



Ability of PEEP induced lung-heart interaction to assess volume responsiveness in perioperative setting

Mogućnost procjene odgovora na nadoknadu tekućine pomoću interakcija pluća-srce uzrokovanim promjenama pozitivnog tlaka na kraju ekspirija

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Descriptors

HEMODYNAMIC MONITORING; PPV;
VOLUME RESPONSIVENESS; PEEP;
PASSIVE LEG RAISING

Deskriptori

HEMODINAMSKI NADZOR; PPV; PEEP;
PASIVNO ODIZANJE NOGU;
PROCJENA VOLUMNOG STATUSA

SUMMARY. *Goal:* Various monitoring methods have been used throughout history to discriminate between volume responsive and volume non-responsive patients: static parameters, dynamic parameters, and maneuver provoked parameters (positive end expiratory pressure (PEEP) induced central venous pressure (CVP) change and passive leg raise (PLR) induced stroke volume index (SVI) change). Goal of this study is to assess whether PEEP induced lung-heart interactions may be used to reliably assess volume responsiveness in mechanically ventilated patients after major abdominal surgery. *Methods:* 50 sedated and relaxed mechanically ventilated patients with 5 mbar of PEEP admitted to a mixed surgical ICU were measured mean arterial pressure (MAP), heart rate (HR), CVP, cardiac index (CI), stroke volume index (SVI) and pulse pressure variation (PPV) at 5 timepoints – baseline, 3 minutes at PEEP of 15 mbar, after return of PEEP to 5 mbar, while performing PLR maneuver of 3-minute duration and after return to supine position. Receiver operator characteristic (ROC) curves were used to assess predictive ability of measured parameters to assess volume responsiveness defined as PLR induced SVI increase $\geq 7\%$. *Results:* Volume responsive patients had lower baseline CVP and SVI, and higher PPV. Both responders and non-responders had a statistically significant PEEP induced drop in SVI and MAP, with an increase of PPV and CVP. During PLR, both groups demonstrated a significant increase in MAP and CVP and decrease in PPV, but only volume responders had a significant increase of CI and SVI and heart rate decrease. ROC curves were used to assess predictive ability of parameters to assess volume responsiveness, and only PPV at 5 mbar PEEP (AUC=0.88), PPV at 15 mbar PEEP (AUC=0.83) and PLR induced HR drop (AUC=0.83) may be considered reliable in clinical practice. *Conclusions:* PEEP induced hemodynamic changes do not predict volume responsiveness reliably in comparison to PPV or PLR induced HR drop. Further studies are needed in hemodynamically unstable or patients with ARDS.

SAŽETAK. *Cilj:* Kroz povijest su korišteni različite metode procjena odgovora na ekspanziju intravaskularnog volumena: statički parametri, dinamički parametri te parametri provocirani manevrima kao što su porast porast središnjeg venskog tlaka (CVP) uzrokovan povećanjem pozitivnog tlaka na kraju ekspirija (PEEP) ili porast indeksa udarnog volumena srca (SVI) uzrokovan pasivnim odizanjem nogu (PLR). Cilj ovog istraživanja je procijeniti da li je porast CVP uzrokovan povećanjem PEEP pouzdan prediktor odgovora na nadoknadu volumena nakon velikih abdominalno kirurških zahvata. *Metode:* 50 sediranih i miorelaksiranih mehanički ventiliranih bolesnika primljenih u jedinicu intenzivne medicine nakon elektivnog abdominalno kirurškog zahvata izmjeren je srednji arterijski tlak (MAP), frekvencija srca (HR), CVP, SVI i varijacija pulsog tlaka (PPV) u 5 vremenskih intervala: početni, nakon 3 minute povećanja PEEP sa 5 na 15 mbar, nakon spuštanja PEEP na 5 mbar, nakon 3 minute PLR i nakon povratka nogu u vodoravan položaj. Porast SVI $\geq 7\%$ smatra se pozitivnim odgovorom na volumnu ekspanziju, a osjetljivost i specifičnost parametara procijenjena je ROC krivuljama. *Rezultati:* Volumno responzivni bolesnici imali su niži početni CVP i SVI i viši PPV. Obje skupine imale su statistički značajan pad SVI i MAP nakon povećanja PEEP, sa porastom PPV i CVP. Tijekom PLR obje skupine imale su značajan porast MAP i CVP i pad PPV, ali samo responzivni pacijenti imali su značajan porast SVI i indeksa srca (CI). Nakon provedene analize ROC krivulja Samo PPV pri 5 mbar PEEP (AUC=0.88), PPV na 15 mbar PEEP (AUC=0.83) i PLR uzrokovan pad HR (AUC=0.83) mogu se smatrati pouzdanim u kliničkoj praksi. *Zaključci:* Hemodinamske promjene uzrokovane porastom PEEP ne mogu se smatrati pouzdanima u procjeni volumnog statusa bolesnika u odnosu na PPV ili PLR induciran pad frekvencije srca. Daljna istraživanja potrebna su na nestabilnim bolesnicima ili bolesnicima sa ARDS.

