

Michael R. Pinsky · Laurent Brochard  
Jordi Mancebo · Massimo Antonelli  
*Editors*

# Applied Physiology in Intensive Care Medicine 2

Physiological Reviews and Editorials  
*Third Edition*

 Springer

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M.R. Pinsky · L. Brochard · J. Mancebo · M. Antonelli (Eds.)

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# Preface

Perhaps no field of medicine witnesses such dynamic change in practice over similar time intervals as the practice of intensive care medicine. Thus, the practice of intensive care medicine is at the very forefront of treatment and monitoring response innovation and discovery. The challenge for the healthcare practitioner facing the critically ill is daunting because the critically ill patient is by definition at the limits of his or her physiologic reserve. Such patients need immediate, aggressive but balanced life-altering interventions to minimize the detrimental aspects of acute illness and hasten recovery. Treatment decisions and response to therapy are usually assessed by measures of physiologic function but also require an understanding of a myriad of new information. However, how one uses such information is often unclear and rarely supported by prospective clinical trials and if clinical trials are available, rarely do they address the specific needs of the specific patient being treated. Thus, the bedside clinician is forced to rely primarily on physiologic principals in determining the best treatments and response to therapy. However, the physiologic foundation present in practicing physicians is uneven and occasionally supported more by habit or prior training than science. Furthermore, although excellent textbooks are available as background information, they are by necessity unable to present the latest changes or place specific novel aspects of applied physiology into perspectives based on new information.

To address this issue we have collected in this volume a series of review articles published in Intensive Care Medicine from 2002 until July 2011. This present volume combines these selected review articles, specifically included for their ability to address central critical care issues and published in the same time interval. This collection of review articles, written by some of the most respected experts in the field, represent an up-to-date and invaluable compendium of practical bedside knowledge essential to the effective delivery of acute care medicine. Although this text could be read from cover to cover, the reader is encouraged to use this text as a reference source, referring to individual review articles that pertain to specific clinical issues. In that way the relevant information will have immediate practical meaning and hopefully become incorporated into routine practice.

We hope that the reader finds these reviews useful in their practice and enjoys reading them as much as we enjoyed editing the original articles.

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# Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care

**Abstract** *Objective:* In mechanically ventilated patients the indices which assess preload are used with increasing frequency to predict the hemodynamic response to volume expansion. We discuss the clinical utility and accuracy of some indices which were tested as bedside indicators of preload reserve and fluid responsiveness in hypotensive patients under positive pressure ventilation. *Results and conclusions:* Although

preload assessment can be obtained with fair accuracy, the clinical utility of volume responsiveness-guided fluid therapy still needs to be demonstrated. Indeed, it is still not clear whether any form of monitoring-guided fluid therapy improves survival.

**Keywords** Positive pressure ventilation · Hypotension · Volume expansion · Cardiac index

Prediction is very difficult, especially about the future.

Niels Bohr

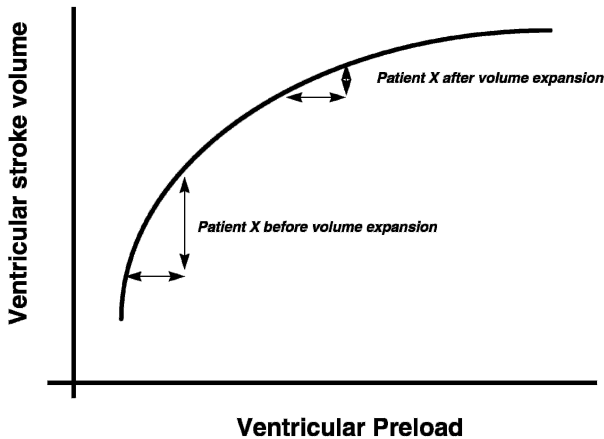
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## Introduction

