Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

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In mechanically ventilated patients with acute circulatory failure related to sepsis, we investigated whether the respiratory changes in arterial pressure could be related to the effects of volume expansion (VE) on cardiac index (CI). Forty patients instrumented with indwelling systemic and pulmonary artery catheters were studied before and after VE. Maximal and minimal values of pulse pressure (Pp_{max} and Pp_{min}) and systolic pressure (Ps_{max} and Ps_{min}) were determined over one respiratory cycle. The respiratory changes in pulse pressure (ΔPp) were calculated as the difference between Pp_{max} and Pp_{min} divided by the mean of the two values and were expressed as a percentage. The respiratory changes in systolic pressure (ΔPs) were calculated using a similar formula. The VE-induced increase in CI was $\geqslant$ 15% in 16 patients (responders) and < 15% in 24 patients (nonresponders). Before VE, ΔPp (24 ± 9 versus 7 ± 3%, $p < 0.001$) and ΔPs (15 ± 5 versus 6 ± 3%, $p < 0.001$) were higher in responders than in nonresponders. Receiver operating characteristic (ROC) curves analysis showed that ΔPp was a more accurate indicator of fluid responsiveness than ΔPs. Before VE, a ΔPp value of 13% allowed discrimination between responders and nonresponders with a sensitivity of 94% and a specificity of 96%. VE-induced changes in CI closely correlated with ΔPp before volume expansion ($r^2 = 0.85$, $p < 0.001$). VE decreased ΔPp from 14 ± 10 to 7 ± 5% ($p < 0.001$) and VE-induced changes in ΔPp correlated with VE-induced changes in CI ($r^2 = 0.72$, $p < 0.001$). It was concluded that in mechanically ventilated patients with acute circulatory failure related to sepsis, analysis of ΔPp is a simple method for predicting and assessing the hemodynamic effects of VE, and that ΔPp is a more reliable indicator of fluid responsiveness than ΔPs.

Volume expansion (VE) is the first-line therapy proposed in septic patients in an attempt to improve hemodynamics (1). Both the increase in microvascular permeability and venous pooling induce inadequate cardiac preload such that a large amount of fluid is usually needed during the early phase of resuscitation (1). However, excessive VE leads to interstitial fluid accumulation, which may worsen gas exchange, decrease myocardial compliance, and limit oxygen diffusion to the tissues (2). Therefore, in septic patients with acute circulatory failure, reliable predictors of fluid responsiveness are needed at the bedside.

By increasing pleural pressure and transpulmonary pressure, mechanical insufflation may respectively decrease systemic venous return, i.e., right ventricular (RV) filling (3), and transiently impair RV ejection (4, 5). Therefore, RV stroke volume may decrease during the inspiratory period, leading to a left ventricular (LV) preload reduction occurring during the expiratory period because of the long pulmonary transit time of blood (6). These respiratory changes in LV preload may induce cyclic changes in LV stroke volume (6, 7). Aortic pulse pressure (systolic − diastolic pressure) is directly proportional to LV stroke volume and inversely related to aortic compliance (8). Thus, the respiratory changes in LV stroke volume have been shown to be reflected by changes in peripheral pulse pressure during the respiratory cycle (6).

Interestingly, the cyclic changes in RV preload induced by mechanical ventilation should result in greater cyclic changes in RV stroke volume when the right ventricle operates on the steep rather than on the flat portion of the Frank-Starling curve (9, 10). The cyclic changes in RV stroke volume and hence in LV preload should also result in greater cyclic changes in LV stroke volume when the left ventricle operates on the ascending portion of the Frank-Starling curve (9, 10). Thus, the magnitude of the respiratory changes in LV stroke volume and hence of the respiratory changes in pulse pressure (ΔPp) should be an indicator of biventricular preload dependence. Consistent with this hypothesis, we have recently demonstrated in mechanically ventilated patients with acute lung injury that ΔPp could be used to monitor the adverse hemodynamic effects of PEEP, which are mainly related to a decrease in systemic venous return (11).