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Introduction

Judicious intravenous fluid administration is one of the cornerstones of successful patient management in the perioperative period. Goal that anesthesiologists and critical care physicians strive to achieve is to optimize stroke volume (and subsequently cardiac output) by targeting the inflection point of the Frank-Starling curve, i.e. administer just enough fluid to sufficiently increase stroke volume while keeping the ventricular filling pressure within acceptable limits¹. Of course, stroke volume may also be increased by using inotropic drugs to increase ventricular contractility, but their use has been linked to an increase in 90-day mortality² and their use is justified only when adequate cardiac output cannot be achieved via volume expansion alone.

Excessive fluid administration is linked to tissue edema, anastomotic leakage, increase of extravascular lung water and intra-abdominal pressures and an increase in in-hospital mortality^{3,4}.

Because of all the afore mentioned reasons, various hemodynamic monitoring methods have been devised over the years to help clinicians hemodynamically stabilize the patient and assess volume responsiveness. Dynamic variables such as pulse pressure variation (PPV, measured as difference between end-inspiratory and end-expiratory pulse pressures), stroke volume variation (SVV, difference between end-inspiratory and end-expiratory stroke volume calculated by arterial waveform analysis) and respiratory cycle variation of inferior vena cava (IVC) diameter (measured with ultrasound) are more sensitive and specific than passive variables^{5–8} (such as central venous pressure and pulmonary capillary wedge pressure) but require specialized monitoring equipment (PPV and SVV) and may be operator dependent which might affect its reliability⁹ (ultrasound). Also, PPV and SVV are applicable only in mechanically ventilated patients with tidal volumes larger than 6–8 ml/kg and are dependent on equal duration of diastole during each heartbeat (i.e., making patients with atrial fibrillation and, depending on the used algorithm, presence of premature beats, unsuitable for such monitoring).

Fluid challenge tests performed by measurement of stroke volume change after intravenous administration of crystalloid or colloids is the most reliable method of fluid responsiveness assessment but may provoke adverse effects in non-responsive patients (with most extreme case being cardiac decompensation and pulmonary edema in patients with left heart failure). Passive leg raising maneuver (PLR) mimics exogenous fluid challenge by increasing preload for approximately 250 ml, which results with stroke volume increase in volume responsive patients of more than 10–15% if the patient was in semi-recumbent position before PLR¹⁰, or more than 7% if the patient was supine¹¹. It

must be noted that changes induced by PLR are rapid and reversible, and therefore systems that do not measure changes in stroke volume rapidly (such as thermodilution) are not as reliable as those which record instantaneous changes¹² (such as arterial waveform analysis, esophageal doppler or stroke volume calculated via echocardiography).

Positive end expiratory pressure (PEEP) is used in mechanically ventilated patients to reduce incidence of atelectotrauma, decrease shunting (especially in dependent areas of the lung) and improve oxygenation¹³. However, it also increases intrathoracic pressure and may decrease preload and subsequently stroke volume^{14,15}, especially in volume depleted patients. Because of that, PEEP induced lung-heart interactions have been suggested as an alternative, readily available and cost effective method of volume responsiveness assessment which do not need specialized monitoring equipment^{11,16}.

Goal of this study is to test the hypothesis that PEEP induced hemodynamic changes are as reliable as pulse pressure variation in discriminating between volume responsive and volume non-responsive patients.

