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 (\Delta Pp) 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 (\Delta Ps) were calculated using a similar formula. The VE-induced increase in CI was \( \geq 5\% \) in 16 patients (responders) and \(< 5\% \) in 24 patients (nonresponders). Before VE, \Delta Pp (24 \pm 9 versus 7 \pm 3, \( p < 0.001 \)) and \Delta Ps (15 \pm 5 versus 6 \pm 3, \( p < 0.001 \)) were higher in responders than in nonresponders. Receiver operating characteristic (ROC) curves analysis showed that \Delta Pp was a more accurate indicator of fluid responsiveness than \Delta Ps. Before VE, a \Delta Pp 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 \Delta Pp before volume expansion (\( r^2 = 0.85, p < 0.001 \)). VE decreased \Delta Pp from 14 \pm 10 to 7 \pm 5 (\( p < 0.001 \)) and VE-induced changes in \Delta Pp correlated with VE-induced changes in CI (\( r^2 = 0.72, p < 0.001 \)).

V 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 related 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 (\Delta Pp) 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 \Delta Pp 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 (\Delta Ps) result from changes in aortic transmural pressure (mainly related to changes in LV stroke volume) and from changes in extramural pressure (i.e., changes in pleural pressure) (7). In contrast, \Delta Pp depends only on changes in transmural pressure, because changes in pleural pressure should affect both systolic and diastolic pressure. A corollary, \Delta Pp is expected to be more reliable than \Delta Ps 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 \Delta Pp could predict the hemodynamic effects of VE, (2) whether changes in \Delta Pp could be used to assess changes in cardiac index (CI) induced by VE, and (3) whether \Delta Pp might be a more reliable indicator of fluid responsiveness than \Delta Ps.

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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Hemodynamic Measurements

Patients were studied while supine, and zero pressure was measured at the midaxial 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). 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.

Respiratory Changes in Arterial Pressure

We used the analog output from the monitor (Monitor M 1092A; Hewlett-Packard, L Leuilly, 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. ∆Pp was calculated as previously described (11): ∆Ps (%) = 100 × (Ps max − Ps min)/Ps max + Ps min. ∆Ps was evaluated using a similar formula: ∆Ps (%) = 100 × (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. ∆Pp and ∆Ps 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 H2O). 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 vasopressor 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 into two groups according to the percent increase in CI in response to VE. A 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 ≥ 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, ∆Pp, and ∆Ps, 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
between $P_{\text{Pmax}}$ and $P_{\text{Pmin}}$ ranged from 1 to 20 mm Hg (mean difference: 5 ± 4 mm Hg) and the difference between $P_{\text{Smax}}$ and $P_{\text{Smin}}$ ranged from 1 to 27 mm Hg (mean difference: 8 ± 6 mm Hg). In all patients, the difference between $P_{\text{Pmax}}$ and $P_{\text{Pmin}}$ was smaller than the difference between $P_{\text{Smax}}$ and $P_{\text{Smin}}$.

Hemodynamic parameters before and after VE are presented in Table 1.

Before VE, $\Delta P_P$ ranged from 1 to 44% and $\Delta P_S$ from 1 to 28%. Before VE, $\Delta P_P$ and $\Delta P_S$ were not correlated with either Pra or Ppao.

VE increased CI from 3.6 ± 0.9 to 4.0 ± 0.9 L/min/m² ($p < 0.001$). Sixteen patients were responders (CI increase ≥ 15%) and 24 were nonresponders. Before VE, $\Delta P_P$ (24 ± 9 versus 7 ± 3%, $p < 0.001$) and $\Delta P_S$ (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 ($\pm SE$) were as follows: 0.98 ± 0.03 for $\Delta P_P$, 0.91 ± 0.04 for $\Delta P_S$, 0.51 ± 0.12 for Pra, and 0.40 ± 0.09 for Ppao (Figure 2). The area for $\Delta P_P$ was significantly greater than the area for $\Delta P_S$ ($p < 0.01$), Pra ($p < 0.01$), and Ppao ($p < 0.01$). The threshold $\Delta P_P$ 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 $\Delta P_P$ before VE and VE-induced changes in CI such that the higher $\Delta P_P$ before VE, the greater was the percent increase in CI [changes in CI (%) = 1.01 × $\Delta P_P - 1.46$] (Figure 3). $\Delta P_S$ 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 $\Delta P_P$ (Figure 3). Conversely, Pra and Ppao measured before VE were not correlated in any way with VE-induced changes in CI.