Hypotension is one of the most frequent clinical signs observed in critically ill patients. To restore normal blood pressure, the cardiovascular filling (preload-defined as end-diastolic volume of both ventricular chambers), cardiac function (inotropism), and vascular resistance (afterload) must be assessed. Hemodynamic instability secondary to effective or relative intravascular volume depletion are very common, and intravascular fluid resuscitation or volume expansion (VE) allows restoration of ventricular filling, cardiac output and ultimately arterial blood pressure [1, 2]. However, in the Frank-Starling curve (stroke volume as a function of preload) the slope presents on its early phase a steep portion which is followed by a plateau (Fig. 1). As a consequence, when the plateau is reached, vigorous fluid resuscitation carries out the risk of generating volume overload and pulmonary edema and/or right-ventricular dysfunction. Thus in hypotensive patients methods able to unmask decreased preload and to predict whether car-

diac output will increase or not with VE have been sought after for many years. Presently, as few methods are able to assess ventricular volumes continuously and directly, static pressure measurements and echocardiographically measured ventricular end-diastolic areas are used as tools to monitor cardiovascular filling. Replacing static measurements, dynamic monitoring consisting in assessment of fluid responsiveness using changes in systolic arterial pressure, and pulse pressure induced by positive pressure ventilation have been proposed. The present review analyses the current roles and limitations of the most frequently used methods in clinical practice to predict fluid responsiveness in patients undergoing mechanical ventilation (MV) (Table 1).

One method routinely used to evaluate intravascular volume in hypotensive patients uses hemodynamic response to a fluid challenge [3]. This method consists in infusing a defined amount of fluid over a brief period of time. The response to the intravascular volume loading can be monitored clinically by heart rate, blood pressure, pulse pressure (systolic minus diastolic blood pressure), and urine output or by invasive monitoring with the measurements of the right atrial pressure (RAP), pulmonary artery occlusion pressure (Ppao), and cardiac output. Such a fluid management protocol assumes that the in-



**Fig. 1** Representation of Frank-Starling curve with relationship between ventricular preload and ventricular stroke volume in patient X. After volume expansion the same magnitude of change in preload recruit less stroke volume, because the plateau of the curve is reached which characterize a condition of preload independency

**Table 1** Studies of indices used as bedside indicators of preload reserve and fluid responsiveness in hypotensive patients under positive-pressure ventilation (*BMI* body mass index, *CO* cardiac output, *CI* cardiac index, *SV* stroke volume, *SVI* stroke volume index, *IAC* invasive arterial catheter, *MV* proportion of patients mechanically ventilated,  $\uparrow$  increase,  $\downarrow$  decrease, *PAC* pulmonary artery catheter, *R* responders, *NR* nonresponders, *FC* fluid challenge,

