Slope Analysis for the Prediction of Fluid Responsiveness by a Stepwise PEEP Elevation Recruitment Maneuver in Mechanically Ventilated Patients

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Research

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Abstract

Objective:

Assessment of fluid responsiveness is problematic in intensive care unit patients. Lung recruitment maneuvers (LRM) can be used as a functional test to predict fluid responsiveness. We propose a new test to predict fluid responsiveness in mechanically ventilated patients, analyzing the variations of central venous pressure (CVP) and systemic arterial parameters during a prolonged sigh breath LRM without the use of a cardiac output measuring device.

Design:

Prospective observational cohort study.

Setting:

Intensive Care Unit, Saint-Etienne University Central Hospital.

Patients:

Patients under mechanical ventilation, equipped with invasive arterial blood pressure, CVP, pulse contour analysis (PICCO^{TM}), requiring volume expansion, with no right ventricular dysfunction.

Interventions:

None.

Measurements and Main Results:

CVP, systemic arterial parameters and stroke volume (SV) were recorded during prolonged LRM followed by a 500mL fluid expansion to asses fluid responsiveness. 25 patients were screened, 18 patients were analyzed. 9 patients were responders to volume expansion and 9 were not. Evaluation of hemodynamics parameters suggested the use of a linear interpolation model. Slopes for systolic aortic pressure, pulse pressure (PP), CVP and SV were all significantly different between responders and non-responders during pressure increase phase of LRM (STEP-UP) ($p = 0.022$, $p = 0.014$, $p= 0.006$ and $p = 0.038$, respectively). PP and CVP slopes during STEP-UP were strongly predictive of fluid responsiveness with an AUC of 0.926 (95% CI, 0.78 to 1.00), sensitivity = 100%, specificity = 89% and an AUC = 0.901 (95% CI, 0.76 to 1.00), sensibility = 78%, specificity = 100%, respectively. Combining sensitivity of PP and specificity of CVP, fluid responsiveness prediction can be obtained with 100% sensibility and 100% specificity (AUC=0.96; 95% CI, 0.90 to 1.00). 1 patient presented inconclusive values using the grey zone approach (5.5%).

Conclusions:

In patients under mechanical ventilation with no right cardiac dysfunction, the association of PP and CVP slope analysis during a prolonged sigh breath lung recruitment maneuver seems to offer a very promising

method for fluid responsiveness prediction without the use and cost of a cardiac output measurement device.

Trial registration: NCT04304521, IRBN902018/CHUSTE

Registered 11 March 2020, Fluid responsiveness predicted by a stepwise PEEP elevation recruitment maneuver in mechanically ventilated patients (STEP-PEEP)

https://www.clinicaltrials.gov/ct2/show/NCT04304521?term=NCT04304521&cntry=FR&draw=2&rank=1

1. Introduction

Hemodynamic and fluid optimization during the perioperative period can reduce postoperative morbidity. *(1)* The assessment of preload and determination of whether the patient is fluid responsive is still challenging. Static preload indices such as central venous pressure are not sufficient to assess fluid responsiveness *(2)* whereas dynamic preload indices such as pulse pressure variation (PPV) and stroke volume (SV) variation have been used successfully. *(3)* However, such indices suffer from several limitations and should be used only under strict conditions. *(4)* Alternative dynamic methods of assessment such as lung recruitment maneuvers (LRM) have been developed. *(5)* LRM can be used to reopen or prevent collapsed lung under mechanical ventilation in order to decrease respiratory complications. *(6)* LRM induce a transient increase in intra-thoracic pressure and decrease in venous return, leading to a decrease in left ventricular end-diastolic area and stroke volume. *(7,8)* Several studies have shown that the PEEP-induced decrease in stroke volume is related to pre-existing preload responsiveness. *(9,10)* A few studies have also shown that LRM can be used as a functional test to predict fluid responsiveness. *(11,12,13)* However, monitoring stroke volume during LRM to assess fluid responsiveness is costly, and cardiac output devices may not be reliable. *(14)* In this context, central venous pressure (CVP) or systemic arterial parameters monitoring represent cost effective and readily available alternatives during major surgery.

LRM can be achieved using a prolonged sigh breath or stepwise increase in PEEP and airway inspiratory pressure with the same driving pressure. *(15,16)* These maneuvers have been described for 2 to 4 minutes periods. Prolonged LRM lead to a lesser increase in transpulmonary pressure for a longer period of time and improve lung aeration as effectively as sustained inflation does, with less risk of hemodynamic compromise and hyperinflation. A recent study has specifically evaluated the hemodynamic response in this context. *(17)*

The aims of the current study were (1) to assess the ability of a LRM with a stepwise increase in PEEP to predict fluid responsiveness in mechanically ventilated patients, (2) to identify the best criteria for fluid responsiveness prediction between variations of systolic aortic pressure (SAP), mean arterial pressure (MAP), diastolic aortic pressure (DAP), pulse pressure (PP) and central venous pressure (CVP), and (3) to compare the ability of these criteria with pulse pressure variation (PPV) to predict fluid responsiveness.

