

Efficacy of Changes in Pulse Pressure Variation During Tidal Volume Challenge Test to Predict Fluid Responsiveness in Low Tidal Volume Ventilated Critically ill Patients

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Abstract

Background: Fluid administration is one of the first-line therapy interventions used to reverse tissue hypoperfusion during acute circulatory failure. Nevertheless, fluid administration is not free of adverse effects, especially when fluids are excessively administered. Assessment of fluid responsiveness might limit fluid administration, potentially reducing the risk of fluid overload, avoiding complications derived from tissue oedema, and increasing mechanical ventilation-free days, among others.

Aim and objectives: Aiming to predict preload response in low tidal volume ventilation by analyzing pulse pressure variation (PPV) fluctuations during a one-minute tidal volume challenge (TVC).

Subjects and methods: From March 2023 through August 2024, sixty patients admitted to the intensive care unit at Al-Azhar University Hospitals were part of this correlational clinical study. After receiving signed informed consents, the study procedure was approved by the department's Ethics Committee.

Results: The responders' PPV increased significantly with TVC, reaching 91.9% specificity and 95.7% sensitivity at the optimal cutoff value of 4. With a statistically best threshold value of 2% decrease in PPV, the changes in PPV induced by the PLR test were 87% sensitive and 86.5% specific.

Conclusion: In critically ill patients ventilated with a low tidal volume of 6ml/kg IBW or less, the variations in PPV can accurately predict preload response when PPV rises to 4 or more during TVC and falls to 2 or less during PLR. There is no need to employ continuous cardiac output monitoring to evaluate the effects of either test; they are both straightforward.

Keywords: Pulse pressure; Fluid responsiveness; Tidal volume challenge test

1. Introduction

Predicting preload fluid response in mechanically ventilated patients has been done using pulse pressure fluctuation.¹

A dynamic measure, pulse pressure fluctuation can be easily recorded from a bedside monitor with arterial lines; it also doesn't need cardiac output monitoring or any additional procedures, which makes it a better option than other conventional indicators.²

Its inaccuracy during low tidal volume breathing, which is becoming more common in patients in the intensive care unit (ICU), is a major downside.³

While end-expiratory occlusion and passive leg raising (PLR) are capable of accurately predicting fluid response and have been suggested as potential substitutes in such cases, they necessitate ongoing monitoring of cardiac output.⁴

The patient is placed in a horizontal supine position with their trunk depressed, and an automatic bed elevation technique is used to perform the passive leg raising test. The knees and ankles are bent at a 45-degree angle. With an estimated sensitivity between 85% and 91%, it has proven to be reliable during low tidal volume breathing, as shown in numerous investigations.⁵

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Recent research has proposed a tidal volume challenge test (TVC) to address this limitation and improve the precision of low tidal volume strategies for protective ventilation. This test involves briefly increasing the tidal volume from 6 ml/kg to 8 ml/kg for 1 minute, followed by the measurement of changes in pulse pressure variation (Δ PPV6-8) to determine the correctness of the strategy.⁶

The study's objective was to determine whether pulse pressure fluctuation variations during a one-minute tidal volume challenge might be used as a predictor of low tidal volume ventilation preload responsiveness.

2. Patients and methods

This correlational clinical study included 60-patients who were admitted to ICU at Al-Azhar University Hospitals from March 2023 till August 2024.

Once the department's Ethics Committee received the signed informed consents, the study protocol was approved.

Sample Size calculation:

Now using Epi Info 7.2.4.0 The following assumptions were taken into account by STATCALC in order to determine the sample size: With a 95% two-sided confidence level, an 80% power of the test, a ratio of 1:1 between the control and case groups, a 50% chance of an exposed outcome, an 11.5% chance of an unexposed outcome, an odds ratio of 7, a minimum of 54 subjects, and an increase of 10% (6 patients) for dropout, the study was conducted with 60 patients to test the hypothesis.⁷

Inclusion criteria:

The goal of this research was to find out how well volume assist-control ventilation (ACV) worked with a low tidal volume approach (6 ml/kg/IBW) in intubated and mechanically ventilated individuals over the age of 18. Oliguria, skin mottling, tachycardia, and hyperlactatemia are indications of acute circulatory failure that led to the patients' selection for this study.