The cyclic changes in peripheral systolic pressure induced by mechanical ventilation have also been studied in animals (12) and in critically ill patients (13, 14). These changes have been shown to be influenced by the volume status (12–14) and have been proposed as an indicator of fluid responsiveness (13, 14). Respiratory changes in systolic pressure (ΔPs) result from changes in aortic transmural pressure (mainly related to changes in LV stroke volume) and from changes in extramural pressure (i.e., from changes in pleural pressure) (7). In contrast, ΔPp depends only on changes in transmural pressure, because changes in pleural pressure should affect both systolic and diastolic pressure. Accordingly, ΔPp is expected to be more reliable than ΔPs as an indicator of the respiratory changes in LV stroke volume and hence of biventricular preload dependence.

Thus, in mechanically ventilated patients with acute circulatory failure related to sepsis, we investigated (*1*) whether ΔPp could predict the hemodynamic effects of VE, (*2*) whether changes in ΔPp could be used to assess changes in cardiac index (CI) induced by VE, and (*3*) whether ΔPp might be a more reliable indicator of fluid responsiveness than ΔPs.

METHODS

The protocol was approved by the institutional review board for human subjects (Comité Consultatif de Protection des Personnes dans la

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(*Received in original form March 4, 1999 and in revised form December 29, 1999*)

Part of this study has been presented at the American Thoracic Society international conference, 1999, San Diego, California.

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Am J Respir Crit Care Med Vol 162. pp 134–138, 2000
Internet address: www.atsjournals.org

Recherche Biomédicale, Bicêtre Hospital) and written informed consent was obtained from all the patients' next of kin.

Patients

We studied 40 mechanically ventilated patients diagnosed with acute circulatory failure related to sepsis. This group comprised 32 men and eight women, aged between 18 and 81 yr (mean age, 55 ± 16 yr). Inclusion criteria were as follows: (*1*) sepsis defined by the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (15); (*2*) acute circulatory failure defined by a systolic blood pressure < 90 mm Hg or the need of vasopressive drugs (dopamine > 5 μg/kg/min or norepinephrine); (*3*) instrumentation with indwelling radial ($n = 15$) or femoral ($n = 25$) arterial and pulmonary artery catheters; (*4*) hemodynamic stability, defined by a variation in heart rate, blood pressure, and cardiac output ($\dot{Q}$) of less than 10% over the 15-min period before starting the protocol. Patients were excluded if they had arrhythmias, severe hypoxemia (ratio of arterial oxygen pressure to fraction of inspired oxygen $[Pa_{O_2}/FI_{O_2}] < 100$ mm Hg), or a pulmonary artery occlusion pressure (Ppao) $\geqslant 18$ mm Hg.

Hemodynamic Measurements

Patients were studied while supine, and zero pressure was measured at the midaxillary line. Right atrial pressure (Pra) and Ppao were recorded throughout the respiratory cycle and measured at end-expiration. The correct position of the pulmonary artery catheter in West's zone 3 was checked using a method previously described (16). $\dot{Q}$ was calculated as the mean of five measurements obtained by injecting 10 ml of dextrose solution randomly during the respiratory cycle. CI, stroke volume index, and systemic and pulmonary vascular resistances were calculated using standard formulas.