2. Material And Methods

We conducted a prospective study in the 23-bed intensive care unit (ICU) at Saint-Etienne University Medical Center, France, between April 2020 and September 2020. The study protocol was approved by the hospital's ethics committee (Ethics Committee, Department of Anesthesiology, Saint-Etienne University Central Hospital, institutional Review Board IORG0007394, Protocol number IRBN902018/CHUSTE). Written informed consent was done to all study patients or relatives if non applicable. Oral consent was obtained and reported in the medical observation. The main inclusion criteria were as follows: invasive arterial blood pressure and pulse contour analysis (PICCO system, Pulsion Medical Systems SE, Feldkirchen, Germany) for cardiac output measurement, central venous pressure monitoring, use of protective mechanical ventilation, patients older than 18 years and indication for volume expansion. A transthoracic echocardiography was performed on all patients before inclusion. Non-inclusion criteria were right ventricular dysfunction, significant valvulopathy, ejection fraction less than 50%, arrhythmia or presence of spontaneous breathing cycles. The inclusion time was at the start of the LRM. Exclusion criteria were: LRM not completed, absence of fluid expansion performed after LRM and patient decline for enrollment after reawakening.

Sedation & monitoring

Each patient was monitored with pulse oximetry and a 5-lead electrocardiography. Central venous pressure was measured continuously for all patients. All patients were equipped with a Transcardiopulmonary Thermodilution-Calibrated Arterial Waveform Analysis (PICCO system) inserted into a femoral artery. Pressure transducers were placed at the level of the mid-axillary line throughout the study protocol. All patients were intubated and ventilated using a volume-controlled mode. Anesthesia was maintained with propofol and/or midazolam in combination with either sufentanil or remifentanil. Neuromuscular blockade was not systematically used. The tidal volume (TV) was set by the clinician to the ideal body weight to obtain [6-8] mL/kg and the ventilatory rate was set in order to maintain arterial CO2 tension between 35 and 45 mmHg.

The lung recruitment maneuver

LRM were performed using a stepwise increase of PEEP and airway inspiratory pressure with the same driving pressure (15 cmH2O), as described in the literature. *(15,16,18)* The LRM consisted of a 5 cmH_2O PEEP and inspiratory pressure increase every 30 seconds. The baseline was 5 cmH_2O PEEP and 20 cmH_2O inspiratory pressure for all patients. The maximum pressure level reached was 30 cmH_2O PEEP and 45 cmH2O inspiratory pressure. PEEP de-escalation was performed following the same pattern (Figure 1). After LRM, ventilatory settings were set back to initial patient settings. We defined the increasing levels of pressure as "STEP-UP" and the decreasing levels of pressure as "STEP-DOWN". LRM were stopped if severe arterial hypotension (systolic arterial pressure less than 70 mmHg) or severe hypoxemia (SpO2 < 80%) was observed. *(18)* All included patients received a fluid expansion after LRM. The fluid challenge consisted of a 500mL Plasmalyte infusion over 10 minutes.

Data collection

We recorded demographic data including weight, age, gender, Simplified Acute Physiology Score (SAPS II), medical history, criteria of admission to ICU and comorbidities. Respiratory parameters (tidal volume, respiratory rate, insufflation pressure [peak], plateau pressure, level of PEEP) and hemodynamic parameters (SAP, DAP, MAP), pulse pressure (PP=SAP-DAP), CVP, heart rate, PPV, and PICCO data (stroke volume and cardiac output (CO)) were also recorded. Baseline PPV was displayed on Phillips monitors. Pharmacological data (vasoactive infusions) and biological data (lactate) were recorded.

Study protocol

When a patient met the inclusion criteria, the investigating physicians collected a set of demographic, ventilatory and hemodynamic data. A transcardiopulmonary thermodilution was performed. Three injections of 20 mL cold fluid bolus were used for SV and CO calculations at baseline (mean of the three bolus). The LRM were then performed following the STEP-PEEP pattern as described above. A video of the hemodynamic monitoring was recorded during the LRM, with the clinician announcing the time and pressure level for each step. Hemodynamic values were later documented by pausing on the video during the two last seconds of each LRM step announced by the physician. Next, a fluid expansion of Plasmalyte 500mL over 10 minutes was performed. A second transcardiopulmonary thermodilution was done after fluid expansion, using the same method. Responders (R) and Non-Responders (NR) were defined with regard to the change in SV (expressed as percentage) after fluid expansion. A fluid responder was defined as a 15% increase in SV after fluid expansion. *(19)*

Statistics

A sample size of 18 patients was calculated to be sufficient to demonstrate that CVP and PP variations can predict fluid responsiveness with an area under curve (AUC) of 0.85, a power of 80%, an alpha risk of 0.05 and a beta risk of 0.2. Data are expressed as mean (SD) or median (25^{th} to 75^{th}). We used the Student T-test for continuous variables. Slopes values obtained by linear correlation calculation are expressed in degrees for the angle (α) between the horizontal axis and the linear regression curve calculated between the drop of pressure (mmHg) and the PEEP level (cmH2O). The threshold for statistical significance was set to $P < 0.05$. A receiver-operating characteristic (ROC) curve was drawn for αSAP, αMAP, αDAP, αPP and αCVP for STEP-UP and STEP-DOWN during LRM, respectively. We selected the threshold that gave the highest Youden index. We defined inconclusive responses (grey zone) for values within the CI 95% of the obtained threshold value according to Cannesson et al. *(20)* The method described by DeLong et al was used to compare the areas under the ROC curve associated with the variables. *(21)* Statistical analyses were performed with XLSTAT software (version 2019.3.2).

3. Results

Patient characteristics

A total of 25 nonconsecutive patients were screened. Five patients were not included due to right ventricular dysfunction (1 patient), ejection fraction less than 50% (1 patient) and presence of arrythmia (3 patients). Two patients were excluded due to absence of fluid expansion performed after LRM. A total of 18 patients

were analyzed (Figure 2). Nine patients (50%) were responders to volume expansion and nine were not. Patients main characteristics, hemodynamic, respiratory, pharmacological and biological variables in both Responders and Non-Responders are shown in table 1.