Variable measured	Technique	n	MV (%)	Volume (ml) and type of plasma substitute	Duration of FC (min)	Definition of R	Definition of NR	p: difference in baseline values R vs. NR	Reference
Rap	PAC	28	46	250 Alb 5%	20–30	$\uparrow$ SVI	$\downarrow$ SVI or unchanged	NS	37
Rap	PAC	41	76	300 Alb 4.5%	30	$\uparrow$ CI	CI $\downarrow$ or unchanged	NS	18
Rap	PAC	25	94.4	NaCl 9‰ + Alb 5% to $\uparrow$ Ppao	Until $\uparrow$ Ppao	$\uparrow$ SV $\geq 10\%$	$\uparrow$ SV $< 10\%$	0.04	31
Rap	PAC	40	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	NS	36
Ppao	PAC	28	46	250 Alb 5%	20–30	$\uparrow$ SVI	$\downarrow$ SVI or unchanged	NS	37
Ppao	PAC	41	76	300 Alb 4.5%	30	$\uparrow$ CI	CI $\downarrow$ or unchanged	NS	18
Ppao	PAC	29	69	300–500 RL	? bolus	$\uparrow$ CO $> 10\%$	CO $\downarrow$ or unchanged	$< 0.01$	40
Ppao	PAC	32	84	300–500 RL	?	$\uparrow$ CI $> 20\%$	$\uparrow$ CI $< 20\%$	NS	41
Ppao	PAC	16	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	0.1	42
Ppao	PAC	41	100	500 pPentastarch	15	$\uparrow$ SV $\geq 20\%$	$\uparrow$ SV $< 20\%$	0.003	25
Ppao	PAC	25	94.4	NaCl 9‰, Alb 5% to $\uparrow$ Ppao	Until $\uparrow$ Ppao	$\uparrow$ SV $\geq 10\%$	$\uparrow$ SV $< 10\%$	0.001	31
Ppao	PAC	40	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	NS	36
Ppao	PAC	19	100	500–750 HES 6%	10	$\uparrow$ CO $> 10\%$	$\uparrow$ SV $< 10\%$	0.0085	39
RVEDV	PAC	29	69	300–500 RL	? bolus	$\uparrow$ CO $> 10\%$	CO $\downarrow$ or unchanged	$< 0.001$	40
RVEDV	PAC	32	84	300–500 RL	?	$\uparrow$ CI $> 20\%$	$\uparrow$ CI $< 20\%$	$< 0.002$	41
RVEDV	PAC	25	94.4	NaCl 9‰, Alb 5% to $\uparrow$ Ppao	Until $\uparrow$ Ppao	$\uparrow$ SV $\geq 10\%$	$\uparrow$ SV $< 10\%$	0.22	31
LVEDV	TEE	16	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	0.005	42
LVEDV	TEE	41	100	500 Pentastarch	15	$\uparrow$ SV $\geq 20\%$	$\uparrow$ SV $< 20\%$	0.012	25
LVEDV	TEE	19	100	8 ml/kg HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	NS	79
LVEDV	TEE	19	100	500–750 HES 6%	10	$\uparrow$ CO $> 10\%$	$\uparrow$ SV $< 10\%$	NS	39
SPV	IAC	16	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	0.0001	42
SPV	IAC	40	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	$< 0.001$	36
SPV	IAC	19	100	500–750 HES 6%	10	$\uparrow$ CO $> 10\%$	$\uparrow$ SV $< 10\%$	0.017	39
$\Delta$ down	IAC	16	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	0.0001	42
$\Delta$ down	IAC	19	100	500–750 HES 6%	10	$\uparrow$ CO $> 10\%$	$\uparrow$ SV $< 10\%$	0.025	39
$\Delta$ PP	IAC	40	100	500 HES 6%	30	$\uparrow$ CI $> 15\%$	$\uparrow$ CI $< 15\%$	$< 0.001$	36

travascular volume of the critically ill patients can be defined by the relationship between preload and cardiac output, and that changing preload with volume infusion affects cardiac output. Thus an increase in cardiac output following VE (patient responder) unmasks an hypovolemic state or preload dependency. On the other hand, lack of change or a decrease in cardiac output following VE (nonresponding patient) is attributed to a normovolemic, to an overloaded, or to cardiac failure state. Therefore, as the fluid responsiveness defines the response of cardiac output to volume challenge, indices which can predict the latter are necessary.

### Static measurements for preload assessment

#### Measures of intracardiac pressures

According to the Frank-Starling law, left-ventricular preload is defined as the myocardial fiber length at the end