Patients, materials, and methods

By design, this study was monocentric, prospective, and single blinded. Institutional ethics board approved the study protocol, and it was registered at www.clinicaltrials.gov with identifier NCT04191408.

50 mechanically ventilated patients older than 18 years admitted during a two month window to a mixed surgical intensive care unit (ICU) after major abdominal surgery with invasive monitoring of arterial blood pressure (radial artery) and central venous pressure (either subclavian or jugular approach) were included in this study. Patients were explained the study protocol and signed the informed consent form at anesthetic evaluation prior to surgery. Patient anonymity and data confidentiality was preserved by assigning computer randomized identification numbers.

Exclusion criteria were pregnancy, atrial fibrillation (for pulse pressure variation measurements), history of heart failure with left ventricle ejection fraction less than 50%, presence of diastolic dysfunction grade III or IV, moderate or worse chronic obstructive pulmonary disease (GOLD III or IV, forced expiratory volume during the first second < 80% of predicted value) and restrictive lung disease with total lung capacity < 80%.

At ICU admission patients were sedated with midazolam 0.1 mg/kg BW and rocuronium 0.6 mg/kg BW was used as muscle relaxant. Mechanical ventilation was initiated using volume controlled mode with decelerating flow pattern (IPPV with AutoFlow, Dräger Evita XL) with tidal volume set to 8 ml/kg ideal body weight (as calculated using the Devine formula where

$IBW_{men} = 50 \text{ kg} + 2.3 \text{ kg} (\text{height, in} - 60)$ and $IBW_{women} = 45.5 \text{ kg} + 2.3 \text{ kg} (\text{height, in} - 60)$, PEEP set to 5 mbar and frequency and I:E ratio set to maintain end-tidal CO_2 between 4.0 and 5.0 kPa with time of expiration > 3 respiratory constants.

Patients were supine, and before measurements took place, pressure transducers were zeroed to atmospheric pressure at mid-axillary line level. No fluid was administered before or during measurements, and none of the patients were receiving inotropes or vasopressors.

Hemodynamic measurements were performed at 5 time points: at baseline, after increasing PEEP from 5 to 15 mbar (PEEP challenge test with duration of 3 minutes), after reverting to baseline PEEP levels, while performing passive leg raise (PLR) maneuver for 3 minutes, and after reversal to supine position.

PLR was performed from supine position with a 45° angle, and stroke volume index increase $\geq 7\%$ during PLR was considered cut-off value which differentiates between volume responders and non-responders, as has previously been suggested^{11,17}.

Hemodynamic parameters were measured with continuous cardiac output monitor (Nihon Kohden Vismo, Nihon Kohden, Tokyo, Japan) using the minimally invasive pulse wave transit analysis algorithm with commercial name *esCCO* (estimated continuous cardiac output). Measured values were systolic, diastolic, and mean arterial pressures, heart rate, central venous pressure (CVP), pulse pressure variation, cardiac index (CI), and stroke volume index (SVI).

Statistical analysis

Data are presented as tables and charts. Normality of distribution was tested using Shapiro-Wilk test and continuous variables are presented as mean and standard deviation (SD) for normally distributed values and median and interquartile range (IQR) for values with non-normal distribution. Independent continuous variables were tested for statistical significance using Student's t test for independent samples or Mann-Whitney U test, depending on distribution of data. Dependent continuous variables were tested for statistical significance using Student's t test for paired samples for normally distributed data and Wilcoxon rank test for data that is not normally distributed. Categorical variables were tested for statistical significance using Fisher's exact test.

Correlation between PLR induced increase in SVI and measured hemodynamic parameters was tested for statistical significance using Spearman's rank correlation coefficient (ρ).

Sensitivity and specificity were assessed using receiver operating characteristic (ROC) curves, with 95% confidence intervals calculated using DeLong method. Optimal cut-off values were calculated using

Youden index. Area under the curve (AUC) higher than 0.7 is considered clinically acceptable, while AUC > 0.8 is considered excellent, as previously suggested¹⁸.

P values <0.05 were considered statistically significant. Software used for statistical analysis and data visualization was R v 3.6.1¹⁹ with pROC library²⁰, jamovi v1.1.2²¹ and JASP v0.13²².