The baseline norepinephrine concentration was higher in the Responders group (R) than in the Non-Responders (NR) group (0.78 ug/kg/min vs 0.24 ug/kg/min, respectively; p=0.031). Baseline PPV was higher in the R than in the NR group (14% vs 6%, respectively; p=0.034). R and NR did not differ for baseline values of SV, CO, MAP, CVP nor lactate level. Static pulmonary compliance was not statistically different between R and NR.

	Overall population	Responders	Non-Responders	p value
	N=18	N=9	N=9	
Age (mean SD), yr	60 (15)	66 (7)	57 (18)	
Gender (M/F)	10/8	5/4	5/4	
BMI (mean SD), kg.m-2	29 (9)	29 (6)	29 (12)	
Ideal body weight (mean SD), kg	66 (14)	63 (11)	66 (17)	
SAPS 2 (mean SD)	61 (22)	69 (22)	57 (21)	
ICU admission criteria				
Septic shock	4	3	1	
Cardiac failure	7	3	4	
Respiratory failure	4	2	2	
Hemorrhagic shock	1	1	0	
Polytrauma	1	0	0	
Cranio-cerebral trauma	1	0	1	
Comorbidities				
Arterial hypertension	8	6	2	
Diabetes	4	2	2	
Coronary artery disease	1	1	0	
Hemodynamic parameters				
Mean arterial pressure (mean SD), mmHg	73 (9)	70 (10)	76 (7)	0.110
Heart Rate (mean SD), HR/min	90 (18)	91 (23)	87 (11)	0.813
Stroke volume (mean SD), mL	62 (26)	53 (20)	64 (29)	0.177
Cardiac output (mean SD), L/min	5.3 (2.2)	4.5 (1.0)	5.5 (2.7)	0.150
PPV (mean SD), %	10 (8)	14 (10)	6 (2)	0.034
Central Venous Pressure (mean SD), mmHg	10 (4)	9 (3)	10 (4)	0.238
Respiratory parameters				
Tidal volume (mean SD), mL	436 (62)	452 (55)	405 (68)	0.288
Tidal volume (mean SD), mL/kg	6.8 (1.2)	7.3 (1.0)	6.4 (1.4)	0.010

Respiratory Rate (mean SD), RR/min	20 (5)	18 (4)	22 (6)	0.218
Positive end expiratory pressure (mean SD), cmH2O	10 (3)	9 (2)	10 (3)	0.671
Plateau pressure (mean SD), cmH2O	22 (6)	19 (3)	23 (8)	0.099
Static pulmonary compliance (mean SD), mL/cmH2O	42 (15)	48 (11)	37 (15)	0.065
P/F (mean SD)	236 (97)	224 (104)	242 (97)	0.679
Neuromuscular blockade, n	9	4	5	
Pharmacological parameters				
Norepinephrine (mean SD), ug/kg/min	0.50 (0.64)	0.78 (0.76)	0.24 (0.35)	0.031
Dobutamine (mean SD), ug/kg/min	2.06 (3.37)	1.44 (2.96)	2.67 (3.81)	0.394
Biological parameters				
Lactates (mean SD), mmol/l	2.2 (1.5)	2.7 (2.1)	2.0 (0.8)	0.215

Table 1: Patient demographic data, hemodynamic, respiratory, pharmacological and biological variables at baseline in Responders (n=9) and Non-Responders (n=9 patients)

Prediction of Fluid Responsiveness

Six data points were available for each parameter for STEP-UP and STEP-DOWN. STEP-UP LRM induced a decrease of SAP, PP, DAP, MAP, and SV and an increase of CVP. Fluid Responders demonstrated a greater decrease of SAP, PP, DAP, MAP, and SV as well as a greater increase of CVP compared to Non-Responders.

Evaluation of all hemodynamic variables suggested the use of a linear interpolation model, especially during STEP-UP LRM. Figure 3 shows the linear regression curves for SAP, PP, MAP, DAP, SV and CVP during LRM. Slopes calculations are shown in table 2. Slopes are reported as αSAP, αDAP and αMAP for systolic, diastolic and mean arterial pressure, αPP for pulse pressure, αCVP for central venous pressure and αSV for stroke volume.

Slope calculations showed greater absolute values for the Responder compared to the Non-Responder group for STEP-UP and STEP-DOWN LRM (Table 2). The ability of αSAP, αPP, αDAP, αMAP, αSV and αCVP to predict fluid responsiveness and the results of AUC analysis are shown in table 3. The best predictive variables for fluid responsiveness during LRM were αPP and αCVP during STEP-UP, with Youden indexes of 0.888 and 0.777 respectively.

αPP during STEP-UP was strongly predictive of fluid responsiveness with an AUC of 0.926 (95% CI, 0.78 to 1.00), and a sensitivity and a specificity of 100% and 89% respectively. Cut-off value was 42.8°. Inconclusive values ranged from 42.8° to 52.1°using the grey zone approach (35% of the patients).

αCVP during STEP-UP was also strongly predictive of fluid responsiveness with an AUC of 0.901 (95% CI, 0.76 to 1.00), a sensibility and a specificity of 78% and 100% respectively. Cut-off value was 20.1°. Inconclusive values ranged from 13.8° to 20.1° using the grey zone approach (44% of the patients).

Combining sensitivity of αPP and specificity of αCVP, fluid responsiveness prediction can be obtained with 100% sensibility and 100% specificity during STEP-PEEP LRM (AUC=0.96; 95% CI, 0.90 to 1.00). One patient (5.5%) presented inconclusive values using the grey zone approach (Figure 4).