Exclusion criteria:

Indications against performing the PLR maneuver include irregular heart rhythms, an open chest, right-sided heart failure, pulmonary hypertension, and airway pressure waveforms that spontaneously trigger cycles that can lead to intracranial, venous compression stockings, and intra-abdominal hypertension.

Methods:

All patients that were considered were on mechanical ventilation with a volume ACV and had a radial arterial line. They were all on a modest tidal volume approach of 6-ml/kg/IBW. To avoid any potential misunderstanding about changes in cardiac output caused by adrenergic

stimulation (pain, cough, discomfort), all patients were given a complete sedative. When necessary, neuromuscular blocking medications were administered.

The initial set of readings, referred to as "baseline 1," included the following: SAP, DAP, MAP, PPV, HR, and cardiac output. As previously detailed by Cherpanath et al., PLR was subsequently conducted.⁵

After one minute of the passive leg raising test, a second set of measures was taken, which were referred to as the 'PLR' set. The second step was to get the patient back into their original semi-recumbent position on the bed and wait for the pulse pressure variance to settle back down to its baseline value, which generally happens within two or three minutes.

Patients were repositioned to the semi-recumbent position and returned to a stable condition before a new set of measures, called foundational 2, was taken. Now we will follow the steps directed by Myatra et al. to conduct the tidal volume challenge (TVC).⁶

A fourth set of measurements (named 'TVC') was recorded. The patient was considered a fluid responder when cardiac output increased above an average threshold of 10%.⁸

Measured parameters:

Patient information (including height, weight, sex, and age). Hemodynamics (HR, SAP, DAP, MAP). While the Nihon Kohden Life Scope monitors automatically displayed the PPV through the arterial catheter, before taking the patient's vital signs, the tech made sure the transducer was flush with the arterial line, level with the right atrium, and set to atmospheric pressure.

In order to measure cardiac output, the patient underwent an electrocardiogram (ECG) procedure. Four surface electrodes were placed on the skin: two pairs on the left side of the neck. The lower thorax has one set of them at the mid-axillary line on the left side, and the xiphoid process level has another set. Additionally, both pre- and post-TVC recordings of respiratory parameters (including plateau pressure, PEEP, and systemic compliance) were made.

Primary Outcome:

Validity of pulse pressure fluctuation variations during tidal volume challenge test as a predictor of response. We will analyze the test's specificity and sensitivity to predict preload response using a (ROC) curve - receiver operating characteristic.

Secondary Outcome:

Predictive power of variations in pulse pressure during a passive leg lifting test. To find out how well this test predicted preload responsiveness, we ran it through a receiver operating characteristic curve study.

Statistical analysis:

I used SPSS v26 (IBM Inc., Chicago, IL, USA) to

complete the statistical analysis. The two groups were compared using an unpaired Student's t-test for quantitative data, which were provided as means and standard deviations (SD). We utilized the Chi-square test to look at the qualitative variables that were given as frequencies and percentages. The definition of a result that was statistically significant was a two-tailed P-value ≤ 0.05 .

3. Results

Table 1. Baseline patient characteristics of the studied groups.

		RESPONDERS GROUP (PLR+) (N=23)	NON-RESPONDERS GROUP (PLR-) (N=37)	P VALUE
AGE(YEARS)		62.78 $\pm$ 10.29	65.35 $\pm$ 11.65	0.376
SEX	Male	14(60.87%)	25(67.57%)	0.600
	Female	9(39.13%)	12(32.43%)	
IDEAL BODY WEIGHT(KG)		66.26 $\pm$ 6.70	65.57 $\pm$ 7.85	0.717
TYPE OF SHOCK	Cardiogenic	0(0%)	1(1.7%)	0.237
	Hypovolemic	6(10%)	4(6.7%)	
	Septic	17(28.3%)	32(53.3%)	
MUSCLE RELAXATION	Yes	15(25%)	27(45%)	0.527
	No	8(13.3)	10(16.7%)	

PLR:passive leg raising, p-value statistically significant at <0.05 .

None of the general patient characteristics were significantly different between both groups, (table 1; figures 1&2).