Results

Out of 50 study participants, 19 were volume responsive, while 31 were not volume responsive.

There were no significant differences in patient age, body mass index, body surface area, ASA status, tidal volume, or mean airway pressure between groups. Patients that were non-responsive had significantly high-

TABLE 1. EPIDEMIOLOGICAL DATA AND BASELINE VENTILATION AND HEMODYNAMIC DATA, STUDENT'S T TEST FOR INDEPENDENT SAMPLES OR MANN WHITNEY U TEST, DEPENDING ON DISTRIBUTION OF DATA. FISHER'S EXACT TEST FOR CONTINGENCY TABLES.

	Responder	Non-responder	p
ASA	3 (3–3)	3 (3–3)	0.391
Age (y)	63 (60–73)	67 (60–74)	0.555
Gender (female/male)	9/10	10/21	0.372
BMI (kg/m ²)	27.1 ± 3.8	28.3 ± 4.4	0.334
BSA (m ²)	1.9 ± 0.2	2.0 ± 0.4	0.583
Mean airway pressure (mbar)	9.6 ± 1.2	9.8 ± 1.3	0.279
Tidal volume (ml)	514 ± 87	511 ± 83	0.921
Baseline MAP (mmHg)	90 ± 16	97 ± 17	0.210
Baseline HR (bpm)	82 (67–95)	74 (60–88)	0.142
Baseline CI (l/min/m ²)	2.9 ± 0.7	3 ± 0.8	0.593
Baseline SVI (ml/b/m ²)	36 ± 9	41 ± 7	0.035
Baseline PPV (%)	17 (12–21)	7 (5–11)	<.001
Baseline CVP (mmHg)	9.2 ± 2.9	11.1 ± 3.6	0.049

TABLE 2. HEMODYNAMIC CHANGES AT 15 MBAR PEEP CHALLENGE (P VALUES COMPARED TO BASELINE AT PEEP OF 5 MBAR) – STUDENT'S T TEST FOR PAIRED SAMPLES OR WILCOXON RANK TEST, DEPENDING ON DISTRIBUTION OF DATA.

	Responder	Non-responder	P _{respon}	P _{non-res}
MAP (mmHg)	82 ± 18	92 ± 18	<.001	0.004
HR (bpm)	83 (68–100)	74 (61–86)	0.10	0.925
CI (l/min/m ²)	2.8 ± 0.8	2.9 ± 0.7	0.20	0.053
SVI (ml/b/m ²)	35 ± 9	40 ± 8	0.002	0.039
PPV (%)	22 (16–26)	11 (7–14)	<.001	0.002
CVP (mmHg)	13 ± 2.6	14.4 ± 3.6	<.001	<.001

TABLE 3. HEMODYNAMIC CHANGES BEFORE AND DURING PLR MANOUVER – STUDENT’S T TEST FOR PAIRED SAMPLES OR WILCOXON RANK TEST, DEPENDING ON DISTRIBUTION OF DATA

	Responder			Non-responder		
	Before	During	p	Before	During	p
MAP (mmHg)	84 (78–94)	88 (84–102)	<.001	95.8 ± 17.9	100.2 ± 17.4	<.001
HR (bpm)	79 (68–99)	71 (66–88)	0.001	69 (62–90)	73 (62–90)	0.113
CI (l/min/m ²)	2.7 (2.3–3.2)	2.9 (2.5–3.3)	<.001	3.0 ± 0.8	3.0 ± 0.8	0.274
SVI (ml/b/m ²)	35 (29–39)	38 (34–43)	<.001	42 (36–46)	42 (37–45)	0.329
PPV (%)	20.7 ± 9.8	18.3 ± 11.8	0.048	9 (6–13)	12 (11–14)	0.012
CVP (mmHg)	9 (8–11)	11 (8–12)	0.002	11 (10–13)	12 (10–14)	<.001