*HES* hydroxyethyl starch, *RL* Ringer's lactate, *Alb* albumin,  $\Delta$ down delta down,  $\Delta$ PP respiratory variation in pulse pressure, *LVEDV* left-ventricular end diastolic volume, *SPV* systolic pressure variation, *SVV* stroke volume variation, *TEE* transesophageal echocardiography, *Ppao* pulmonary artery occlusion pressure, *RAP* right atrial pressure, *RVEDV* right-ventricular-end diastolic volume, *FC* fluid challenge)

of the diastole. In clinical practice, the left-ventricular end-diastolic volume is used as a surrogate to define left-ventricular preload [4]. However, this volumetric parameter is not easily assessed in critically ill patients. In normal conditions, a fairly good correlation exists between ventricular end-diastolic volumes and mean atrial pressures, and ventricular preloads are approximated by RAP and/or Ppao in patients breathing spontaneously [5, 6]. Critically ill patients often require positive pressure ventilation, which modifies the pressure regimen in the thorax in comparison to spontaneous breathing. Indeed, during MV RAP and Ppao rise secondary to an increase in intrathoracic pressure which rises pericardial pressure. This pressure increase induces a decrease in venous return [7, 8] with first a decrease in right and few heart beats later in left-ventricular end-diastolic volumes, respectively [9, 10]. Under extreme conditions such as acute severe pulmonary emboli and/or marked hyperinflation, RAP may also rise secondary to an increase afterload of the right ventricle. Moreover, under positive pressure ventilation not only ventricular but also thoracopulmonary compliances and abdominal pressure variations are observed over time. Thus a variable relationship between cardiac pressures and cardiac volumes is often observed [11, 12, 13, 14]. It has also been demonstrated that changes in intracardiac pressure (RAP, Ppao) no longer directly reflect changes in intravascular volume [15]. Pinsky et al. [16, 17] have demonstrated that changes in RAP do not follow changes in right-ventricular end-diastolic volume in postoperative cardiac surgery patients under positive pressure ventilation. Reuse et al. [18] observed no correlation between RAP and right-ventricular end-diastolic volume calculated from a thermodilution technique in hypovolemic patients before and after fluid resuscitation. The discordance between RAP and right-ventricular end-diastolic volume measurements may result from a systematic underestimation of the effect of positive-pressure ventilation on the right heart [16, 17]. Nevertheless, the RAP value measured either with a central venous catheter or a pulmonary artery catheter is still used to estimate preload and to guide intravascular volume therapy in patient under positive pressure ventilation [19, 20].

On the left side, the MV-induced intrathoracic pressure changes, compared to spontaneously breathing, only minimally alters the relationship between left atrial pressure and left-ventricular end-diastolic volume measurement in postoperative cardiac surgery patients [21]. However, several other studies show no relationship between Ppao and left-ventricular end-diastolic volume measured by either radionuclide angiography [12, 22], transthoracic echocardiography (TTE) [23], or transesophageal echocardiography (TEE) [24, 25, 26]. The latter findings may be related to the indirect pulmonary artery catheter method for assessing left atrial pressure [27, 28], although several studies have demonstrated

that Ppao using PAC is a reliable indirect measurement of left atrial pressure [29, 30] in positive-pressure MV patients.

#### *Right atrial pressure used to predict fluid responsiveness*

Wagner et al. [31] reported that RAP was significantly lower before volume challenge in responders than in nonresponders ( $p=0.04$ ) when patients were under positive pressure ventilation. Jellinek et al. [32] found that a RAP lower than 10 mmHg predicts a decrease in cardiac index higher than 20% when a transient 30 cm H<sub>2</sub>O increase in intrathoracic pressure is administered. Presuming that the principle cause of decrease in cardiac output in the latter study was due to a reduction in venous return [9, 33, 34, 35], RAP predicts reverse VE hemodynamic effect. Nevertheless, some clinical investigations studying fluid responsiveness in MV patients have reported that RAP poorly predicts increased cardiac output after volume expansion [18, 36, 37]. Indeed, in these studies RAP did not differentiate patients whose cardiac output did or did not increase after VE (responders and nonresponders, respectively).