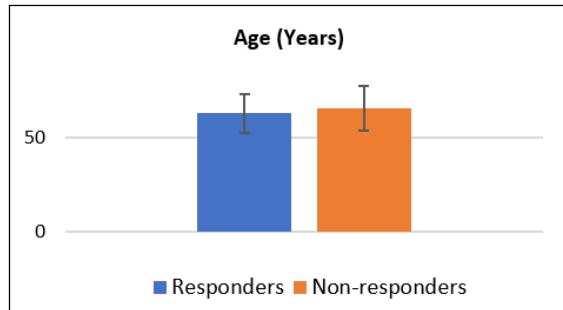


Figure 1. Age of the studied groups.

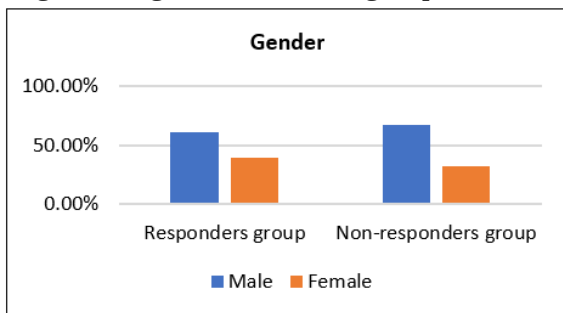


Figure 2. Sex of the studied groups.

Table 2. Heart rate of the studied groups.

	RESPONDERS GROUP (N=23)	NON-RESPONDERS GROUP (N=37)	P VALUE
BASELINE1	102.04 $\pm$ 11.33	106.70 $\pm$ 7.24	0.087
PLR	100.70 $\pm$ 10.11	106.30 $\pm$ 7.10	0.025*
BASELINE2	101.74 $\pm$ 10.87	106.41 $\pm$ 7.29	0.077
TVC	103.04 $\pm$ 11.57	107.0 $\pm$ 8.04	0.151
CHANGE IN HR DURING PLR	1.35 $\pm$ 1.34	0.41 $\pm$ 0.55	0.003*
CHANGE IN HR DURING TVC	1.30 $\pm$ 0.93	0.68 $\pm$ 0.88	0.013*

PLR:Passive leg raising, TVC: Tidal volume challenge, *:Significantly different as P-value ≤ 0.05 .

Heart rate was insignificantly different at

baseline1, baseline2 and TVC between both groups. It was significantly lower at PLR in responders group than non-responders group and significantly higher at TVC in responders group than non-responders group (P-value <0.05), (table 2; figures 3).

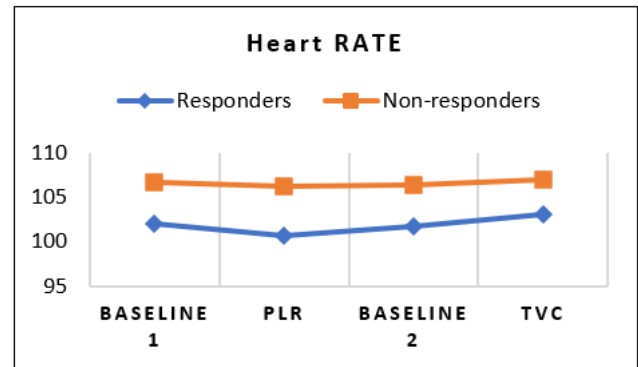


Figure 3. Heart rate of the studied groups.

Table 3. SAP, DAP & MAP of the studied groups.

PARAMETER	GROUP	BASELINE1	PLR	BASELINE2	TVC
SAP	Responders	97.04 $\pm$ 7.05	100.39 $\pm$ 7.48	97.35 $\pm$ 7.18	95.26 $\pm$ 6.87
	Non-responders	93.35 $\pm$ 7.60	94.22 $\pm$ 7.35	93.70 $\pm$ 7.51	91.86 $\pm$ 7.46
	P value	0.062	0.003*	0.066	0.078
DAP	Responders	56.83 $\pm$ 7.51	60.61 $\pm$ 7.93	57.13 $\pm$ 7.59	55.04 $\pm$ 7.39
	Non-responders	54.46 $\pm$ 7.28	55.43 $\pm$ 7.24	54.81 $\pm$ 7.22	52.97 $\pm$ 7.16
	P value	0.236	0.015*	0.247	0.291
MAP	Responders	70.26 $\pm$ 7.21	73.82 $\pm$ 7.70	70.57 $\pm$ 7.30	68.48 $\pm$ 7.06
	Non-responders	67.27 $\pm$ 7.44	68.24 $\pm$ 7.29	67.62 $\pm$ 7.36	65.78 $\pm$ 7.30
	P value	0.129	0.008*	0.137	0.162