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

### Table 1: Effects of VE on Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>VE</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>110 ± 22</td>
<td>106 ± 21</td>
</tr>
<tr>
<td>$P_{\text{a}}$, mm Hg</td>
<td>69 ± 13</td>
<td>80 ± 13</td>
</tr>
<tr>
<td>Pra, mm Hg</td>
<td>9 ± 3</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>$P_{\text{pa}}$, mm Hg</td>
<td>24 ± 6</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>Ppao, mm Hg</td>
<td>10 ± 3</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.6 ± 0.9</td>
<td>4.0 ± 0.9</td>
</tr>
<tr>
<td>SVI, ml/m²</td>
<td>34 ± 12</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>SVRI, dyne . s/cm⁵/m²</td>
<td>1,418 ± 430</td>
<td>1,442 ± 424</td>
</tr>
<tr>
<td>PSVR, dyne . s/cm⁵/m²</td>
<td>325 ± 154</td>
<td>315 ± 128</td>
</tr>
<tr>
<td>$\Delta P_P$, %</td>
<td>14 ± 10</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>$\Delta P_S$, %</td>
<td>9 ± 6</td>
<td>6 ± 4</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = cardiac index; HR = heart rate; $P_{\text{a}}$ = mean arterial pressure; $\Delta P$ = respiratory changes in pulse pressure; $P_{\text{pa}}$ = mean pulmonary arterial pressure; Ppao = pulmonary artery occlusion pressure; Pra = right atrial pressure; $\Delta P_S$ = respiratory changes in systolic pressure; PSVR = 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.

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

Figure 3. (Upper panel) Relationship between $\Delta P_P$ before VE (Baseline $\Delta P_P$) and the VE-induced changes in CI. (Lower panel) Relationship between $\Delta P_S$ before VE (Baseline $\Delta P_S$) and the VE-induced changes in CI. (Dotted line = identity line.)
In contrast, our results demonstrate that $\Delta Pp$ is an accurate indicator of fluid responsiveness in mechanically ventilated patients with acute circulatory failure related to sepsis. Indeed, a patient with a baseline $\Delta Pp$ value of more than 13% was very likely to respond to VE by increasing CI by $\geq 15\%$ (positive predictive value of 94%). In contrast, if $\Delta Pp$ was $< 13\%$, the patient was unlikely to respond to a fluid challenge (negative predictive value of 96%). Moreover, $\Delta Pp$ 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 $\Delta Pp$ before VE (Figure 3). These findings suggest that analysis of $\Delta Pp$ could be particularly helpful in the decision-making process concerning VE in such patients.

VE induced a significant decrease in $\Delta Pp$ 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 $\Delta Pp$ decreased with VE, we cannot determine which mechanism was predominant. It is interesting to note that the decrease in $\Delta Pp$ induced by VE correlated with the contemporaneous increase in CI (Figure 4). This finding suggests that analysis of changes in $\Delta Pp$ could be useful in assessing the effects of VE on Q.

$\Delta Ps$ 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 $P_{ps_{max}}$ and $P_{ps_{min}}$ was greater than the difference between $P_{pp_{max}}$ and $P_{pp_{min}}$ (8 ± 6 versus 5 ± 4 mm Hg). This finding suggests that $\Delta Ps$ was a less specific indicator of changes in LV stroke volume than $\Delta Pp$ and probably explains why (1) the area under the ROC curve was significantly higher for $\Delta Pp$ than for $\Delta Ps$, and (2) there was a closer correlation between $\Delta Pp$ and VE-induced changes in CI than between $\Delta Ps$ and changes in CI. Consequently, it may be preferable to use $\Delta Pp$ rather than $\Delta Ps$ 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, $\Delta Pp$ 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 \( \Delta P_p \). 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 \( \Delta P_p \) may be an attractive alternative approach to pulmonary artery catheterization in these patients, it does not allow measurement of \( Q \) and pulmonary pressures.

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

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References