PPV_8	12.86 ± 6.41	9.46 ± 2.3	3.4 (-2.56, 9.35)	0.219
ΔPPV_{6-8}	4.43 ± 1.99	1.85 ± 1.21	2.58 (1.09, 4.08)	0.002*
CO_2 (baseline before loading)	4 ± 0.59	4.09 ± 1.02	-0.09 (-0.98, 0.79)	0.829
CI_2 (baseline before loading)	2.36 ± 0.29	2.44 ± 0.63	-0.08 (-0.61, 0.46)	0.767
CO FL	4.97 ± 0.97	4.45 ± 1.07	0.52 (-0.5, 1.54)	0.301
CI FL	2.93 ± 0.54	2.65 ± 0.66	0.28 (-0.33, 0.9)	0.350

* is mean statistical significance

Abbreviations: CO_1 (baseline before EEO): Cardiac output baseline before EEO; CI_1 (baseline before EEO): Cardiac index baseline before EEO; CO EEO: Cardiac output after EEO; CI EEO: Cardiac index after EEO; CO_2 (baseline before loading): Cardiac output baseline before loading fluid; CI_2 baseline before loading): Cardiac index baseline before loading fluid; CO FL: Cardiac output after loading fluid; CI FL: Cardiac index after loading fluid; PPV_6: Pulse pressure variation at tidal volume 6 ml/kg; PPV_8: Pulse pressure variation at tidal volume 8 ml/kg; ΔPPV_{6-8}: Change of PPV from tidal volume 6 ml/kg to 8 ml/kg

Table 4. Predictability and accuracy in various cut-off point of alteration of cardiac index (ΔCI%) and pulse pressure variation (ΔPPV).

Variable(s)	Cut off >=	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR-	Youden index
ΔCI%	2.15	7	12	0	1	100.0%	7.7%	36.8%	100.0%	40.0%	1.08	0.00	0.077
	2.25	7	11	0	2	100.0%	15.4%	38.9%	100.0%	45.0%	1.18	0.00	0.154
	2.41	7	10	0	3	100.0%	23.1%	41.2%	100.0%	50.0%	1.30	0.00	0.231
	2.50	7	9	0	4	100.0%	30.8%	43.8%	100.0%	55.0%	1.44	0.00	0.308
	2.53	7	8	0	5	100.0%	38.5%	46.7%	100.0%	60.0%	1.63	0.00	0.385
	2.67	7	7	0	6	100.0%	46.2%	50.0%	100.0%	65.0%	1.86	0.00	0.462
	2.86	7	6	0	7	100.0%	53.8%	53.8%	100.0%	70.0%	2.17	0.00	0.538
	2.94	7	5	0	8	100.0%	61.5%	58.3%	100.0%	75.0%	2.60	0.00	0.615
	3.14	7	4	0	9	100.0%	69.2%	63.6%	100.0%	80.0%	3.25	0.00	0.692
	3.33	7	3	0	10	100.0%	76.9%	70.0%	100.0%	85.0%	4.33	0.00	0.769
	3.71	7	2	0	11	100.0%	84.6%	77.8%	100.0%	90.0%	6.50	0.00	0.846
***	4.60	7	1	0	12	100.0%	92.3%	87.5%	100.0%	95.0%	13.00	0.00	0.923
	5.20	6	1	1	12	85.7%	92.3%	85.7%	92.3%	90.0%	11.14	0.15	0.780
	5.41	5	1	2	12	71.4%	92.3%	83.3%	85.7%	85.0%	9.29	0.31	0.637
	5.63	4	1	3	12	57.1%	92.3%	80.0%	80.0%	80.0%	7.43	0.46	0.495
	6.91	4	0	3	13	57.1%	100.0%	100.0%	81.3%	85.0%	NA	0.43	0.571
	10.46	3	0	4	13	42.9%	100.0%	100.0%	76.5%	80.0%	NA	0.57	0.429
	14.19	2	0	5	13	28.6%	100.0%	100.0%	72.2%	75.0%	NA	0.71	0.286
	16.35	1	0	6	13	14.3%	100.0%	100.0%	68.4%	70.0%	NA	0.86	0.143
	18.14	0	0	7	13	0.0%	100.0%	100.0%	65.0%	65.0%	NA	1.00	0.000
ΔPPV	1	7	11	0	2	100.0%	15.4%	38.9%	100.0%	45.0%	1.18	0.00	0.154
	2	7	8	0	5	100.0%	38.5%	46.7%	100.0%	60.0%	1.63	0.00	0.385
***	3	6	4	1	9	85.7%	69.2%	60.0%	90.0%	75.0%	2.79	0.21	0.549
	4	4	1	3	12	57.1%	92.3%	80.0%	80.0%	80.0%	7.43	0.46	0.495
	5	3	0	4	13	42.9%	100.0%	100.0%	76.5%	80.0%	NA	0.57	0.429
	6	2	0	5	13	28.6%	100.0%	100.0%	72.2%	75.0%	NA	0.71	0.286