SAP:Systolic arterial pressure, DAP:Diastolic arterial pressure, MAP:Mean arterial pressure, PLR:Passive leg raising, TVC:Tidal volume challenge, *:Significantly different as P-value ≤ 0.05 .

Table 4. PPV of the studied groups.

	RESPONDERS GROUP (N=23)	NON-RESPONDERS GROUP (N=37)	P-VALUE
BASELINE1(PPV 0)	11.74 $\pm$ 3.82	7.65 $\pm$ 2.89	$<0.001^*$
PLR(PPV1)	8.43 $\pm$ 2.83	7.03 $\pm$ 2.24	0.05*
BASELINE2(PPV2)	11.57 $\pm$ 3.75	7.49 $\pm$ 2.67	$<0.001^*$
TVC(PPV3)	16.30 $\pm$ 4.75	9.65 $\pm$ 3.33	$<0.001^*$
CHANGE IN PPV AFTER PLR (DELTA PPV1) (PPV1-PPV0)	3.30 $\pm$ 1.43	0.62 $\pm$ 0.86	$<0.001^*$
CHANGE IN PPV AFTER TVC (DELTA PPV3) (PPV3-PPV2)	4.74 $\pm$ 1.32	2.16 $\pm$ 1.17	$<0.001^*$

PPV:Pulse pressure variation, PLR:Passive leg raising, TVC:Tidal volume challenge, *:Significantly different as P-value ≤ 0.05 .

PPV was significantly higher at baseline1, baseline2, PLR and TVC in responders group than non-responders group. Delta change in PPV was significantly higher after TVC and PLR in responders group than non-responders group, (table 4; figure 5).

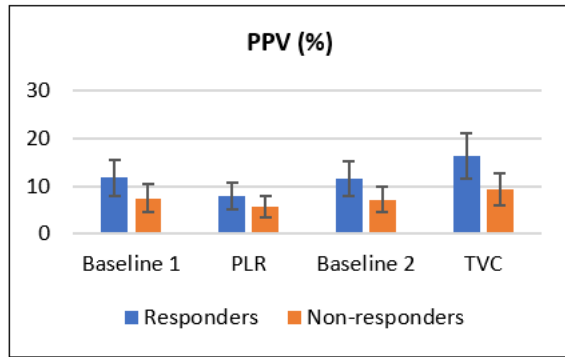


Figure 5. PPV of the studied groups.

Table 5. Diagnostic ability of various variables to predict fluid responsiveness.

VARIABLE	P-VALUE	AUC 95% CL	SENSITIVITY %	SPECIFICITY %	CUT-OFF	*PPV	*NPV
PPV0	<0.001*	0.797 (0.682-0.913)	69.6	73	≥10	68	82.9
PPV1	0.05*	0.626 (0.478-0.774)	---	---	---	---	---
Delta PPV1	<0.001*	0.939 (0.884-0.995)	87	86.5	≥2	83.3	91.7
PPV3	<0.001*	0.877 (0.782-0.971)	87	83.8	≥12	84	94.3
Delta PPV3	<0.001*	0.922 (0.846-0.999)	95.7	91.9	≥4	88	97.1

AUC:Area under the curve, *PPV:Positive predictive value, NPV:Negative predictive value, PPV0:Baseline PPV at 6 ml/kg tidal volume, PPV1:PPV at PLR, Delta PPV1:change in PPV during PLR, PPV3:PPV during TVC at 8 ml/kg tidal volume, Delta PPV3:change in PPV during TVC, *:Significantly different as P-values≤0.05.