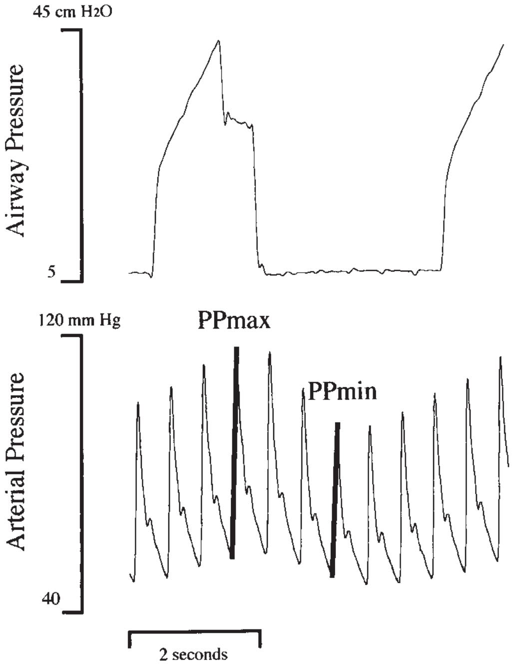

Figure 1. Simultaneous recording of systemic arterial and airway pressure curves in one illustrative patient with large Ps and Pp variations. Systolic and diastolic pressure were measured on a beat-to-beat basis and Pp was calculated as the difference between systolic and diastolic pressure. Pp_{max} and Pp_{min} were determined over a single respiratory cycle. The respiratory changes in pulse pressure (ΔPp) were calculated as the difference between Pp_{max} and Pp_{min} divided by the mean of the two values, and were expressed as a percentage. The respiratory changes in systolic pressure (ΔPs) were evaluated using a similar formula.

Respiratory Changes in Arterial Pressure

We used the analog output from the monitor (Monitor M1092A; Hewlett-Packard, Les Ullis, France) via an analog-to-digital converter to record the arterial pressure and airway pressure curves over at least 3 breaths simultaneously onto a computer (Toshiba 3200 SX, Tokyo, Japan). Recording was performed at a sampling rate of 500 Hz using customized acquisition software. Systolic and diastolic arterial pressure were measured on a beat-to-beat basis and pulse pressure (Pp) was calculated as the difference between systolic and diastolic pressure. Maximal and minimal values for systolic (Ps_{max} and Ps_{min}, respectively) and pulse pressure (Pp_{max} and Pp_{min}, respectively) were determined over a single respiratory cycle. ΔPp was calculated as previously described (11): $\Delta Pp\ (\%) = 100 \times (Pp_{max} - Pp_{min})/[(Pp_{max} + Pp_{min})/2]$. ΔPs was evaluated using a similar formula: $\Delta Ps\ (\%) = 100 \times (Ps_{max} - Ps_{min})/[(Ps_{max} + Ps_{min})/2]$. An example of our data and their analysis for one subject is shown in Figure 1. ΔPp and ΔPs were evaluated in triplicate over each of three consecutive respiratory cycles. The mean values of the three determinations were used for statistical analysis.

Study Protocol

All patients were sedated and mechanically ventilated in a volume-controlled mode with a tidal volume of 8 to 12 ml/kg and an inspiratory/expiratory (I/E) ratio of one-third to one-half. Thirty-two patients were ventilated with a positive end-expiratory pressure (7 ± 4 cm H_2O). Nine patients were therapeutically paralyzed on the decision of the attending physician. In eight of the 31 remaining patients, spontaneous breathing activity was detected by visual inspection of the airway pressure curve. To ensure that the respiratory changes in arterial pressure reflected only the effects of positive pressure ventilation, these eight patients were temporarily paralyzed. Measurements were performed in duplicate, first before VE and then 30 min after VE using 500 ml 6% hydroxyethylstarch. Ventilatory settings and dosages of inotropic and vasopressive drugs were held constant.

Statistical Analysis

The effects of VE on hemodynamic parameters were assessed using a nonparametric Wilcoxon rank sum test (17). Patients were divided in two groups according to the percent increase in CI in response to VE. According to Stetz and coworkers (18), we assumed that a 15% change in CI was needed for clinical significance. Therefore, patients with a CI increase induced by VE $\geqslant 15\%$ and $< 15\%$ were classified as responders and nonresponders, respectively. The comparison of hemodynamic parameters before VE in responder and nonresponder patients was assessed using a nonparametric Mann-Whitney U test. Results were expressed as mean values ± SD. Receiver operating characteristic (ROC) curves were generated for Pra, Ppao, ΔPp, and ΔPs, varying the discriminating threshold of each parameter. The areas under the ROC curves (± SE) were calculated for each parameter and compared (19). Linear correlations were tested using the Spearman rank method. A p value less than 0.05 was considered statistically significant.