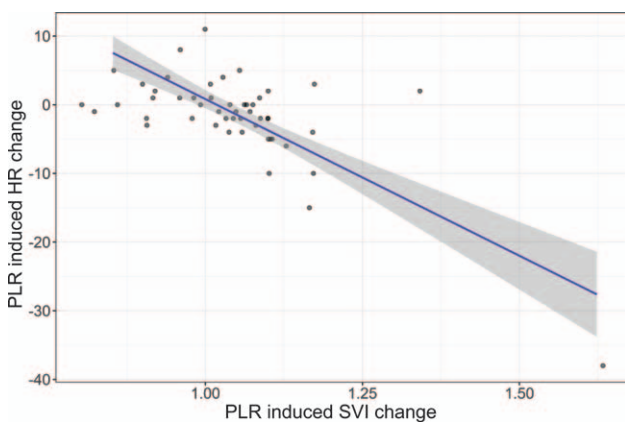


FIGURE 1. SCATTER PLOT SHOWING CORRELATION BETWEEN PLR INDUCED HR CHANGE AND PLR INDUCED SVI CHANGE (SPEARMAN’S RANK CORRELATION TEST, $\rho=-0.62$, $P<.001$)

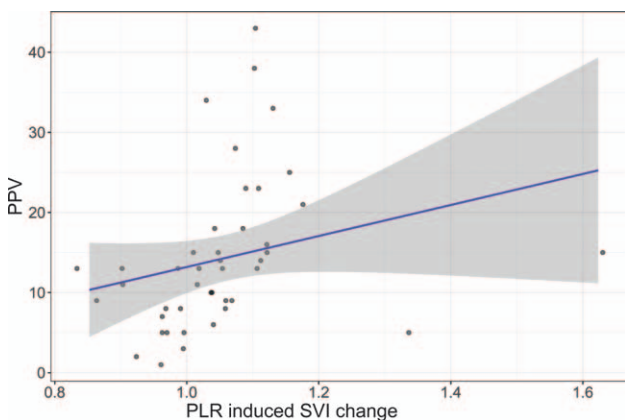


FIGURE 2. SCATTER PLOT SHOWING CORRELATION BETWEEN PPV AT 5 MBAR PEEP AND PLR INDUCED SVI CHANGE (SPEARMAN’S RANK CORRELATION TEST, $\rho=0.63$, $P<.001$)

er CVP and SVI and lower PPV compared to responders. There were no statistically significant differences in other hemodynamic parameters (MAP, HR, CI) between groups (Table 1).

During PEEP challenge, both groups had a statistically significant drop in SVI and MAP, coupled with an increase of PPV and CVP. There were no statistically significant changes in CI and HR values (Table 2).

TABLE 4. PREDICTIVE VALUE OF CVP, PPV, PEEP INDUCED CHANGE IN CVP, PEEP INDUCED CHANGE IN HR, PEEP INDUCED CHANGE IN MAP, PLR INDUCED CHANGE IN CVP, PLR INDUCED CHANGE IN HR AND PLR INDUCED CHANGE IN MAP IN ASSESSING VOLUME RESPONSIVENESS.

Parameter	AUC (95%CI)	Cut-off (sens%, spec%)
CVP	70.2 (55.2–85.2)	10 mmHg (52.6, 77.4)
PPV	88.3 (76.8–99.9)	14% (83.3, 88.0)
PEEP _{CVP}	57.6 (42.4–72.9)	+3 mmHg (94.1, 16.1)
PEEP _{HR}	56.9 (40.5–73.2)	-1 bpm (42.1, 74.2)
PEEP _{MAP}	66.8 (50.9–82.7)	-7mmHg (52.7, 80.7)
PEEP _{PPV}	82.8 (70.7–95.0)	18% (72.2, 89.3)
PLR _{CVP}	49.5 (32.9–66.0)	+3 mmHg (10.5, 100)
PLR _{HR}	83.2 (70.9–95.5)	-2 bpm (78.9, 77.4)
PLR _{MAP}	58.2 (42.1–74.2)	+2 mmHg (89.5, 32.3)