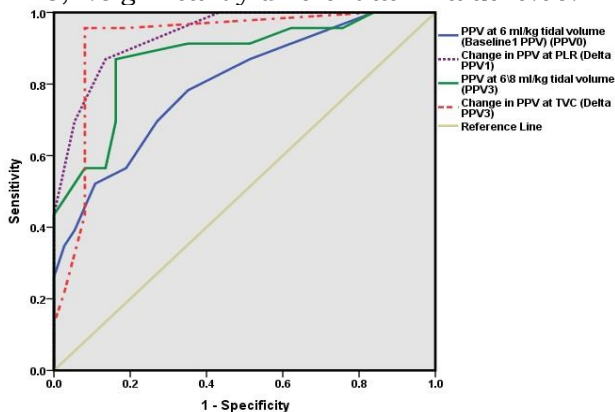


Figure 6. Receiver-operating characteristic curve comparing the ability of various variables to discriminate between fluid responders and non-responders.

With the best cutoff value of 10% or higher, the responders group had a considerably higher PPV at 6ml TV(Baseline1) (PPV0). The specificity was 73% and the area under the ROC curve was 0.797, while the sensitivity was 69.6%.

The responders group showed a considerably larger change in PPV after PLR (Delta PPV1) with the optimum cutoff value of ≥%. With a sensitivity of 87% and a specificity of 86.5%, the area under

the receiver operating characteristic curve was 0.939.

With a best cutoff value of ≥12%, the responders group had a considerably higher PPV at 8ml TV (PPV3). With a sensitivity of 87% and a specificity of 83.8%, the area under the receiver operating characteristic curve was 0.877.

The group of responders with the best cutoff value of ≥4% had a considerably larger change in PPV following TVC (Delta PPV3). With a sensitivity of 95.7% and a specificity of 91.9%, the area under the receiver operating characteristic curve was 0.922,(table 5; figure 6).

4. Discussion

A good indicator of fluid responsiveness, PPV is both simply applied and among the most dynamic indices.⁹

Conditions where pulse pressure change might be difficult to interpret include low respiratory compliance, arrhythmia, low tidal volume ventilation, and spontaneous breathing.¹⁰

In the current study, there were 23 patients (38.3%) who had a ≥10% increase in cardiac output with PLR considered as the responder group, and 37 patients (61.7%) who had a <10% increase in cardiac output considered as the non-responder group.

Comparable with the current study, Kaur et al.,¹¹ showed that out of 67 patients, (67.2% were fluid responders, while Mallat et al.,¹² found that 60.7% were fluid responders.

We also found that out of the 60-patients included in the current study, 80.7 % (49-patients) had septic shock compared to 16.7% (10-patients) and 1.7% (1-patient) for hypovolemic shock and cardiogenic shock respectively with no statistically significant difference regarding fluid responsiveness between them.

Elsayed et al.,¹³ It was discovered that PPV at Vt 6mL/kg IBW demonstrated strong predictive capabilities, with cutoff values of ≥10.5%, an area under the curve of 0.870, and a sensitivity and specificity of 87.5% and 83.3%, respectively. Possible explanations for the discrepancy in predictive value include the varied sample sizes' average PPV. Elsayed et al.,¹³ used a sample of patients with larger mean than us (16.81±7.3).

Shi et al.,⁹ proved that PPV at 6mL/kg IBW allowed for the evaluation of preload responsiveness with cutoff values of 6.5% or higher, an area under the curve of 0.850, a sensitivity of 74%, and a specificity of 79%.

De Backer et al.,¹⁴ and Myatra et al.,⁶ found that PPV can't predict fluid responsiveness at low tidal volume ventilation lower than 8mL/kg IBW. This difference in predictive value may be because of our larger mean of PPV 11.74±3.82, which compared to 6.2(3.3–15.1) and 8±3 in De Backer

et al.,¹³ and Myatra et al.,⁶ respectively.