Absolute variations for SAP, PP, MAP, DAP, SV and CVP between baseline (PEEP=5mmHg, Inspiratory pressure=20mmHg) and maximum pressure level (PEEP=30mmHg, Inspiratory pressure=45mmHg) are reported as ΔSAP, ΔPP, ΔMAP, ΔDAP, ΔSV and ΔCVP. Their ability to predict fluid responsiveness is shown in table 3.

PPV at baseline was available for 11 patients. A PPV of more than 12% before LRM discriminated responders with an AUC of 0.711 (95% CI, 0.42 to 1.00), a sensitivity and a specificity of 63% and 100% respectively. Inconclusive values ranged from 4% to 10% using the grey zone approach (45% of the patients) (Figure 4).

	STEP-UP			**STEP-DOWN**		
	Responders	Non-Responders	p value	Responders	Non-Responders	p value
	N=9	N=9		N=9	N=9	
α SAP (SD)	-59.4° (5.79)	-37.5° (13.1)	0.022	57.1° (8.25)	40.8° (12.6)	0.034
α PP (SD)	-51.9° (7.24)	-31.6° (10.7)	0.014	48.8° (8.26)	31.8° (10.6)	0.010
α DAP (SD)	-23.6° (8.77)	-11.4° (10.0)	0.126	24.3° (9.44)	18.5° (10.1)	0.528
α MAP (SD)	-40.3° (8.50)	-24.2° (11.9)	0.089	39.6° (9.51)	30.1° (11.5)	0.228
α SV (SD)	-43.5° (9.65)	-27.4° (8.64)	0.038	25.9° (20.1)	29.0° (9.60)	0.837
α CVP (SD)	19.8° (2.66)	13.1° (3.03)	0.006	-18.2° (2.05)	-13.4° (2.60)	0.003

Table 2: Slopes (degrees) for systolic aortic pressure (αSAP), pulse pressure (αPP), diastolic aortic pressure (αDAP), mean aortic pressure (αMAP), stroke volume (αSV) and central venous pressure (αCVP) for STEP-

UP and STEP-DOWN during lung recruitment maneuver

STEP-UP	αSAP	αPP	αDAP	αMAP	αSV	αCVP
Cut-off value (degrees)	47.8°	42.8°	10.1°	20.1°	34.2°	20.1°
ROC AUC	0.864	0.926	0.765	0.777	0.854	0.901
Sensitivity	1	1	1	1	0.875	0.777
Specificity	0.666	0.888	0.666	0.666	0.777	1
Positive predictive value	0.75	0.9	0.75	0.75	0.777	1
Negative predictive value	1	1	1	1	0.875	0.818
Youden index	0.666	0.888	0.666	0.666	0.653	0.777
Grey zone (degrees)	[47.8°-59.6°]	[42.8°-52.1°]	[10.1°-34.2°]	[20.1°-42.8°]	[24.3°-46.1°]	[13.8°-20.1°]
	ΔSAP	**ΔPP**	**ΔDAP**	**ΔMAP**	**ΔSV**	**ΔCVP**
Cut-off value (mmHg)	23	21	4	9	16	8
ROC AUC	0.901	0.920	0.777	0.790	0.753	0.883
Sensitivity	1	1	1	1	0.777	0.777
Specificity	0.666	0.777	0.666	0.666	0.777	0.888
Positive predictive value	0.75	0.818	0.75	0.75	0.777	0.875
Negative predictive value	1	1	1	1	0.777	0.8
Youden index	0.666	0.777	0.666	0.666	0.555	0.666
Grey zone (mmHg)	[23-39]	[21-28]	[4-14]	[9-23]	[0-25]	[5-9]
STEP-DOWN	**αSAP**	**αPP**	**αDAP**	**αMAP**	**αSV**	**αCVP**
Cut-off value	55.4°	47.8°	20.4°	34.7°	43.2°	14.1°

(degrees)						
ROC AUC	0.777	0.815	0.666	0.685	0.666	0.877
Sensitivity	0.777	0.666	0.777	0.777	0.375	0.888
Specificity	0.777	0.888	0.666	0.666	1	0.777
Positive predictive value	0.777	0.857	0.7	0.7	1	0.8
Negative predictive value	0.777	0.727	0.75	0.75	0.643	0.875
Youden index	0.555	0.555	0.444	0.444	0.375	0.666
Grey zone (degrees)	[38.7°-67.8°]	[32.4°-52.3°]	[3.9°-36.0°]	[9.76°-50.6°]	[13.2°-43.2°]	[13.8°-20.1°]
	ΔSAP	**ΔPP**	**ΔDAP**	**ΔMAP**	**ΔSV**	**ΔCVP**
Cut-off value (mmHg)	32	21	8	17	15	5
ROC AUC	0.809	0.852	0.741	0.735	0.642	0.888
Sensitivity	0.777	0.777	0.777	0.777	0.666	1
Specificity	0.888	0.888	0.777	0.777	0.666	0.666
Positive predictive value	0.875	0.875	0.777	0.777	0.666	0.75
Negative predictive value	0.8	0.8	0.777	0.777	0.666	1
Youden index	0.666	0.666	0.555	0.555	0.333	0.666
Grey zone (mmHg)	[11-46]	[13-30]	[0-16]	[4-29]	[0-25]	[5-8]

Table 3: Diagnostic performance of slopes for systolic aortic pressure (αSAP), pulse pressure (αPP), diastolic aortic pressure (αDAP), mean aortic pressure (αMAP), stroke volume (αSV), central venous pressure (αCVP) and relative variations from baseline of systolic arterial pressure (ΔSAP), pulse pressure (ΔPP), diastolic arterial pressure (ΔDAP), mean arterial pressure (ΔMAP), stroke volume (ΔSV) and central venous pressure (ΔCVP) between baseline (PEEP=5, Inspiratory Pressure=20cmH2O) and maximum pressure level (PEEP=30, Inspiratory Pressure=45cmH2O) to predict fluid responsiveness during STEP-UP and STEP-DOWN lung recruitment maneuver