RESULTS

The 40 patients studied had clear evidence of sepsis (bacterial pneumonia: 30 patients; abdominal sepsis: eight patients; meningitis: two patients). Thirty-two patients received vasopressor support (norepinephrine: 20 patients; dopamine: 12 patients) and the eight remaining patients had severe hypotension (systolic blood pressure = 81 ± 7 mm Hg). Underlying diseases included chronic obstructive pulmonary disease ($n = 11$), diabetes mellitus ($n = 9$), ischemic cardiopathy ($n = 8$), hypertension ($n = 8$), peripheral vascular disease ($n = 5$), and chronic renal failure ($n = 3$). Echocardiography was performed in 22 patients and revealed LV systolic dysfunction in 12 patients. Twenty-two patients survived.

In all patients, maximal pulse and systolic pressures were exhibited during the inspiratory period and minimal pulse and systolic pressures during the expiratory period. The difference

TABLE 1

EFFECTS OF VE ON HEMODYNAMIC PARAMETERS*

	Baseline	VE
HR, beats/min	110 ± 22	106 ± 21†
$\overline{\text{Pa}}$, mm Hg	69 ± 13	80 ± 13†
Pra, mm Hg	9 ± 3	12 ± 4†
$\overline{\text{Ppa}}$, mm Hg	24 ± 6	29 ± 6†
Ppao, mm Hg	10 ± 3	14 ± 3†
CI, L/min/m^2	3.6 ± 0.9	4.0 ± 0.9†
SVI, ml/m^2	34 ± 12	39 ± 11†
SVRI, dyne · s/cm^5/m^2	1,418 ± 430	1,442 ± 424
PVRI, dyne · s/cm^5/m^2	325 ± 154	315 ± 128
ΔPp, %	14 ± 10	7 ± 5†
ΔPs, %	9 ± 6	6 ± 4†

Definition of abbreviations: CI = cardiac index; HR = heart rate; $\overline{\text{Pa}}$ = mean arterial pressure; ΔPp = respiratory changes in pulse pressure; $\overline{\text{Ppa}}$ = mean pulmonary arterial pressure; Ppao = pulmonary artery occlusion pressure; Pra = right atrial pressure; ΔPs = respiratory changes in systolic pressure; PVRI = pulmonary vascular resistance index; SVI = stroke volume index; SVRI = systemic vascular resistance index; VE = volume expansion.

* Values are means ± SD.

† $p < 0.001$, VE versus baseline.

between Pp_{max} and Pp_{min} ranged from 1 to 20 mm Hg (mean difference: 5 ± 4 mm Hg) and the difference between Ps_{max} and Ps_{min} ranged from 1 to 27 mm Hg (mean difference: 8 ± 6 mm Hg). In all patients, the difference between Pp_{max} and Pp_{min} was smaller than the difference between Ps_{max} and Ps_{min}. Hemodynamic parameters before and after VE are presented in Table 1.

Before VE, ΔPp ranged from 1 to 44% and ΔPs from 1 to 28%. Before VE, ΔPp and ΔPs were not correlated with either Pra or Ppao.

VE increased CI from 3.6 ± 0.9 to 4.0 ± 0.9 L/min/m^2 ($p < 0.001$). Sixteen patients were responders (CI increase $\geqslant$ 15%) and 24 were nonresponders. Before VE, ΔPp (24 ± 9 versus 7 ± 3%, $p < 0.001$) and ΔPs (15 ± 5 versus 6 ± 3%, $p < 0.001$) were higher in responder than in nonresponder patients, whereas Pra (9 ± 3 versus 9 ± 4 mm Hg) and Ppao (10 ± 3 versus 11 ± 2 mm Hg) were not significantly different between the two groups. The areas under the ROC curves (± SE) were as follows: 0.98 ± 0.03 for ΔPp, 0.91 ± 0.04 for ΔPs, 0.51 ± 0.12 for Pra, and 0.40 ± 0.09 for Ppao (Figure 2). The area for ΔPp was significantly greater than the area for ΔPs ($p < 0.01$), Pra ($p < 0.01$), and Ppao ($p < 0.01$). The threshold ΔPp value of 13% allowed discrimination between responder and nonresponder patients with a sensitivity of 94% and a specificity of 96%.

