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Pulse pressure variation as a predictor of fluid responsiveness in mechanically ventilated patients with spontaneous breathing activity: a pragmatic observational study

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ABSTRACT

Introduction: Pulse pressure variation predicts fluid responsiveness in mechanically ventilated patients passively adapted to the ventilator. Its usefulness in actively breathing ventilated patients was examined only by few studies with potential methodological shortcomings. This study sought to describe the performance of pulse pressure variation as a predictor of fluid responsiveness in hypotensive critically ill patients who trigger the ventilator.

Methods: We studied forty two hypotensive, mechanically ventilated patients with documented spontaneous breathing activity in whom a fluid challenge was deemed necessary by the attending physician. All patients were ventilated with a Maquet Servo-i Ventilator in different ventilatory modes with a flow-regulated inspiratory trigger set on position 4. Pulse pressure variation, mean and systolic arterial pressure were observed before and after the fluid challenge, which consisted in the intravenous administration of a 250 ml bolus of 6% hetastarch. Fluid responsiveness was defined as a more than 15% increase in arterial pressure after volume expansion.

Results: The area under the receiver operator characteristic curve for pulse pressure variation was 0.87 (95% CI 0.74-0.99; $p < 0.0001$) and the grey zone limits were 10% and 15%. Pulse pressure variation was correlated with increase in systolic arterial pressure ($r2 = 0.32$; $p < 0.001$) and mean arterial pressure ($r2 = 0.10$; $p = 0.037$).

Conclusions: Pulse pressure variation predicts fluid responsiveness in patients who actively interact with a Servo-i ventilator with a flow-regulated inspiratory trigger set on position 4.

Keywords: *dynamic indices, pulse pressure variation, fluid responsiveness, preload reserve, hemodynamic optimization, spontaneous breathing.*

INTRODUCTION

Intravenous fluid administration is the first intervention to correct hemodynamic instability in critically ill patients. However, only roughly 50% of treated patients will benefit from plasma volume expansion in terms of enhanced cardiac output (1) while the rest will suffer the detrimental effects of excessive fluid loading, including heart failure and interstitial tissue edema. Hence, predicting in advance fluid responsiveness in intensive care medicine is advantageous.

Nowadays it is widely accepted that the dynamic indices pulse pressure variation (PPV), stroke volume variation (SVV)

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and systolic pressure variation (SPV) accurately predicts fluid responsiveness in mechanically ventilated patients passively adapted to the ventilator (2, 3). During the inspiratory phase, if both ventricles are on the ascending limb of the Frank-Starling curve (i.e. they still have a preload reserve), the venous return to the right heart is hampered by the positive intrathoracic pressure. This will lead to a reduction of the right ventricle stroke volume (SV) that, with a few cardiac cycles delay, will cause a change in left ventricular filling and SV resulting in a change in the arterial pressure curve. When the plateau of the Frank-Starling curve is reached, i.e. the preload reserve is exhausted, this phenomenon is greatly reduced. For this purpose the delivered tidal volume must be 8-10 ml/kg of body weight (4), the patients should not be suffering right ventricle dysfunction (5), and pulmonary compliance should not be excessively reduced (6, 7).

In patients who actively interact with the ventilator the regularity of the intrathoracic pressure swings can be altered by various degrees by inspiratory and expiratory efforts and by variations in respiratory rate. According to the published evidence the accuracy of dynamic indices is lost in this setting (3, 8). However, only few studies addressed this issue, they considered heterogeneous indices without mentioning the algorithm used to measure them and they did not report key aspects of ventilator setting like inspiratory and expiratory trigger (9-11). Inspiratory and expiratory trigger could indeed act as airway resistors and profoundly affect the amplitude of intrathoracic pressure variations and, as a consequence, the dynamic indices and their fluid responsiveness predictive ability (12). Based on clinical observations made in our intensive care unit (ICU), where PPV is routinely monitored, we hypothesized that PPV's clinical usefulness in actively breathing ventilated patients is critically influenced by the interaction between a specific ventilator setting and a specific PPV measurement algorithm. We, therefore, decided to undertake an observational study aimed at understanding if PPV is a clinically useful predictor of fluid responsiveness in mechanically ventilated ICU patients with spontaneous breathing activity.

While the standard method to assess the effect of volume expansion relies on cardiac output (CO) or SV measurement, recent data suggest that, although there are some limitations (13), arterial pressure accurately tracks blood flow changes immediately after a fluid challenge (14-16). We opted therefore to use an arterial pressure-based definition of fluid responsiveness.