*** is highest youden index in each method

Abbreviations: TP: True positive; FP: False positive; FN: False negative; TN: True negative; PPV: Positive predictive value; NPV: Negative predictive value; LR+: Likelihood ratio for positive; LR-: Likelihood ratio for negative

a sensitivity of 100% and a specificity of 92.3%, resulting in an overall accuracy of 95%. Upon subsequent evaluation, the determined cutoff value suggests that a 4.6% rise in cardiac index from baseline serves as the optimal threshold for discerning fluid responders, yielding a Youden index of 0.923. (Table 3 and Table 4)

Tidal volume challenge test

An increase in pulse pressure variation exceeding 3.5 demonstrates a significant ability to differentiate between fluid responders and non-responders (p = 0.002). This test yields a sensitivity of 57.1% and a specificity of 92.3%, resulting in an overall accuracy rate of 80%. Upon reassessment of the threshold value, it has been established that the optimal point for discerning fluid responders is a 3.0 increase in pulse pressure variation from the baseline, corresponding to a Youden index of 0.549. (Table 3 and Table 4)

EEO and TVC

In the comparison between the EEO and TVC tests, both have demonstrated statistically significant assessment of fluid responsiveness. The AUROC for EEO stands at 0.967 (p = 0.001), while that for TVC is 0.874 (p = 0.007). In terms of reliability, EEO exhibits higher reliability than TVC, with respective kappa values of 0.894 and 0.529. (Figure 2 and Table 5)

DISCUSSION

The findings of our study indicate that the EEO test exhibits a higher degree of reliability in differentiating between fluid-responsive and non-responsive states compared to the tidal volume challenge test. This contrasts with a previous study conducted by Rui Shi [10], in which both methods were found to be equally effective. The observed disparity may be attributed to the varying standards employed in classifying fluid responsiveness. Notably, Rui Shi's study utilized the Trendelenberg test as the standard, whereas our study utilized the administration of 500 ml of crystalloid fluid as the reference standard method for assessing fluid responsiveness across distinct patient populations, including patients with ARDS and perioperative patients. Moreover, norepinephrine was not administered to any patients in our study, unlike the previous study where it was administered to 83% of the patients. Additionally, our research specifically focused on patients experiencing hypotension, while the primary objective of the previous study was to assess fluid responsiveness more generally.

In a recent 2022 study [14], Alvarado Sanchez JL et al. demonstrated that, among low tidal volume ventilated patients, the TVC and EEO methods outperformed other tests in determining fluid responsiveness. However, it was

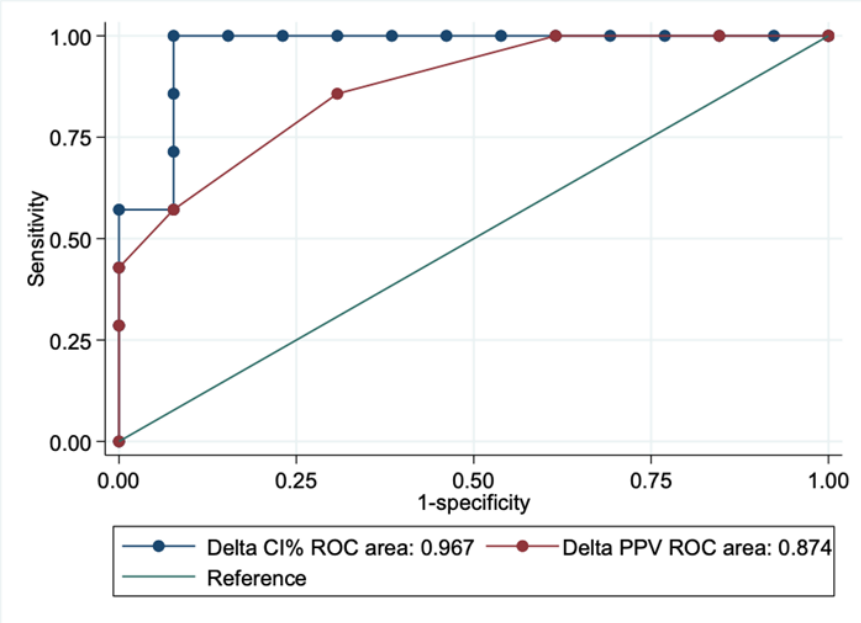


Figure 2. Receiver operating characteristic curve (ROC curve) of end expiratory occlusion (EEO) and tidal volume challenge (TVC).