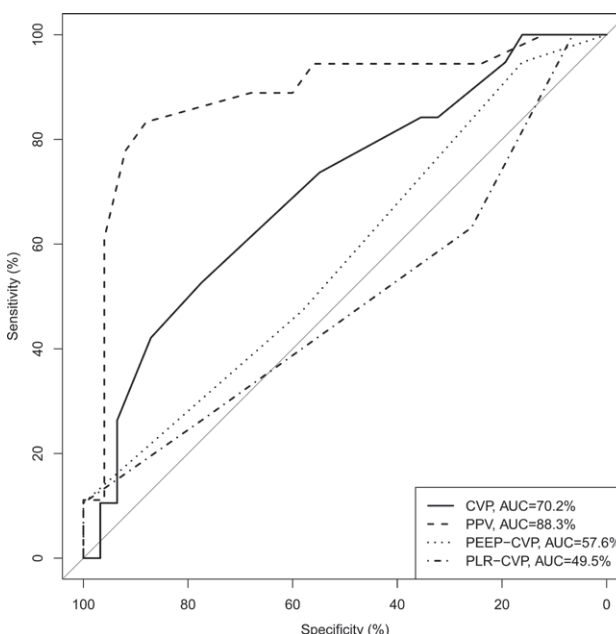


FIGURE 3. ROC CURVES DEPICTING SENSITIVITY AND SPECIFICITY OF PEEP INDUCED CHANGE IN CVP, CVP WHILE PERFORMING PLR, ABSOLUTE VALUE OF CVP AND PPV IN PREDICTING PLR INDUCED INCREASE OF SVI OF MORE THAN 7%.

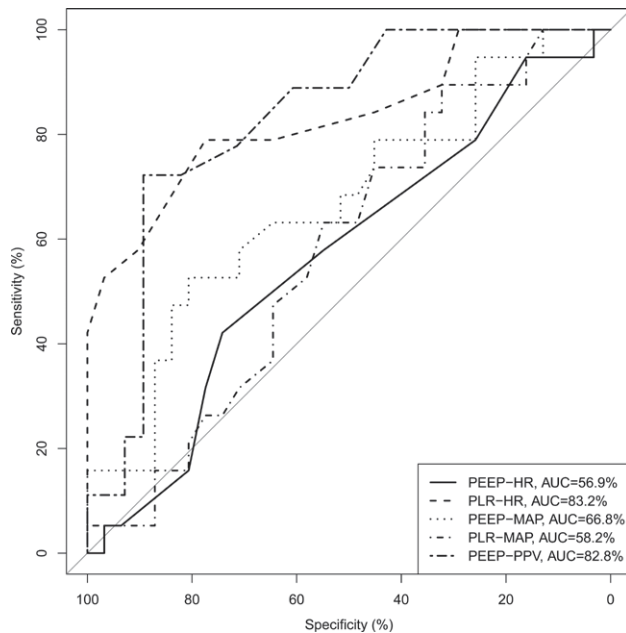


FIGURE 4. ROC CURVES DEPICTING SENSITIVITY AND SPECIFICITY OF PEEP INDUCED CHANGES IN MAP, PPV AND HR AND PLR INDUCED CHANGES IN HR AND MAP IN PREDICTING PLR INDUCED INCREASE OF SVI OF MORE THAN 7%.

Both responders and non-responders showed a statistically significant increase of MAP, CVP and decrease of PPV during PLR, but only volume responsive patients had a significant increase of CI and SVI (Table 3).

Only PLR induced drop in HR ($\rho=-0.62$, $p<.001$) and PPV at both PEEP levels (5 mbar $\rho=0.63$, $p<.001$; 15 mbar $\rho=0.52$, $p<.001$) showed moderate but statistically significant correlation to PLR induced SVI increase (Figures 1 and 2).

Only PPV at baseline PEEP, PPV during PEEP challenge and PLR induced drop in HR showed AUC higher than 0.8 (88.3%, 82.8%, and 83.2% respectively), while CVP during PLR showed worst predictive value in assessing volume responsiveness (AUC 49.5%) – table 4 and figures 3 and 4.

Discussion

Results of this study suggest that in our cohort of patients PEEP induced hemodynamic changes are not as reliable as PPV in predicting volume responsiveness in fully sedated mechanically ventilated patients after major abdominal surgery.