METHODS

The local ethics committee approved the protocol and, because of the strictly observational characteristics of the study, waived the need for informed consent. We enrolled in the study 42 patients admitted to our general, 13 bed ICU who, in any moment of their ICU stay, were at the same time hypotensive, were mechanically ventilated in any ventilatory mode through a tracheal tube or a tracheostomy, had spontaneous breathing activity, had a valid PPV reading and in whom the attending physician thought indicated to perform a fluid challenge.

Hypotension was defined as a systolic arterial pressure (SAP) less than 90 mm Hg and/or a mean arterial pressure (MAP) less than 65 mm Hg as measured invasively from a radial or femoral artery. Spontaneous breathing activity was defined as an evident respiratory activity if in pressure support ventilation (PSV) or a measured respiratory rate at least 20% higher than

the respiratory rate set on the ventilator if in all other ventilation modalities. A valid PPV reading was defined as a readily available PPV value measured and displayed according to monitoring details described below. The use of the vasoactive drugs dobutamine and/or noradrenaline was left at the discretion of the attending physician. Exclusion criteria were age 18 years or less, heart rhythm that precluded PPV reading, pregnancy and a change in sedation level or in vasoactive drugs while the data collection was carried out as described below. The protocol did not allow any change in ventilation or monitoring strategies diverting from normal procedures routinely carried out in our ICU based on good clinical practice criteria. All patients were ventilated with a Servo-i ventilator (Maquet, Rastatt, Germany) and were studied while under stable respiratory conditions, i.e. with an SpO2 of at least 90% and normocapnia without the need to adjust ventilation parameters over a consistent period of time. Ventilator setting was decided by the attending physician with the general aim to reach a Pa_O2 of at least 60 mm Hg and a PaCO2 between 35 and 45 mm Hg with a 6-8 ml/kg tidal volume (TV) while avoiding peak airway pressure higher than 35 cm H2O. The inspiratory trigger was kept, according to our standard clinical practice, at a threshold not imposing unnecessary inspiratory effort, i.e. at flow position 4. This means that to trigger the ventilator the patient had to generate a flow of at least 1,4 l/min, which is the 70% of the basal flow (2 l/min). Expiratory trigger was again set by clinical judgment independent from study enrollment between 25% and 40%, depending on the individual estimated risk of dynamic hyperinflation. PEEP was applied as deemed clinically appropriate between 0 and 10 cm/H2O. Blood pressure was measured through a standard transducer (Pressure Monitoring Kit, Edwards Lifesciences, Irvine, California, USA). In all patients PPV was measured through a Philips Intellivue MP 70 monitor (Philips, Suresnes, France). The device calculates PPV from the arterial pressure curve using a specific algorithm developed by Aboy in 2004 (17) and later clinically validated by Canesson (18).

Once a patient was enrolled, demographic and anthropometric data, admission diagnosis, vasoactive drug dosages, ventilation modality, peak airway pressure, PEEP, PPV, SAP and MAP values were manually recorded. Fluid challenge was than administered with standard criteria used in everyday clinical practice in our ICU, which is to say a 250 ml 6% hydroxyethyl starch (Amidolite, B.Braun, Melsungen AG, Germany) intravenous bolus delivered at the highest available infusion rate. Immediately after the end of the fluid challenge PPV, SAP and MAP values were again recorded. A patient was defined as fluid responder if the arterial pressure on which he was defined hypotensive (SAP and/or MAP) increased by at least 15% as compared with pre-fluid challenge values. Fluid responder status was than manually recorded as a binary variable (yes or no).

In order to test the PPV fluid responsiveness prediction performance we a priori decided to analyze data with receiver operator characteristic (ROC) curve analysis. A power analysis showed that to detect an expected area under the ROC curve (AUC) of 0.85 or higher with the alfa level set a 0.05, the beta level at 0.20 (i.e. with a power of 80%) and assuming equal sample size in the two groups, a minimum of 20 patients per group would have been required. We scheduled to enroll 50 patients to compensate for incomplete data. The optimal PPV threshold was determined with the Youden's index (19). In line with a more clinically useful approach that was recently suggested (19-21) we also adopted a "grey

zone", or two cutoffs, approach to describe the PPV range of values for which formal clinical conclusions cannot be reached. To this purpose we determined the PPV values with both specificity and sensitivity lower than 90% and plotted a two-curves graph. The positive and negative likelihood ratios (LR), the positive and negative predictive values (PV) and their 95% confidence intervals (CI) were calculated.