Table 5. The area under the receiver operating characteristic (AUROC) of end-expiratory occlusion (EEO) and tidal volume challenge (TVC).

Variable(s)	AUC	95%CI		p-value	Paired AUC	Kappa
		Lower Bound	Upper Bound		p-value	
ΔCI%	0.967	0.894	1	0.001*	0.213	0.894
ΔPPV	0.874	0.715	1	0.007*		0.529

* is mean statistical significance

Abbreviations: AUC: Area under the curve; ΔCI%: Alteration of cardiac index; ΔPPV: Alteration of pulse pressure variation

noted that the methods used for categorizing patients as fluid responders or non-responders post-final fluid loading significantly influenced the reliability of PPV and, consequently, TVC. In line with our own investigation, EEO exhibited greater reliability than TVC. This could be attributed to constraints in the equipment used for accurate measurement of differences or the marginal impact of a mere 2 ml alteration in tidal volume in the prone position, which may exert a lesser influence on intrathoracic pressure compared to the supine position. Notably, intrathoracic pressure variations in individuals with ARDS may surpass those in non-ARDS patients. Consequently, adhering to the previous cutoff point may compromise reliability.

To achieve statistically significant results and ensure adequate reliability, the study necessitates a sample size of 38 participants in each group. It is imperative to acknowledge that the preliminary findings are based on a mere 25% of the stipulated sample size. Thus, it is paramount to conduct further data collection before reinterpreting the results. Furthermore, it is plausible that the tidal volume challenge test may be correlated with fluid responsiveness assessment, as demonstrated in a study by Rui Shi. Subsequent investigation with a larger sample size will yield more conclusive evidence regarding the relationship between the tidal volume challenge test and fluid responsiveness assessment.

The potential risks associated with this research project are classified as moderate, arising from the potential for patients to receive fluid volumes exceeding normal levels. In the final stage of the study, each patient will receive 500 ml of fluid, thereby increasing the possibility of fluid overload and exacerbating the patient's condition. To address this risk, the researcher will assess each patient thoroughly before administering fluid in the final stage. Should a high risk and potential harm be identified, consideration will be given to withholding fluid administration and discontinuing the study for that patient. Additionally, meticulous monitoring and care will be provided to all patients receiving fluid administration, and close attention will be paid to signs of fluid overload. Moreover, the researcher will modify the fluid volume as needed by employing diuretics or initiating renal replacement therapy if trends indicate an increased risk. Another notable risk pertains to arterial and venous catheter insertion for connection to the pulse contour analysis device, which bears the potential for bloodstream infections or misplacement of the venous catheter into the arterial vessel at the neck. To mitigate the risk of catheter misplacement, ultrasound guidance will be utilized during venous catheter insertion at the neck, and strict adherence to infection prevention measures will be upheld, including the timely removal of catheters when no longer necessary. Continuous vigilance for infections will be maintained, and immediate treatment will be initiated in the event of infections. Therefore, patients will be subject to close monitoring from the start to the completion of the research project, with the provision of appropriate treatment in response to any adverse events that may occur.

Limitations of this study include some confounding factors that cannot be excluded due to a single-center study. The power of the study was 80% due to low participation in our hospital. If we escalate power to 90%, the population of this study must be increased to 224. This result cannot be extrapolated to prone patients without respiratory support.

CONCLUSION

In hemodynamically unstable patients undergoing mechanical ventilation in the prone position with low tidal volumes, both the EEO test lasting for 15 seconds and the tidal volume challenge test are viable methods for assessing fluid responsiveness. The end-expiratory occlusion test is considered to be more dependable than the tidal volume challenge test.

CONFIDENTIALITY

I confirm that this manuscript is original and has not been shared beyond the intended submission process. I acknowledge and adhere to the journal's confidentiality policies, ensuring that all unpublished content, including participant data, remains secure and is handled in accordance with ethical and regulatory guidelines. This study has obtained ethical approval from the institutional review board, and informed consent was obtained from all human participants, ensuring compliance with ethical standards for research.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Jaras Pitawiwathananont, Anan Chuasuwan; (II) Data curation: Thanadate Sirithanasarn; (III) Formal analysis: Thanadate Sirithanasarn; (IV) Methodology: Thanadate Sirithanasarn, Jaras Pitawiwathananont, Anan Chuasuwan; (V) Project administration: Thanadate Sirithanasarn, Jaras Pitawiwathananont; (VI) Writing – original draft: Thanadate Sirithanasarn; (VII) Writing – review & editing: Jaras Pitawiwathananont, Anan Chuasuwan.

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