4. Discussion

Our results show that αCVP and αPP changes induced by a progressive lung pressure (STEP-PEEP) recruitment maneuver are the best hemodynamic parameters for the prediction of fluid responsiveness in mechanically ventilated patients in ICU, with or without neuromuscular blockade. STEP-PEEP LRM offered the possibility to evaluate the effects of LRM with a non-binary approach based on bi-level sustained insufflation. Six data points were available for STEP-UP and STEP-DOWN for all parameters, giving the possibility to study their evolution and conclude to a linear evolution, especially during STEP-UP. Absolute variations of PP and CVP between PEEP = 5cmH2O and PEEP = 30cmH2O during STEP-UP provide interesting results with a view to discriminate fluid responders and non-responders. Nevertheless, slopes calculations were the best parameters compared to absolute variation of SAP, MAP, DAP, PP, SV and CVP (Table 3). PPV was significantly different between Responders and Non-Responders at baseline but showed inferior statistical values compared to slope analysis.

During LRM, a transient increase in intra-pulmonary pressure is transmitted to the adjacent intra-thoracic compartments. Most effects of LRM act on the right ventricle. No patients had right ventricular cardiac dysfunction as they were excluded in our study. Preload and afterload of the right ventricle are affected by high intra-thoracic pressure. This increase of intra-thoracic pressure is transmitted to abdominal compartment which increases resistance to venous return due to collapse of the inferior vena cava and the hepatosplanchnic venous circulation. *(7,22)* High intra-thoracic pressure increase the right ventricle afterload and ejectional impedance. *(23)* These effects on right ventricle are particularly large when preload is low. *(22,24)* All patients in our study displayed a significant decrease in SV and systemic arterial pressure, and an increase in CVP during LRM. Hemodynamic changes were more important in the Responders group.

PP slope calculation (αPP) after linear regression during STEP-PEEP proved to offer an excellent sensibility. This can be explained by the fact that if no variation of systemic arterial pressure is induced by a transient increase of intra-thoracic pressure, the right ventricle preload status is probably sufficient to avoid a drop of SV after the left ventricle. αPP variation below cut-off value during STEP-UP could therefore exclude fluid responsiveness with a 100% sensibility in our study.

CVP slope calculation (αCVP) during STEP-LRM proved to offer an excellent specificity. This can be explained by the fact that if a transient increase of intra-thoracic pressure induces an important variation of CVP, the right ventricle preload status is probably low and easily subject to external pressure. αCVP above cut-off value during STEP-UP could affirm fluid responsiveness with 100% specificity in our study.

Clinicians can therefore choose to benefit from the sensibility of αPP using only an arterial catheter, or the sensibility of αCVP using a central venous catheter for fluid responsiveness prediction. For patients equipped with both, combination of αPP and αCVP during STEP-UP allows clinicians to predict fluid responsiveness with 100% sensibility and specificity.

This study has several limitations. This pilot study was monocentric and 18 patients have been studied. Further larger studies are needed to confirm our preliminary results. Next, SV during LRM was calculated with pulse contour analysis. Surprisingly, the SV results for absolute variation and derivate coefficient were

inferior to results for SAP, PP and CVP. This can be explained by the likely imprecision of pulse contour analysis subject to increasing levels of pressure and variation of systemic vascular resistances from baseline initial transcardiopulmonary thermodilution. Of note, thermodilution is the method of choice for cardiac output measurement and was used before LRM, and after fluid challenge.

Calculation of the slope may be challenging on bedside but a calculation of the α angle according to the successive values of CVP and PP can easily be automated on a computer or smartphone.

All patients were not consecutive patients, introducing a potential selection bias. Before inclusion, all patients required a fluid expansion decided by the clinician in charge. Inclusions were conducted exactly the same way for all patients, Responder or Non-Responder status being determined offline only after fluid expansion. This last point shows that our current tools are not accurate enough to discriminate Responders and Non-Responders.

The choice of LRM can be debated. High intrathoracic pressures can have harmful effects on patients without lung disease. STEP-PEEP lung recruitment maneuver was chosen from literature as it showed lesser increase in transpulmonary pressure for a longer period of time and improved lung aeration as effectively as sustained inflation does, with less risk of hemodynamic compromise and hyperinflation. *(15,16)*

5. Conclusion

In mechanically ventilated patients, a progressive STEP-PEEP lung recruitment maneuver could predict fluid responsiveness with the slope analysis of pulse pressure (αPP) and central venous pressure (αCVP) evolutions. αPP variation below cut-off value during STEP-UP can exclude fluid responsiveness. αCVP above cut-off value during STEP-UP can affirm fluid responsiveness. In this pilot study, the association of αPP and αCVP during STEP-UP recruitment maneuver provides a high sensitivity and high specificity and seems to offer a very promising method for fluid responsiveness prediction without the use and cost of a cardiac output measurement device.

Declarations

Ethical Approval and Consent to participate

The study protocol was approved by the hospital's ethics committee (Ethics Committee, Department of Anesthesiology, Saint-Etienne University Central Hospital, institutional Review Board IORG0007394, Protocol number IRBN902018/CHUSTE).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Department of Anesthesiology, Saint-Etienne University Central Hospital

Authors' contributions

SV designed, included and made statistic calculations for this study.