A positive and close linear correlation ($r^2 = 0.85$, $p < 0.001$) was found between ΔPp before VE and VE-induced changes in CI such that the higher ΔPp before VE, the greater was the percent increase in CI [changes in CI (%) = 1.01 × ΔPp − 1.46] (Figure 3). ΔPs before VE was also significantly correlated with the VE-induced changes in CI ($r^2 = 0.69$, $p < 0.001$), although less strongly than was ΔPp (Figure 3). Conversely, Pra and Ppao measured before VE were not correlated in any way with VE-induced changes in CI.

VE decreased both ΔPp (from 14 ± 10 to 7 ± 5%, $p < 0.001$) and ΔPs (from 9 ± 6 to 6 ± 4%, $p < 0.001$). VE-induced changes in ΔPp (ΔPp after VE minus ΔPp before VE) were correlated with VE-induced changes in CI ($r^2 = 0.72$, $p < 0.001$) such that the greater the decrease in ΔPp, the greater the increase in CI induced by VE (Figure 4). VE-induced

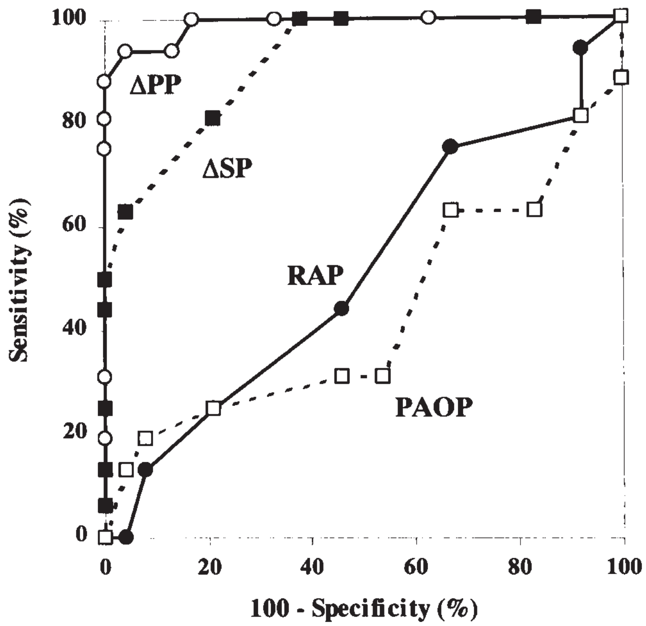

Figure 2. ROC curves comparing the ability of ΔPp, ΔPs, Pra, and Ppao to discriminate responder (CI increase $\geqslant$ 15%) and nonresponder patients to VE. The area under the ROC curve for ΔPp was greater than for ΔPs, Pra, and Ppao ($p < 0.01$).

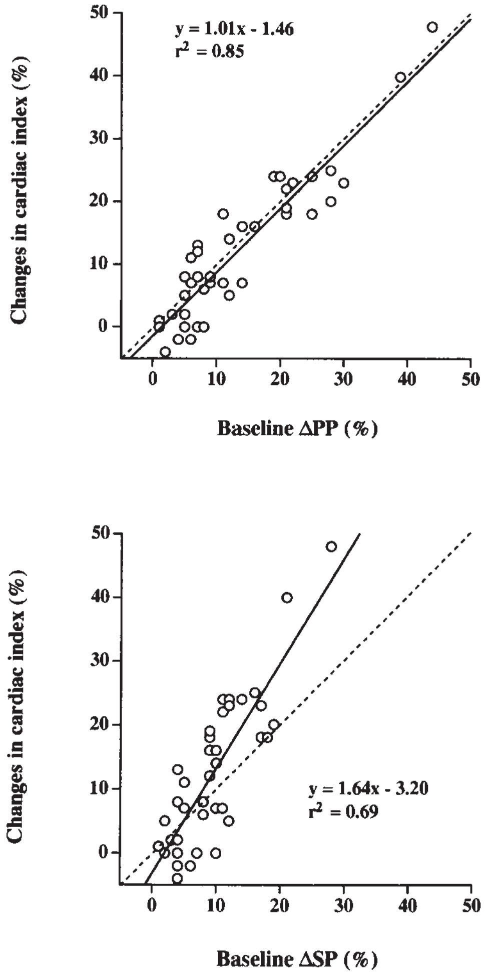

Figure 3. (*Upper panel*) Relationship between ΔPp before VE (Baseline ΔPp) and the VE-induced changes in CI. (*Lower panel*) Relationship between ΔPs before VE (Baseline ΔPs) and the VE-induced changes in CI. (Dotted line = identity line).