The relation between PPV and fluid responder status was explored also with logistic regression while linear regression was used to study the association between baseline PPV and percentage variation in MAP and SAP after fluid challenge. Differences between independent groups were analyzed with the Mann-Whitney rank sum test or the independent samples t-test and differences between paired groups were studied with the Wilcoxon test or the paired samples t-test as appropriate. Normality was checked with the Kolmogorov-Smirnov test. We used the MedCalc version 12.2.1 statistical software (MedCalc, Mariakerke, Belgium).

RESULTS

We studied 42 patients between December 2010 and April 2012. None of the enrolled patient was excluded from the study. The study was terminated before reaching the scheduled sample size (50 patients) because of slow enrollment rate and because data quality at a sample size sufficient to guarantee adequate power was satisfactory. No patient had incomplete data except one, for which body weight was missing. According

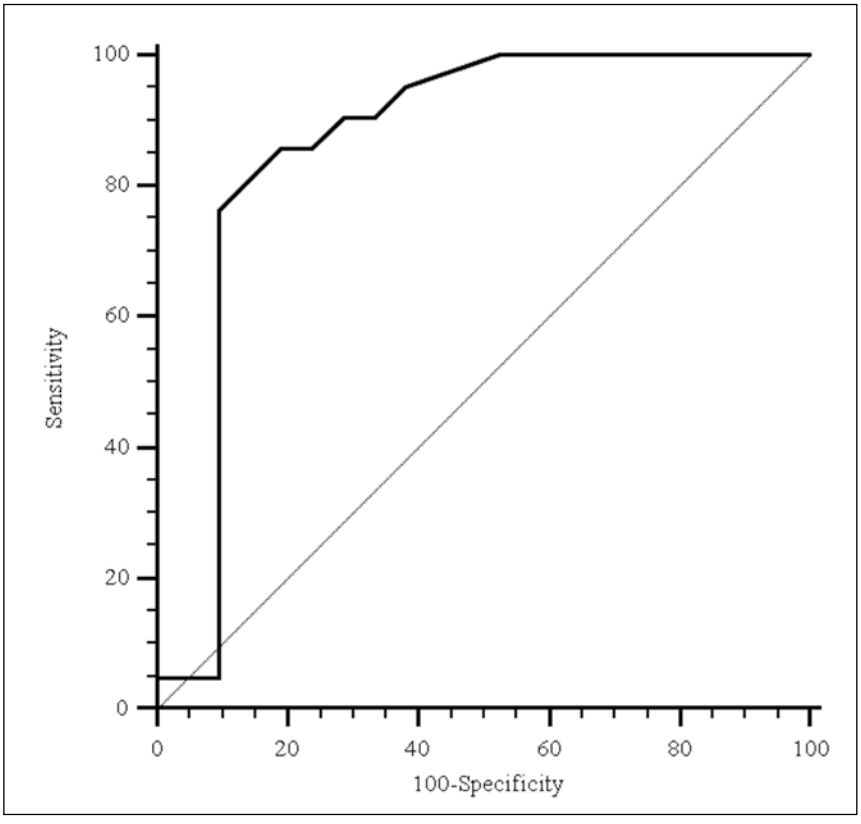

Figure 1
Receiver operator characteristic curve for pulse pressure variation with "responder" as classification variable (Area under the curve = 0.87; p < 0.0001).

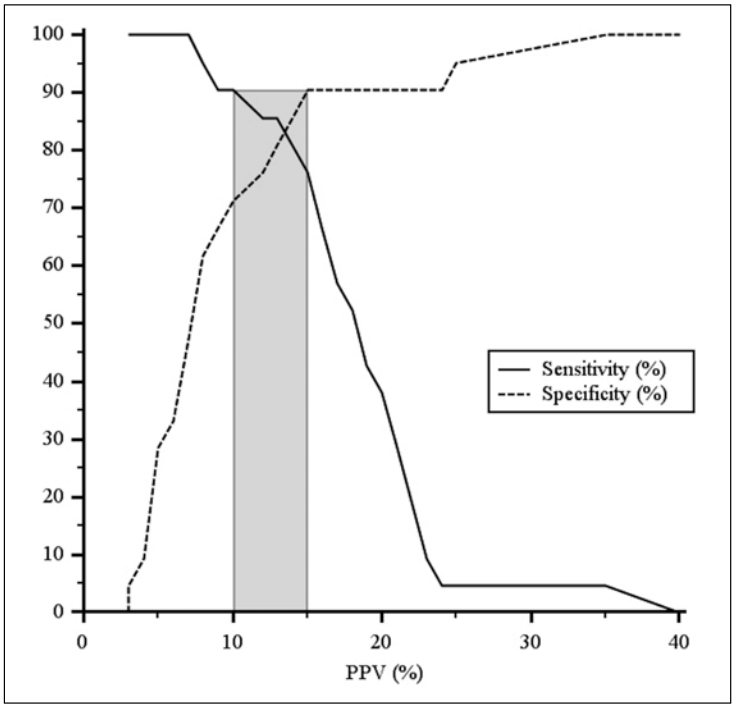

Figure 2
Receiver operator characteristic curve analysis-derived two-curves graph showing the grey zone. The grey zone is determined by the pulse pressure variation values with both sensitivity and specificity below 90 %. Its lower and upper limits are, respectively, 10 % and 15 %.