Compared to a similar study performed on 20 cardiac surgery patients by Geerts and al¹¹ which showed outstanding reliability of PEEP induced change in CVP to predict volume responsiveness (AUC for CVP_{PEEP} of 0.99, SVV of 0.90 and CVP of 0.85), there were certain differences in study participants and protocol. In this study, volume responsiveness was assessed by measuring changes in SVI in contrast to changes in CO which

were used in the mentioned study. Due to baroreceptor reflex, rapid volume expansion and increase of arterial pressure cause a drop in heart rate (and subsequently increase of SVI, calculated by dividing CI by heart rate) which was also present in our patients which were volume responsive compared to those that were not. Also, while PAC is still widely used in hemodynamic monitoring, it is an intermittent technique (including continuous cardiac output monitors which calculate averages) and its ability to capture rapid changes in CO or SV, is not as good as those provided by continuous arterial waveform analysis²³ or *esCCO* which was used in our study. It must be noted that none of the patients included in this study received vasoactive drugs, and none of them had confounders which might affect airway pressure effect on hemodynamics – chest drains or opened pleura (which is usually done when performing interior mammary artery graft preparation for coronary artery bypass graft surgery). These reasons might explain different obtained results. Also, in that study, dynamic parameter measured to assess volume responsiveness was SVV, compared to PPV which we used, but these two methods are equally reliable (AUC of 0.87 for SVV vs 0.86 for PPV, as reported by Cannesson et al⁵) and should not affect interpretation of results. Our patients were also ventilated with lower tidal volumes (8 ml/PBW compared to 8 ml/kg actual body weight) due to ethical board requirements and implemented policy of lung protective ventilation²⁴, but even with these lower tidal volumes, we found that PPV was as sensitive and specific as with higher tidal volumes used in other studies^{5,7}. We also found that PPV has acceptable reliability (AUC 0.83) to predict fluid responsiveness in patients that are ventilated with higher (15mbar) levels of PEEP, contrary to variation of IVC diameter which has excellent AUC (0.88) for patients that are ventilated with PEEP levels < 5 mbar and TV > 8 ml/kg but much lower AUC (0.70) for patients that are ventilated with PEEP levels > 5mbar and TV < 8ml/kg, as reported by Si et al⁸.

This finding suggests that PPV may be used to guide fluid administration in patients with ARDS that are ventilated using lower tidal volumes, but further studies are needed to confirm these results in ARDS patients which have lower respiratory system compliance compared to our cohort of patients.

In this study we also found that heart rate drop during PLR is present in volume responsive patients, and that it has much higher AUC compared to PEEP induced change of CVP or absolute CVP value before PLR. However, its clinical usefulness in hemodynamically unstable patients (such as those in septic or hemorrhagic shock) is questionable because these patients are usually administered high doses of vasoactive drugs

(mostly catecholamines) which might cause tachycardia due to beta adrenergic agonistic mechanism of action which most of them possess.

Since no special equipment is needed to measure PLR induced changes in heart rate drop, its clinical utility when appropriate hemodynamic monitoring equipment is not available should not be ignored, especially when limited resources are available. Of course, the fact that all the test subjects were hemodynamically stable and were not receiving any vasoactive drugs must be considered when interpreting the obtained results. Similar inexpensive and readily available methods to predict volume responsiveness during PLR maneuver are plethysmographic changes during PLR²⁵ and change of pulse pressure²⁶.

There were certain limitations of this study. Pulse wave transit time analysis cardiac output measurement method (*esCCO*) which was used to perform hemodynamic measurements due to financial constraints is not as accurate in its trending ability of CO changes compared to arterial waveform analysis algorithms (such as Edwards Lifesciences *FloTrac*), although there is contrasting published data regarding clinical utility of *esCCO*^{27,28}. One other conditional limitation is the fact that the patients were hemodynamically stable and without significant cardiac or pulmonary comorbidities, so further studies are needed to further determine clinical utility of these methods.

Conclusion

Results of this study suggest that PEEP induced changes in HR, CVP and MAP are not reliable predictors of volume responsiveness after major abdominal surgery in comparison to pulse pressure variation or PLR induced drop in heart rate.

It must be noted that these patients were hemodynamically stable at baseline, and that in clinical practice, even if a patient is volume responsive, fluid loading is not necessary if the patient is hemodynamically stable. Further studies are needed in hemodynamically unstable and/or patients with ARDS.

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