JBB designed and included patients.

OD reviewed the article and made significant corrections.

CF included patients.

DR reviewed and corrected english syntax.

SM made this work possible in his department of anesthesia and intensive care, reviewed the article and made significant corrections.

LG designed, included and made statistical calculations.

JM made this work possible in his intensive care unit and made significant corrections to the manuscript.

All authors read and approved the final manuscript

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Figures

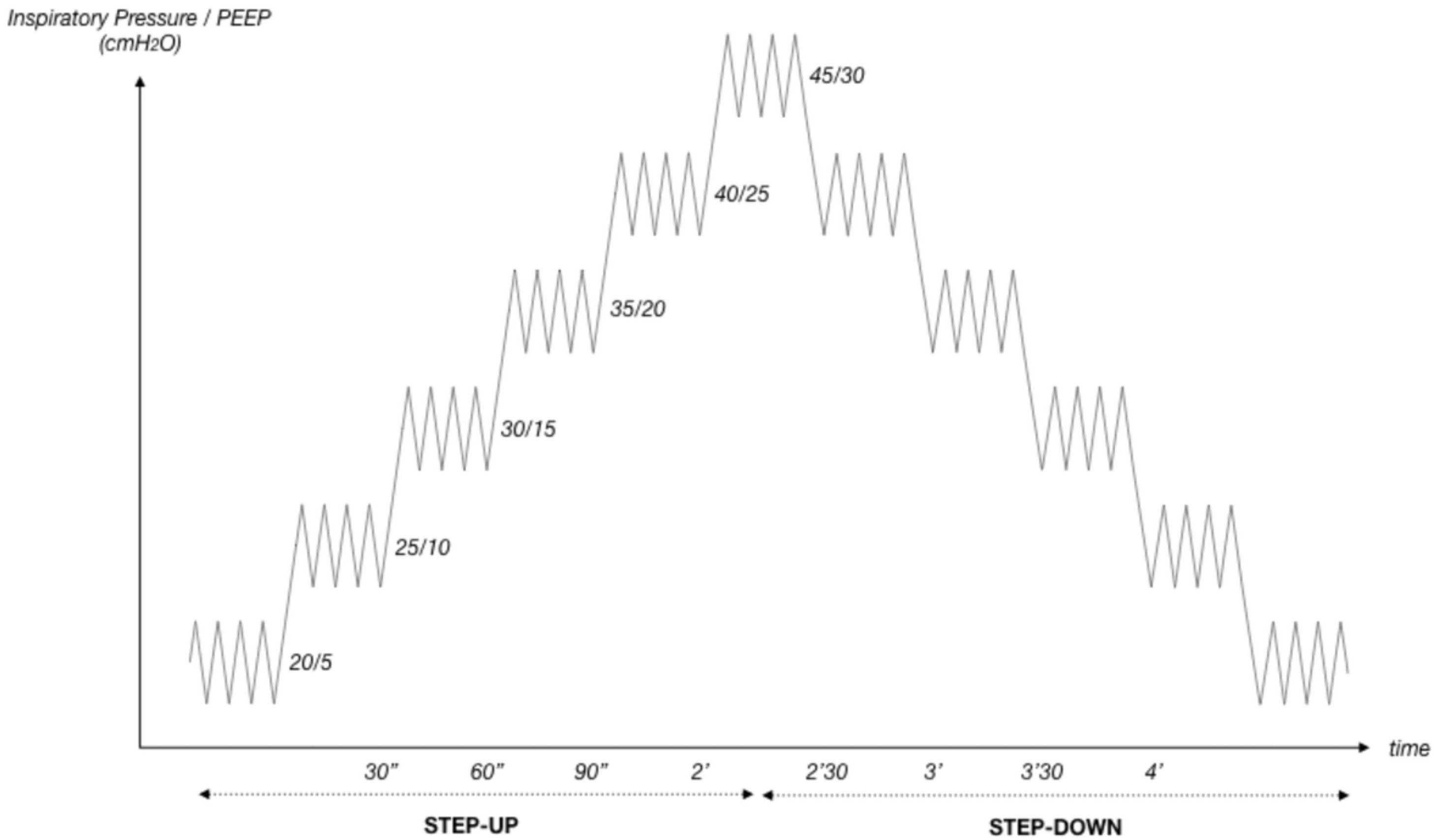

Figure 1

Schematic representation of STEP-PEEP lung recruitment maneuver

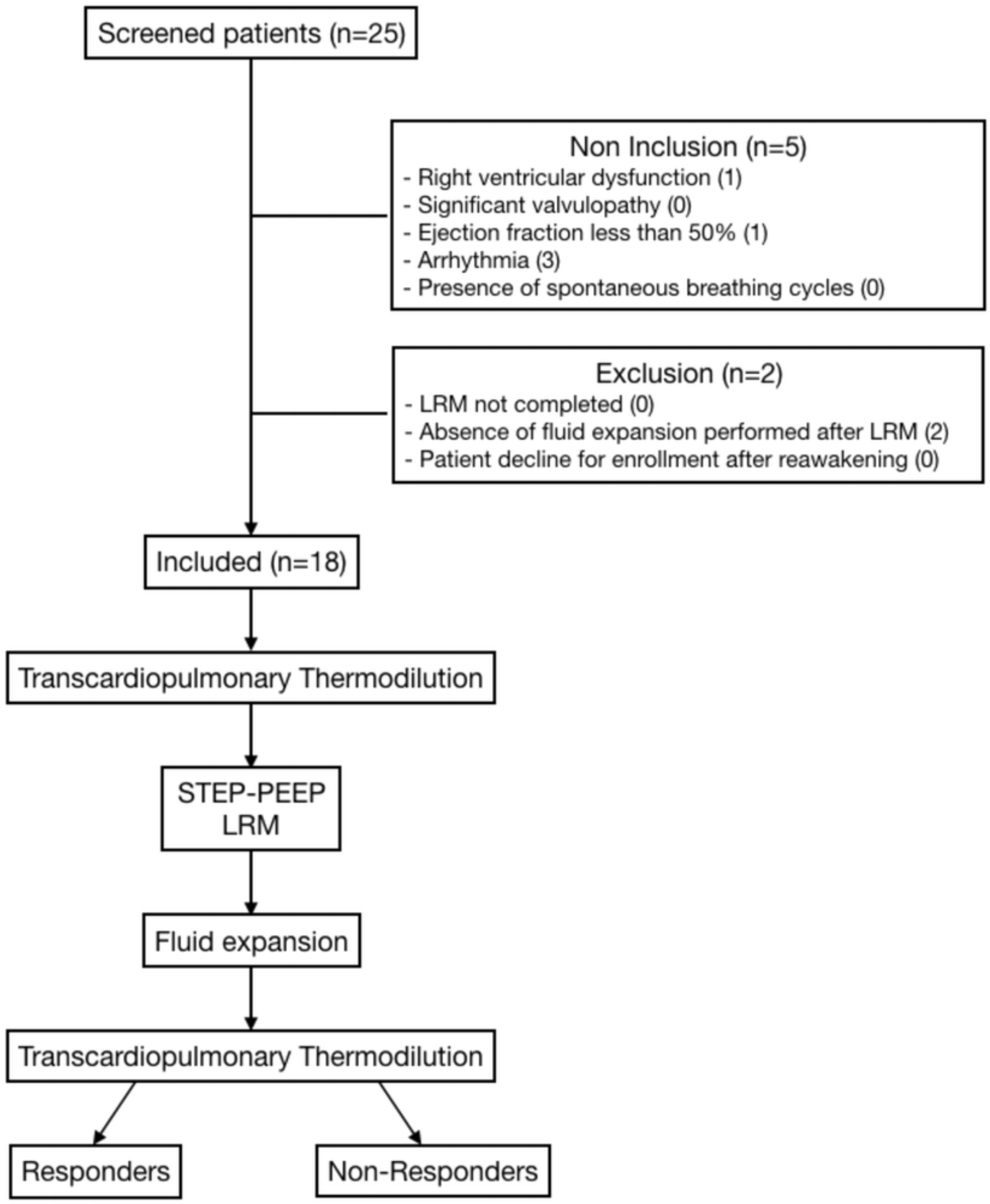

Figure 2

Study flow chart

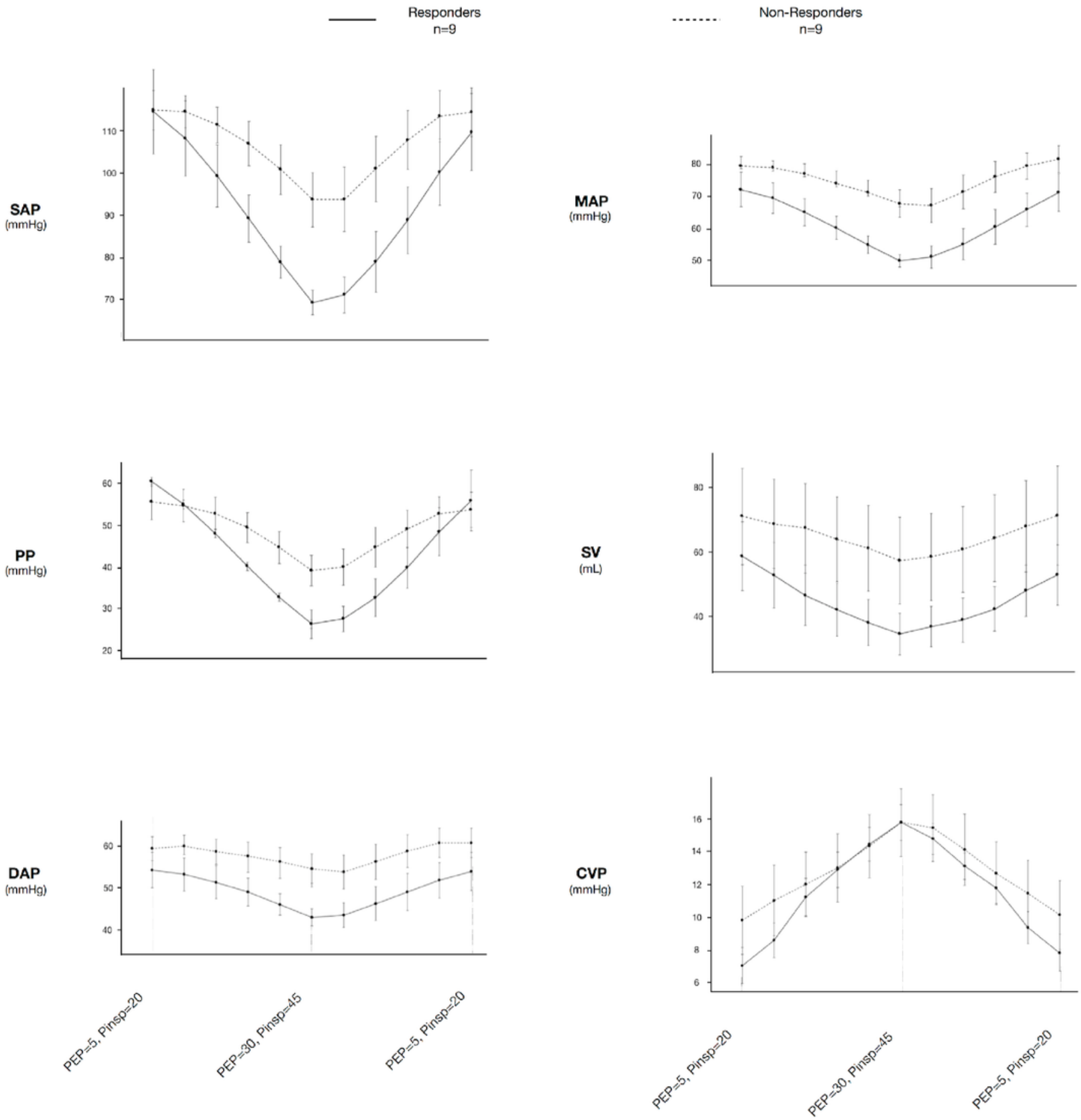

Figure 3

Linear regression of mean values and SD of systolic aortic pressure (SAP), pulse pressure (PP), diastolic aortic pressure (DAP), mean aortic pressure (MAP), stroke volume (SV) and central venous pressure (CVP) during