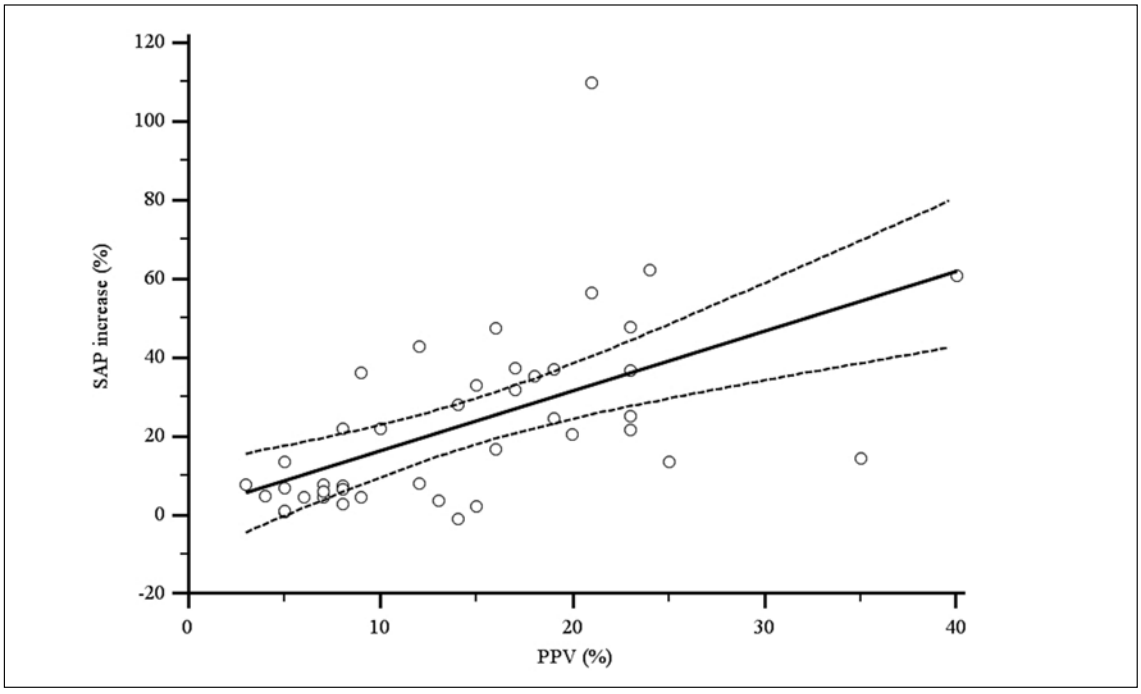

Figure 3 - *Regression line showing the association between baseline pulse pressure variation and percent increase in systolic arterial pressure after fluid challenge. Dotted lines delimit 95 % confidence intervals (r2 = 0.32; p < 0.001).*