#### *Ppao used to predict fluid responsiveness*

Some studies have demonstrated that Ppao is a good predictor of fluid responsiveness [13, 31, 38]. Recently Bennett-Guerrero et al. [39] also found that Ppao was a better predictor of response to VE than systolic pressure variation (SPV) and left-ventricular end-diastolic area measured by TEE. However, several other studies noted that Ppao is unable to predict fluid responsiveness and to differentiate between VE-responders and VE-nonresponders [18, 25, 36, 37, 40, 41, 42]. The discrepancy between the results of these studies may partly reflect differences in patients' baseline characteristics (e.g., demographic differences, medical history, chest and lung compliances) at study entry. Furthermore, differences in location of the pulmonary artery catheter extremity relative to the left atrium may be present [43]. Indeed, according to its position, pulmonary artery catheter may display alveolar pressure instead of left atrial pressure (West zone I or II) [44]. The value of Ppao is also influenced by juxtacardiac pressure [45, 46] particularly if positive end-expiratory pressure (PEEP) is used [28]. To overcome the latter difficulty in MV patients when PEEP is used, nadir Ppao (Ppao measured after airway disconnection) may be used [46]. However, as nadir Ppao requires temporary disconnection from the ventilator, it might be deleterious to severely hypoxemic patients. No study has yet evaluated the predictive value of nadir Ppao for estimating fluid responsiveness in MV patients.

In brief, although static intracardiac pressure measurements such as RAP and Ppao have been studied and used for many years for hemodynamic monitoring, their low predictive value in estimating fluid responsiveness in MV patients must be underlined. Thus using only intravascular static pressures to guide fluid therapy can lead to inappropriate therapeutic decisions [47].

#### Measures of ventricular end-diastolic volumes

Radionuclide angiography [48], cineangiocardiology [49], and thermodilution [50] have been used to estimate ventricular volumes for one-half a century. In intensive care units, various methods have been used to measure ventricular end-diastolic volume at the bedside, such as radionuclide angiography [51, 52], TTE [23, 53, 54], TEE [55], and a modified flow-directed pulmonary artery catheter which allows the measurement of cardiac output and right-ventricular ejection fraction (and the calculation of right-ventricular end-systolic and end-diastolic volume) [31, 41].

#### *Right-ventricular end-diastolic volume measured by pulmonary artery catheter used to predict fluid responsiveness*

During MV right-ventricular end-diastolic volume measured with a pulmonary artery catheter is decreased by PEEP [56] but is still well correlated with cardiac index [57, 58] and is a more reliable predictor of fluid responsiveness than Ppao [40, 41]. On the other hand, other studies have found no relationship between change in right-ventricular end-diastolic volume measured by pulmonary artery catheter and change in stroke volume in two series of cardiac surgery patients [16, 18]. Similarly, Wagner et al. [31] found that right-ventricular end-diastolic volume measured by pulmonary artery catheter was not a reliable predictor of fluid responsiveness in patients under MV, and that Ppao and RAP were superior to right-ventricular end-diastolic volume. The discrepancy between the results of these studies may partly reflect the measurement errors of cardiac output due to the cyclic change induced by positive pressure ventilation [59, 60, 61, 62], the inaccuracy of cardiac output measurement obtained by pulmonary artery catheter when the flux is low [63], and the influence of tricuspid regurgitation on the measurement of cardiac output [64]. Moreover, as right-ventricular end-diastolic volume is calculated (stroke volume divided by right ejection fraction), cardiac output becomes a shared variable in the calculation of both stroke volume and right-ventricular end-diastolic volume, and a mathematical coupling may have contributed to the close correlation observed between these two variables. Nevertheless, right-ventricular end-diastolic volume compared to Ppao may be useful in a small group of patients with

high intra-abdominal pressure or when clinicians are reluctant to obtain off-PEEP nadir Ppao measurements [65].

#### *Right-ventricular end-diastolic volume measured by echocardiography used to predict fluid responsiveness*

TTE has been shown to be a reliable method to assess right-ventricular dimensions in patients ventilated with continuous positive airway pressure or positive-pressure ventilation [66, 67]. Using this approach, right-ventricular end-diastolic area is obtained on the apical four chambers view [68]. When no right-ventricular window is available, TEE is preferred to monitor right-ventricular end-volume in MV patients [53, 55, 69, 70, 71]. The latter method has become more popular in recent years due to technical improvements [72]. Nevertheless, no study has evaluated right-ventricular size measurements by TTE or TEE as a predictor of fluid responsiveness in MV patients.