lung recruitment maneuver for Responders (R, n=9) and Non-Responders (NR, n=9)

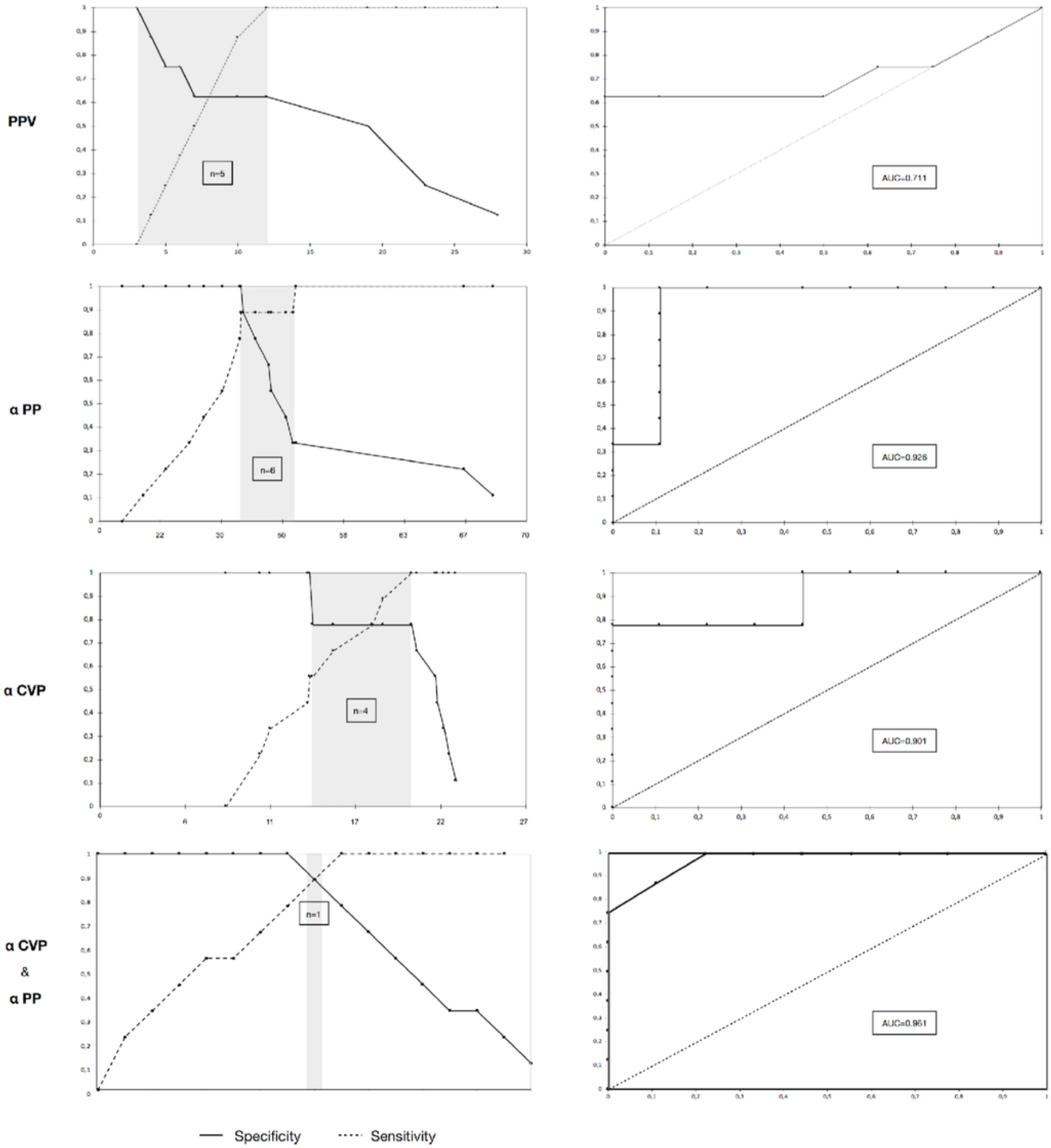

Figure 4

Sensitivity, specificity, grey zone and Receiver Operating Curves generated of pulse pressure variation (PPV) at baseline and slopes for changes in pulse pressure (αPP), central venous pressure (αCVP) and combination of αPP sensitivity & αCVP specificity during STEP-UP lung recruitment maneuver, with a view to discriminating between fluid expansion Responders and Non-Responders