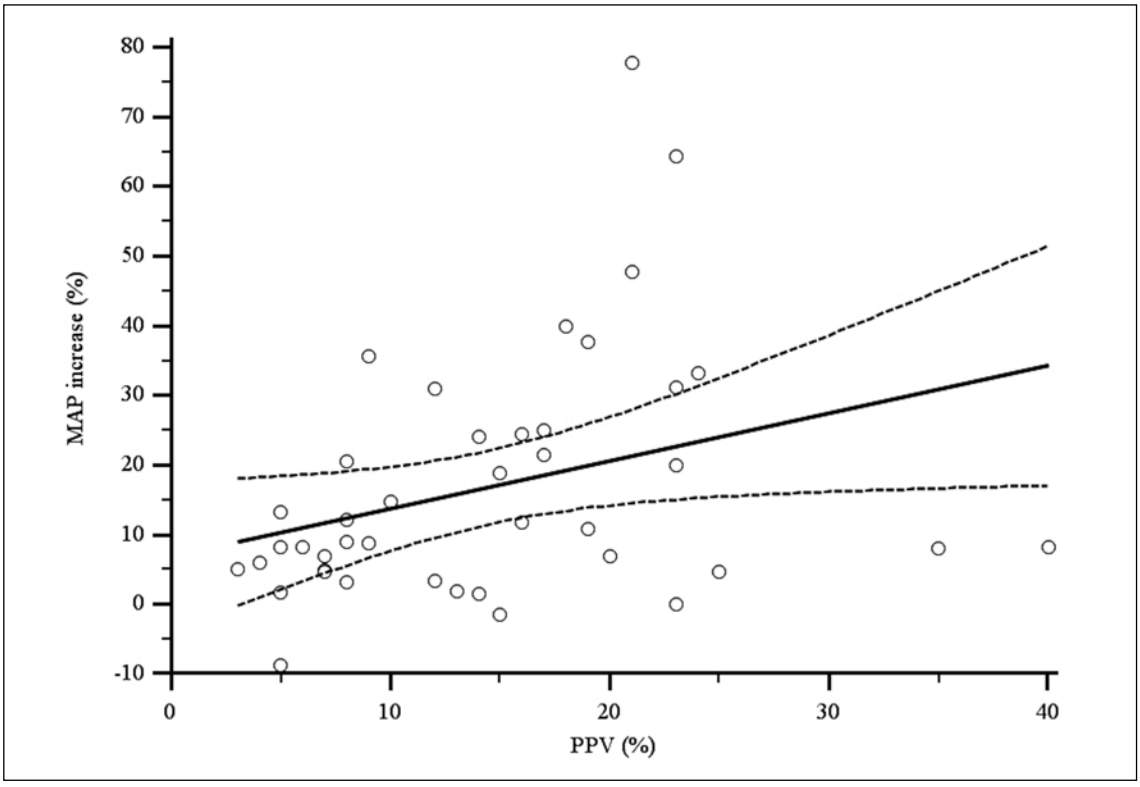

Figure 4 - *Regression line showing the association between baseline pulse pressure variation and percent increase in mean arterial pressure after fluid challenge (r2 = 0.10; p = 0.037).*

to the adopted criterion exactly 50% of patients were responders to fluid administration. Patients' characteristics and differences between responders and non responders are summarized in *Table 1*. Ventilation modalities are shown in *Table 2*.

The area under the ROC curve for PPV with responder status as classification variable was 0.87 (95% CI 0.74 to 0.99; p<0.0001; *Figure 1*). The optimal single cutoff value was 13%, yielding a sensitivity of 85.71% (95% CI 63.70 to 97.00) and a specificity of 80.95% (95% CI 58.10 to 94.60). The lower and higher cutoffs delimiting the gray zone were, respectively, 10% and 15% (*Figure 2*). Eight patients (19%) had PPV values included in this interval. The negative LR corresponding with the lower limit of the grey zone was 0.13 (95% CI 0.03 to 0.60) and the positive LR corresponding with the higher limit of the grey zone was 8.00 (95% CI 6.10 to 10.50). The negative LR remained equal to 0.00 for all PPV values lower than 8% while the highest positive LR was 8.00 and it corresponded to a PPV=15%. Somehow unexpectedly, the positive LR decreased after peaking at this point. Overall, ROC curve analysis defined PPV as a good predictor of fluid responsiveness in the studied setting (19-22).

Logistic regression confirmed this finding: the odds ratio (OR) for PPV with responder status as classification variable was 1.21 (95% CI 1.07 to 1.37; p=0.002). Linear regression showed a significant relationship between PPV and percentage increase in SAP after fluid administration (r2=0.32; p<0.001; *Figure 3*).

Table 1 - *Patients characteristics. Fluid responsiveness defined as more than 15 % increase in arterial pressure after fluid challenge.*

	Overall	Responders	Non responders	p
Patients (n°)	42	21	21	
Age (years)	65 (13)	68 (11)	62 (14)	0.15
Male gender (n°)	24	11	13	0.70
Weight (kg)	76 (17)	73 (14)	78 (19)	0.29
Height (cm)	171 (8)	168 (7)	173 (9)	0.04*
Body surface area (m^2)	1.86 (0.20)	1.81 (0.20)	1.92 (0.20)	0.07
Noradrenaline (γ/kg/min)	0.20 (0.40)	0.23 (0.38)	0.17 (0.42)	0.49
Dobutamine (γ/kg/min)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	NA
Peak airway pressure (cm/H_2O)	23 (6)	22 (9)	24 (6)	0.41
PEEP (cm/H_2O)	5 (2)	5 (0)	6 (3)	0.28
Baseline PPV (%)	14 (8)	19 (6)	10 (7)	0.0002*
Baseline MAP (mm Hg)	59 (6)	58 (7)	60 (5)	0.49
Baseline SAP (mm Hg)	88 (9)	84 (8)	88 (20)	0.009*
Increase MAP (%)	17 (17)	28 (18)	5 (5)	< 0.0001*
Increase SAP (%)	23 (22)	39 (20)	7 (5)	< 0.0001*
Diagnostic groups				
Sepsis	9	5	4	
Neurology/neurosurgery	8	3	5	
Respiratory failure	7	4	3	
Trauma	6	3	3	
Complicated surgery	6	5	1	
Cardiac	5	1	4	
Liver failure	1	0	1	