#### *Left-ventricular end-diastolic volume measured by echocardiography used to predict fluid responsiveness*

TTE has been used in the past to measure left-ventricular end-diastolic volume and/or area [23, 67, 73, 74] in MV patients. However, no study has evaluated the left-ventricular end-diastolic volume and/or area measured by TTE as predictors of fluid responsiveness in MV patients. Due to its greater resolving power, TEE easily and accurately assesses left-ventricular end-diastolic volume and/or area in clinical practice [53, 75] except in patients undergoing coronary artery bypass grafting [76]. However, different studies have reported conflicting results about the usefulness of left-ventricular end-diastolic volume and/or area measured by TEE to predict fluid responsiveness in MV patients. Cheung et al. [26] have shown that left-ventricular end-diastolic area measured by TEE is an accurate method to predict the hemodynamic effects of acute blood loss. Other studies have reported either a modest [25, 42, 77] or a poor [78, 79] predictive value of left-ventricular end-diastolic volume and area to predict the cardiac output response to fluid loading. Recent studies have also produced conflicting results. Bennett-Guerrero et al. [39] measuring left-ventricular end-diastolic area with TEE before VE found no significant difference between responders and nonresponders. Paradoxically, Reuter et al. [80] found that left-ventricular end-diastolic area index assessed by TEE before VE predicts fluid responsiveness more accurately than RAP, Ppao, and stroke volume variation (SVV). In the future three-dimensional echocardiography could supplant other methods for measuring left-ventricular end-diastolic volume and their predictive value of fluid responsiveness. In a word, although measurements of

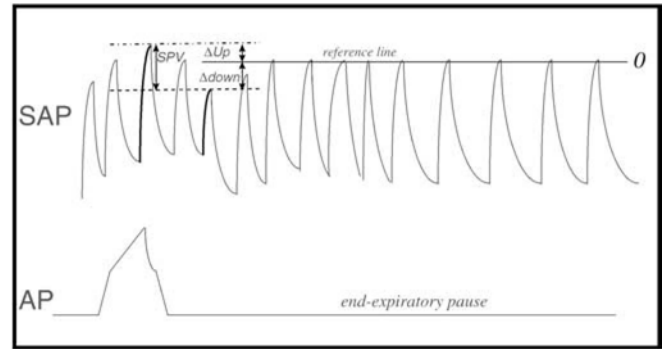
ventricular volumes should theoretically reflect preload dependence more accurately than other indices, conflicting results have been reported so far. These negative findings may be related to the method used to estimate end-diastolic ventricular volumes which do not reflect the geometric complexity of the right ventricle and to the influences of the positive intrathoracic pressure on left-ventricular preload, afterload and myocardial contractility [81].

### Dynamic measurements for preload assessment

Measure of respiratory changes in systolic pressure, pulse pressure, and stroke volume

Positive pressure breath decreases temporary right-ventricular end-diastolic volume secondary to a reduction in venous return [7, 82]. A decrease in right-ventricular stroke volume ensues which become minimal at end positive pressure breath. This inspiratory reduction in right-ventricular stroke volume induces a decrease in left-ventricular end-diastolic volume after a phase lag of few heart beats (due to the pulmonary vascular transit time [83]), which becomes evident during the expiratory phase. This expiratory reduction in left-ventricular end-diastolic volume induces a decrease in left-ventricular stroke volume, determining the minimal value of systolic blood pressure observed during expiration. Conversely, the inspiratory increase in left-ventricular end-diastolic volume determining the maximal value of systolic blood pressure is observed secondary to the rise in left-ventricular preload reflecting the few heart beats earlier increased in right-ventricular preload during expiration. Furthermore, increasing lung volume during positive pressure ventilation may also contribute to the increased pulmonary venous blood flow (related to the compression of pulmonary blood vessels [84]) and/or to a decrease in left-ventricular afterload [85, 86, 87], which together induce an increase in left-ventricular preload. Finally, a decrease in right-ventricular end-diastolic volume during a positive pressure breath may increase left-ventricular compliance and then left-ventricular preload [88]. Thus due to heart-lung interaction during positive pressure ventilation the left-ventricular stroke volume varies cyclically (maximal during inspiration and minimal during expiration).