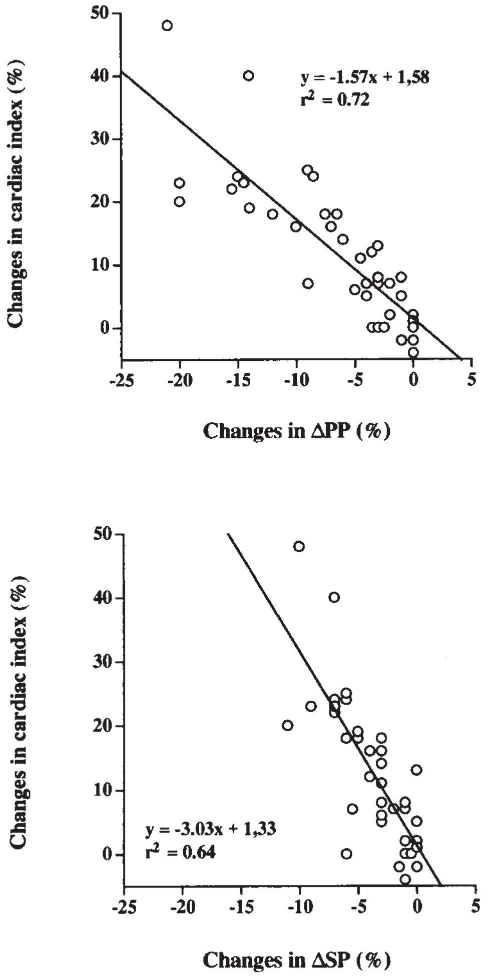

Figure 4. (*Upper panel*) Relationship between the decrease in ΔPp induced by VE (changes in ΔPp = ΔPp after VE minus ΔPp before VE) and the VE-induced changes in CI. (*Lower panel*) Relationship between the decrease in ΔPs induced by VE (changes in ΔPs = ΔPs after VE minus ΔPs before VE) and the VE-induced changes in CI.

changes in ΔPs (ΔPs after VE minus ΔPs before VE) were also correlated with VE-induced changes in CI ($r^2 = 0.64$, $p < 0.001$) (Figure 4).

DISCUSSION

In mechanically ventilated patients with acute circulatory failure related to sepsis, our results demonstrate a close relationship between ΔPp and the effects of VE on $\dot{Q}$. These results strongly suggest that ΔPp before VE accurately predicts the effects of VE on $\dot{Q}$ and that ΔPp is a more reliable indicator of fluid responsiveness than ΔPs. They also suggest that changes in ΔPp induced by VE can be used in assessing contemporaneous changes in $\dot{Q}$.

Pra and Ppao have been proposed for identifying patients who would benefit from VE (20, 21). In the present study, Pra and Ppao before VE were not significantly different between responders and nonresponders and did not correlate with the VE-induced changes in CI. Moreover, the area under the ROC curves for Pra and Ppao indicated that measuring these parameters to assess fluid responsiveness was no better than chance. These findings are in agreement with other reports (14, 22, 23) demonstrating that Pra and Ppao are of little value in predicting the hemodynamic effects of VE in septic patients.

In contrast, our results demonstrate that ΔPp is an accurate indicator of fluid responsiveness in mechanically ventilated patients with acute circulatory failure related to sepsis. Indeed, a patient with a baseline ΔPp value of more than 13% was very likely to respond to VE by increasing CI by ⩾ 15% (positive predictive value of 94%). In contrast, if ΔPp was < 13%, the patient was unlikely to respond to a fluid challenge (negative predictive value of 96%). Moreover, ΔPp before VE closely correlated with the VE-induced increase in CI. Interestingly, the percent increase in CI induced by the infusion of 500 ml 6% hydroxyethylstarch was approximately equal to ΔPp before VE (Figure 3). These findings suggest that analysis of ΔPp could be particularly helpful in the decision-making process concerning VE in such patients.