Data are presented as mean (SD) or median (interquartile range), as appropriate. * = significantly different between responders and non responders, PEEP = positive end-expiratory pressure, PPV = pulse pressure variation, MAP = mean arterial pressure, SAP = systolic arterial pressure, NA = not appropriate. The diagnostic groups show the number of patients.

Table 2 - *Ventilation modalities.*

Ventilation modality	Patients number
PSV	17
SIMV + PSV	15
PRVC	9
PCV	1

PSV = pressure support ventilation, SIMV = synchronized intermittent mandatory ventilation, PRVC = pressure regulated volume controlled, PCV = pressure controlled ventilation.

The relationship was marginal, although still significant, for MAP ($r2=0.10$; $p=0.037$; *Figure 4*) possibly reflecting an increase in pulse pressure which modified SAP and diastolic arterial pressure (DAP) leaving MAP almost unchanged as a consequence of volume expansion. Overall, only 2 patients were treated with dobutamine and they were both responders while 14 received noradrenaline, 8 of which

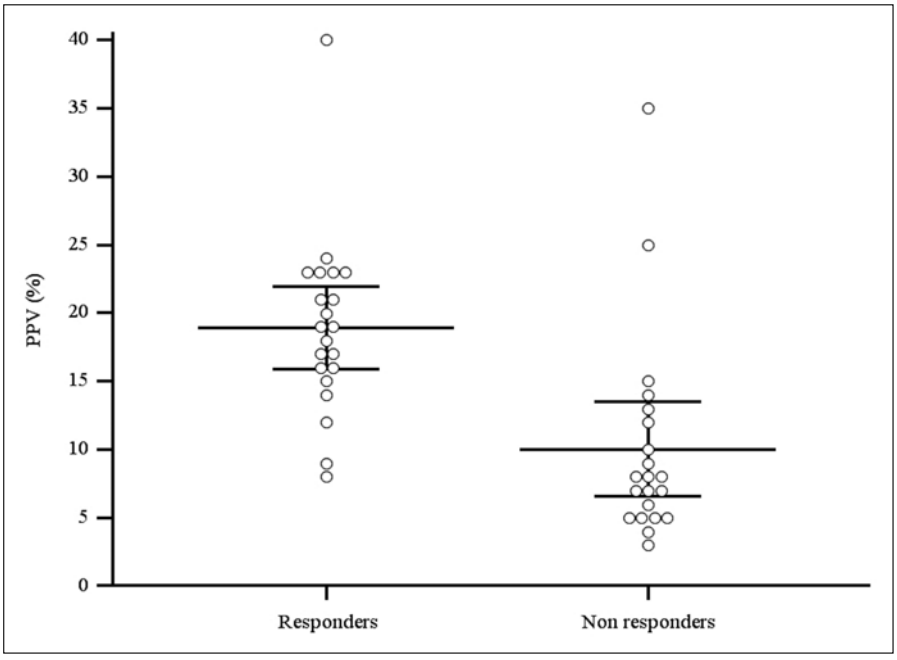

Figure 5
Baseline pulse pressure variation in responders versus non responders ($p = 0.0002$). Central lines are means, whiskers are their 95% confidence intervals.

were responders to volume expansion. While dobutamine, by increasing myocardial contractility, affects PPV the effect of noradrenaline on this parameter is much less predictable. However, there was no significant difference between responders and non responders in terms of both drugs (*Table 1*) and the fluid challenge was done while keeping drug infusion constant.
Baseline PPV was higher in respond-