These variations have been used clinically to assess preload status and predict fluid responsiveness in deeply sedated patients under positive pressure ventilation. In 1983 Coyle et al. [89] in a preliminary study demonstrated that the SPV following one mechanical breath is increased in hypovolemic sedated patients and decreased after fluid resuscitation. This study defined SPV as the difference between maximal and minimal values of systolic blood pressure during one positive pressure me-



**Fig. 2** Systolic pressure variation (SPV) after one mechanical breath followed by an end-expiratory pause. Reference line permits the measurement of  $\Delta_{up}$  and  $\Delta_{down}$ . **SPV** Maximal and minimal pulse pressure. **AP** Airway pressure; **SAP** systolic arterial pressure

chanical breath. Using the systolic pressure at end expiration as a reference point or baseline the SPV was further divided into two components: an increase ( $\Delta_{up}$ ) and a decrease ( $\Delta_{down}$ ) in systolic pressure vs. baseline (Fig. 2). These authors concluded that in hypovolemic patients  $\Delta_{down}$  was the main component of SPV. These preliminary conclusions were confirmed in 1987 by Perel et al. [90] who demonstrated that SPV following a positive pressure breath is a sensitive indicator of hypovolemia in ventilated dogs. Thereafter Coriat et al. [91] demonstrated that SPV and  $\Delta_{down}$  predict the response of cardiac index to VE in a group of sedated MV patients after vascular surgery. Exploring another pathophysiological concept, Jardin et al. [92] found that pulse pressure (PP; defined as the difference between the systolic and the diastolic pressure) is related to left-ventricular stroke volume in MV patients. Using these findings, Michard et al. [35, 36,] have shown that respiratory changes in PP [ $\Delta PP = \text{maximal PP at inspiration (PPmax)} - \text{minimal PP at expiration (PPmin)}$ ]; (Fig. 2) and calculated as:  $\Delta PP (\%) = 100 (PP_{max} - PP_{min}) / (PP_{max} + PP_{min}) / 2$ ] predict the effect of VE on cardiac index in patients with acute lung injury [35] or septic shock [36]. The same team proposed another approach to assess SVV in MV patients and to predict cardiac responsiveness to VE [79]. Using Doppler measurement of beat-to-beat aortic blood flow, they found that respiratory change in aortic blood flow maximal velocity predicts fluid responsiveness in septic MV patients. Measuring SVV during positive pressure ventilation by continuous arterial pulse contour analysis, Reuter et al. [80] have recently demonstrated that SVV accurately predicts fluid responsiveness following volume infusion in ventilated patients after cardiac surgery.