VE induced a significant decrease in ΔPp in our patients. This decrease could be explained as follows. First, VE is assumed to increase RV preload such that the operating point of the right ventricle moves rightward, i.e., toward the flatter portion of the Frank-Starling curve (9, 10). Each inspiratory decrease in RV preload would therefore have a less marked effect on RV stroke volume after VE than before (9, 10). Second, by increasing pulmonary capillary pressure, VE may induce recruitment of pulmonary capillaries, leading to a decrease in West's zone 2 (16, 24) and hence a potential decrease in RV afterload during insufflation. Thus, through these two mechanisms, VE should attenuate the inspiratory decrease in RV stroke volume and hence the subsequent expiratory decrease in LV preload. This latter phenomenon, in combination with a VE-induced rightward shift of the LV operating point, should result in attenuated changes in LV stroke volume and Pp over the respiratory cycle. However, because our study was not designed to elucidate why ΔPp decreased with VE, we cannot determine which mechanism was predominant. It is interesting to note that the decrease in ΔPp induced by VE correlated with the contemporaneous increase in CI (Figure 4). This finding suggests that analysis of changes in ΔPp could be useful in assessing the effects of VE on $\dot{Q}$.

ΔPs results not only from changes in aortic transmural pressure (mainly related to changes in LV stroke volume) but also from changes in extramural pressure (i.e., from changes in pleural pressure) (7). Accordingly, in all of our patients, the difference between Ps_{max} and Ps_{min} was greater than the difference between Pp_{max} and Pp_{min} (8 ± 6 versus 5 ± 4 mm Hg). This finding suggests that ΔPs was a less specific indicator of changes in LV stroke volume than ΔPp and probably explains why (*1*) the area under the ROC curve was significantly higher for ΔPp than for ΔPs, and (*2*) there was a closer correlation between ΔPp and VE-induced changes in CI than between ΔPs and changes in CI. Consequently, it may be preferable to use ΔPp rather than ΔPs for monitoring fluid responsiveness.

It must be underlined that arrhythmias and spontaneous breathing activity lead to misinterpretation of respiratory changes in arterial pressure. Patients with arrhythmias were therefore excluded from the present study and those with spontaneous breathing activity were temporarily paralyzed during the protocol. As mentioned previously, the Pp depends not only on stroke volume but also on arterial compliance. Therefore, for a given change in LV stroke volume, ΔPp may vary from one patient to another according to the arterial compliance. To this extent, large changes in Pp could be theoretically observed despite small changes in LV stroke volume if arterial compliance is low (elderly patients with peripheral vascular disease). Similarly, small changes in Pp could be observed despite large changes in LV stroke volume if arterial compliance is high (young patients without any vascular disease). In fact, our results observed in patients with a large range of age and comorbidities suggest that arterial compliance poorly affected the relationship between respiratory changes in LV stroke volume and ΔPp. Given that we studied patients with acute circulatory failure related to sepsis, our results cannot be extrapolated to other clinical situations. Finally, although analysis of ΔPp may be an attractive alternative approach to pulmonary artery catheterization in these patients, it does not allow measurement of $\dot{Q}$ and pulmonary pressures.

To summarize, our findings suggest that in mechanically ventilated patients with acute circulatory failure related to sepsis, (*1*) ΔPp accurately predicts the hemodynamic effects of VE, (*2*) changes in ΔPp could be used to assess changes in CI induced by VE, and (*3*) ΔPp is a more reliable indicator of fluid responsiveness than ΔPs. The analysis of ΔPp is easy to perform in patients who have an indwelling arterial catheter for continuous monitoring of blood pressure. Therefore, calculation of ΔPp could facilitate the hemodynamic management of ventilated patients with acute circulatory failure related to sepsis.

***Acknowledgment*:** The authors thank the physicians and nursing staff of the ICU for their valuable cooperation and Dr. Pierre Ducq for statistical advice.

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