Our patients' baseline PPV at 6 mL/kg IBW was somewhat predictive, but after receiving TVC, the accuracy of the predictions improved dramatically. Reliability of PPV improves with tidal volume challenge because intrathoracic pressure cannot be significantly changed with a low tidal volume of less than 8 mL/kg.¹

Myatra et al.,⁶ discovered that the predictive value of the change in PPV during TVC was stronger, with a sensitivity of 94%, a specificity of 100%, and cutoff values of 3.5%. The area under the curve was 0.99. Potentially attributable to variations in sample size, sensitivity, and specificity have been found to vary. Sixty examples were utilized, as opposed to thirty in Myatra et al.⁶

Shi et al.,¹⁰ found that a preload responsiveness assessment with an area under the receiver operating characteristic (AUROC) curve of 0.94, sensitivity of 98%, and specificity of 86% was achieved when an absolute change in PPV $\geq 3.5\%$ occurred during a TVC.

In Elsayed et al.,¹³ In the study, participants had a notable rise in PPV when administered a tidal volume challenge ranging from 6-8 mL/kg IBW. The optimal cutoff value was 3.5, and the area under the curve was 0.95. The sensitivity and specificity were 93.8% and 93.9%, for the participants.

When comparing the groups that responded and those that did not, we found no statistically significant change in lung compliance. Identical outcomes were detailed by Elsayed et al.,¹³; Myatra et al.,⁶ and Shi et al.¹⁰

Shi et al.,¹⁰ discovered that both the responder and non-responder groups' lung compliance reduced following TVC. They may have accounted for this variation by placing patients suffering from acute respiratory distress syndrome in a prone posture.

Predictive value of PPV in individuals with acute respiratory distress syndrome is minimal due to reduced transmission of airway pressure and lower intrathoracic pressure in patients with low lung compliance.^{7,1,8,1}

PPV is an unreliable predictor of fluid responsiveness when lung compliance is below 30 mL/cm H₂O compared to when it is at least 30 mL/cm H₂O. In our investigation, responders exhibited a notable reduction in PPV during PLR (Δ PPV1), with cutoff values of $< -2\%$, an area under the curve of 0.939, a sensitivity of 87%, and a specificity of 86.5%.⁸

The primary benefits of the PLR test include the lack of necessity for fluid infusion and the swiftly reversible hemodynamic effects.¹⁵

By transferring around 300 milliliters of blood from the lower extremities to the right side of the heart, PLR can simulate a fluid challenge.¹⁵

Taccheri et al.,¹⁶ showed similar results with higher sensitivity and specificity. In their study, they found that in mechanically ventilated patients with a tidal volume of 6 mL/kg, PLR-induced PPV reduction accurately predicted fluid responsiveness (AUC=0.98) with a cutoff value $\leq -2\%$ (sensitivity of 93%, specificity of 93%). This difference may be due to our larger sample (60 patients) compared to (30 patients) in his study, which is twice as many as their patients.

Mallat et al.,¹² discovered that a 0.92 area under the curve, 89% sensitivity, 87% specificity, and 2.5% threshold values for the predictive value of the change in PPV during PLR were superior. Our study's definition of preload responsiveness was based on changes in cardiac output caused by PLR, whereas his study's definition was based on volume expansion. This could explain the discrepancy.

Hamzaoui et al.,¹⁷ conducted a study on 56 patients who were ventilated with a low tidal volume (6 mL/kg IBW) and discovered that the absolute change in PPV during PLR was not a very reliable indicator of fluid responders or non-responders, with a sensitivity of 87% and a specificity of 68%. The study also used a cutoff value of 1% and an area under the curve of 0.78. The fact that his research included individuals whose breathing cycles occurred naturally could account for this discrepancy.

Limitations: In order to identify patients who responded to fluids, we did not rely on volume expansion. But in the past, while evaluating the efficacy of preload responsiveness tests, a postural maneuver (PLR) was substituted for fluid delivery.

There are other constraints to using PPV during low tidal volume ventilation, such as the existence of cardiac arrhythmias and spontaneous breathing, which the "tidal volume challenge" cannot resolve.

We need more research to compare our results with those of patients whose baseline PPV was outside of the gray zone (8-12).

4. Conclusion

The changes in PPV variation can reliably predict preload responsiveness when PPV increases to ≥ 4 during TVC and when PPV decreases to ≥ 2 during PLR ventilated critically sick patients with a low tidal volume of 6 mL/kg IBW or less. Both tests can be simply used with no need for continuous cardiac output monitoring to assess their effects.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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