### *Systolic pressure variation used to predict fluid responsiveness*

The evaluation of fluid responsiveness by SPV is based on cardiopulmonary interaction during MV [93, 94]. In 1995 Rooke et al. [95] found that SPV is a useful monitor of volume status in healthy MV patients during anesthesia. Coriat et al. [91] confirmed the usefulness of SPV for estimating response to VE in MV patients after vascular surgery. Ornstein et al. [96] have also shown that SPV and  $\Delta$ down are correlated with decreased cardiac output after controlled hemorrhage in postoperative cardiac surgical patients. Furthermore, Tavernier et al. [42] found  $\Delta$ down before VE to be an accurate index of the fluid responsiveness in septic patients, and that a  $\Delta$ down value of 5 mmHg is the cutoff point for distinguishing responders from nonresponders to VE. Finally, in septic patients Michard et al. [36] found that SPV is correlated with volume expansion-induced change in cardiac output. However, Denault et al. [81] have demonstrated that SPV is not correlated with changes in left-ventricular end-diastolic volume measured by TEE in cardiac surgery patients. Indeed, in this study, SPV was observed despite no variation in left-ventricular stroke volume, suggesting that SPV involves processes independent of changes in the left-ventricular preload (airway pressure, pleural pressure, and its resultant afterload) [81].

### *Pulse pressure variation used to predict fluid responsiveness*

Extending the concept elaborated by Jardin et al. [92], Michard et al. [36] found that  $\Delta$ PP predicted the effect of VE on cardiac output in 40 septic shock hypotensive patients. These authors demonstrated that both  $\Delta$ PP and SPV, when greater than 15%, are superior to RAP and Ppao, for predicting fluid responsiveness. Moreover,  $\Delta$ PP was more accurate and with less bias than SPV. These authors proposed  $\Delta$ PP as a surrogate for stroke volume variation concept [93], which has not been validated yet. In another study these authors [35] included VE in six MV patients with acute lung injury and found that  $\Delta$ PP is a useful guide to predict fluid responsiveness.

### *Stroke volume variation to predict fluid responsiveness*

Using Doppler TEE, Feissel et al. [79] studied changes in left-ventricular stroke volume induced by the cyclic positive pressure breathing. By measuring the respiratory variation in maximal aortic blood flow velocity these authors predicted fluid responsiveness in septic MV patients. Left-ventricular stroke volume was obtained by multiplying flow velocity time integral over aortic valve

by valve opening area during expiration. However, this finding may be biased, as expiratory flow velocity time integral is a shared variable in the calculation of both cardiac output and expiratory maximal aortic blood flow velocity and a mathematical coupling may contribute to the observed correlation between changes in cardiac output and variation in maximal aortic blood flow velocity. Finally, Reuter et al. [80] used continuous arterial pulse contour analysis and found that SVV during positive pressure breath accurately predicts fluid responsiveness following VE in ventilated cardiac surgery patients [80]. Using the receiver operating characteristics curve, these authors demonstrated that the area under the curve is statistically greater for SVV (0.82; confidence interval: 0.64–1) and SPV (0.81; confidence interval: 0.62–1) than for RAP (0.45; confidence interval: 0.17–0.74) ( $p < 0.001$ ) [97]. Concisely, dynamic indices have been explored to evaluate fluid responsiveness in critically ill patients. All of them have been validated in deeply sedated patients under positive-pressure MV. Thus such indices are useless in spontaneously breathing intubated patients, a MV mode often used in ICU. Moreover, regular cardiac rhythm is an obligatory condition to allow their use.

## **Conclusion**

Positive pressure ventilation cyclically increases intrathoracic pressure and lung volume, both of which decrease venous return and alter stroke volume. Thus VE which rapidly restore cardiac output and arterial blood pressure is an often used therapy in hypotensive MV patients and indices which would predict fluid responsiveness are necessary. RAP, Ppao, and right-ventricular end-diastolic volume, which are static measurements, have been studied but produced conflicting data in estimating preload and fluid responsiveness. On the other hand, SPV and  $\Delta$ PP, which are dynamic measurements, have been shown to identify hypotension related to decrease in preload, to distinguish between responders and nonresponders to fluid challenge (Table 1), and to permit titration of VE in various patient populations.

Although there is substantial literature on indices of hypovolemia, only few studies have evaluated the cardiac output changes induced by VE in MV patients. Moreover, therapeutic recommendations regarding unmasked preload dependency states without hypotension need further studies. Finally, another unanswered question is related to patients outcome: does therapy guided by fluid responsiveness indices improve patients survival?

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