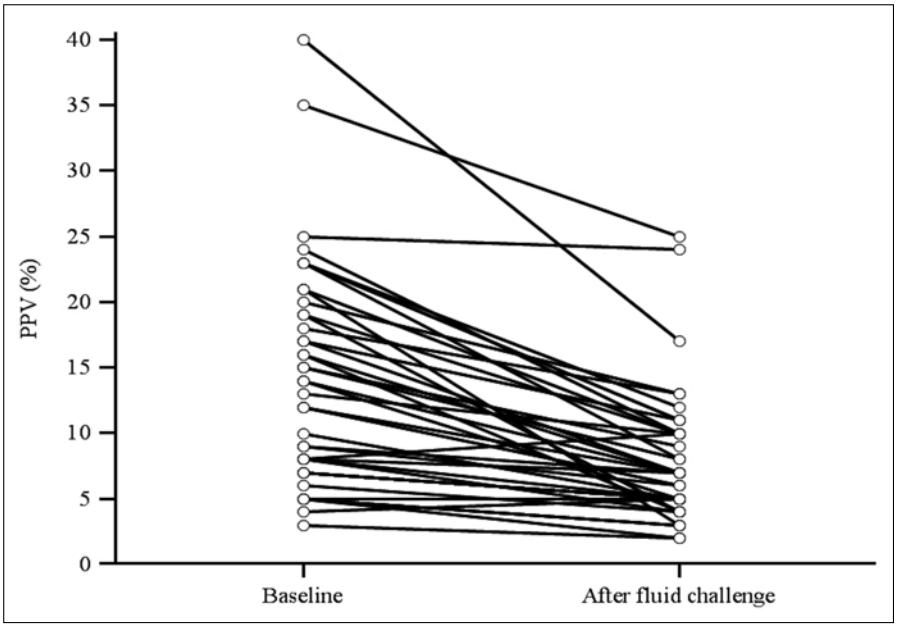

Figure 6
Pulse pressure variation before versus after fluid challenge in the whole sample ($p < 0.0001$).

ers than in non responders (19% vs 10%; p=0.0002; *Figure 5*) and PPV was overall significantly higher before than after fluid challenge (14% vs 8%; p<0.0001; *Figure 6*).

DISCUSSION

The results of this observational study show that PPV has a good accuracy in predicting the response to plasma volume expansion even in mechanically ventilated patients who actively trigger the ventilator. This is the first time that such a finding is reported, the dominating concept being that PPV is a clinically useful tool only under strictly mandatory ventilation in patients passively adapted to the ventilator.

The most peculiar aspect of our study is probably the criterion used to define fluid responsiveness.

To our knowledge, this is the first time that arterial pressure changes were used to this purpose instead of flow-based indices (namely CO or SV), the standard method in previous studies. Increasing the arterial pressure is an obvious goal in hemodynamically unstable patients and reaching a MAP of at least 65 mm Hg by mean of fluids administration is indeed one of the main endpoints, for example, in septic shock guidelines (23). Furthermore, arterial pressure monitoring is usually performed well before a CO measurement which is often unavailable for all patients with hemodynamic derangement treated at the same time in a modern ICU. We found therefore reasonable to define "fluid responder" a hypotensive patient who significantly improves his or her arterial pressure as a consequence of a fluid challenge, in the absence of confounding factors like agitation or pain.

Arterial pressure is the product of cardiac output and systemic vascular resistance and there is no mechanism by which plasma volume expansion should cause vasoconstriction, at least in the short time. Hence, an increase in arterial pressure immediately after a fluid challenge can reasonably be attributed to an increase in CO and the percentage change in arterial pressure should equal the percentage change in cardiac output.

This concept was confirmed by a study by Monnet (15) that showed, in hypotensive patients, a good correlation between the rate of change in CO and percentage change in pulse pressure and in SAP after a fluid challenge. Interestingly, this study found a poor correlation between CO changes and MAP changes after volume expansion. This seems in agreement with our data showing that baseline PPV is more correlated with changes in SAP than in MAP after fluid administration. Furthermore, flow-based indices measurement systems are very often characterized by a delay in displaying values due to the specific sampling time while arterial pressure monitoring through a standard transducer allows real time beat-to-beat reading allowing immediate detection of the changes induced by volume expansion.

While the strict need to measure CO to verify fluid responsiveness was recently questioned (14), a subsequent study performed by Pierrakos (13) on septic shock patients failed to find an association between changes in arterial pressure and changes in CO after a fluid challenge. Although the peculiarity of vasomotor alterations found in septic shock could be responsible for these findings, we believe that the discrepancy with our and Pierrakos' data are mainly due to the fact that in that study hypotension was not a prerequisite for enrollment, and that patients could have been, in general, in stable hemodynamic conditions. Indeed, both responders and non responders had normal CO and MAP before as well as after fluid challenge (13). Furthermore,

as pointed out by the authors, the CO was measured by a slow-response system that, as mentioned previously, could have been unable to promptly track flow changes induced by the fluid challenge. However, in this study, no patients who increased significantly the MAP after the fluid challenge failed to show a significant increase in CO.

This confirms the basis of our pressure-based definition of fluid responsiveness i.e., in hypotensive patients, in the short time after volume expansion there is no arterial pressure increase without an increase in CO. This was recently confirmed by Le Manach et al. (16) who demonstrated that there is a significant relationship between volume expansion-induced changes in arterial pressure and CO and that volume expansion-induced changes in arterial pressure detect a more than 15% increase in CO with reasonable sensitivity and specificity. While the authors questioned the clinical (but not the physiological) relevance of this finding it must be noticed that this study was performed in surgical patients in the perioperative period while we studied critically ill ICU patients. Different clinical implications of the results are therefore somehow plausible. We believe therefore that standard invasive arterial pressure monitoring is a simple, cheap and reliable method to assess "fluid responsiveness", and that this definition can be used even when an arterial pressure based criterion is adopted. If, and in which clinical situation, plasma volume expansion can lead to an increase in CO without an increase in arterial pressure should be further defined.

When spontaneous breathing develops in a mechanically ventilated patient, it inevitably produces some form of negative inspiratory intrathoracic pressure and possibly a certain degree of positive expiratory (and end-expiratory) pressure both of which can lead to a PPV which is no more correlated with the patient's preload reserve. It seems reasonable to think, however, that the entity of this phenomenon must critically depend on some aspects of the ventilator setting and performance. First of all, we hypothesized that the inspiratory trigger characteristics could critically affect the venous return and, hence, the PPV accuracy in predicting the preload reserve by regulating the entity both in magnitude and in time of the negative pressure generated by the patient's inspiratory effort. A sensitive, fast-response trigger which starts the inspiratory phase allowing only a minimal airway pressure drop should have a different effect on venous return than a "hard" trigger on a slow-response ventilator.

Different inspiratory triggers and different ventilators could, therefore, differently influence the cardiorespiratory interactions at the base of PPV monitoring. The application of an inspiratory resistor, to which an inadequate inspiratory trigger can be assimilated, was indeed demonstrated to increase PPV even at normo- and hypervolemia (12). The positive results of our study could be at least in part explained by the hypothesis that, with the ventilator Maquet Servo-i, a sensitive flow-based inspiratory trigger would lead to a ventilation pattern similar to that of a controlled mode in a passive patient. In all the studied patients, the inspiratory trigger was set on the same flow mode level (position 4) independently from the underlying pathology.

We choose this setting because we thought it could reasonably guarantee the avoidance of unnecessary respiratory work without the risk of autotriggering. We speculate that this setting allowed minimal negative intrathoracic pressure with negligibly different effects on venous return with respect with a controlled positive pressure ventilation mode. Expiratory trigger setting is in our opinion another important point that

can have effects on lung mechanics and as a consequence on the entity and clinical usefulness of PPV.

All our patients had the expiratory trigger set to minimize the risk of dynamic hyperinflation: thus when intrinsic positive end-expiratory pressure (iPEEP) was suspected, expiratory flow-based cycling threshold was increased from our default 25% level to the value that allowed an expiration time sufficiently long to avoid clinically relevant iPEEP. This could have contributed to maintain the association between PPV and fluid responsiveness since the application of an expiratory resistor had been demonstrated to affect the PPV accuracy as a fluid responsiveness predictor (12). As far as external PEEP is concerned, applied levels were generally low in all patients (*Table 1*).

While non responders had slightly higher PEEP than responders, the difference was minimal and not statistically significant. We believe, therefore, that differences in this parameter did not affect our results.

Our study has some limitations. First, we did not record the TV of the studied patients. TV is a major determinant of PPV and other dynamic circulatory indices (3) and we acknowledge that the lack of information about this parameter could impede clear interpretation of the data.

While we cannot formally exclude a difference in TV between responders and non responders we also believe that this could not have distorted the final and pragmatically relevant interpretation of our data, which is that, in the setting found in everyday clinical practice in our ICU, in patients who actively trigger the ventilator in PSV, SIMV, PRVC or PCV and who are in stable respiratory conditions, PPV remains a very accurate predictor of response to plasma volume expansion.

Second, all our patients were ventilated and monitored with the same devices. We believe that, when spontaneous breathing is present, the usefulness of PPV critically depends on the specific performance of both ventilator and monitoring algorithm. We cannot exclude, therefore, that different results could have been found if different technology and different settings were used. Third, we could not calculate the confidence interval of the best single cutoff because our statistical software lacked this possibility.

CONCLUSION

Our data suggest that in critically ill patients with spontaneous breathing activity ventilated with a Servo-i ventilator with the inspiratory trigger set on flow position 4, PPV, when measured through a Philips Intellivue MP 70 monitor, is a clinically useful tool that accurately predicts fluid responsiveness.

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