The respiratory change in prejection period: a new method to predict fluid responsiveness

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Bendjelid, Karim, Peter M. Suter, and Jacques A. Romand. The respiratory change in prejection period: a new method to predict fluid responsiveness. J Appl Physiol 96: 337–342, 2004; 10.1152/ japplphysiol.00435.2003.—The accuracy and clinical utility of preload indexes as bedside indicators of fluid responsiveness in patients after cardiac surgery is controversial. This study evaluates whether respiratory changes (Δ) in the prejection period (PEP; ΔPEP) predict fluid responsiveness in mechanically ventilated patients. Sixteen post-coronary artery bypass surgery patients, deeply sedated under mechanical ventilation, were enrolled. PEP was defined as the time interval between the beginning of the Q wave on the electrocardiogram and the upstroke of the radial arterial pressure. ΔPEP (%) was defined as the difference between expiratory and inspiratory PEP measured over one respiratory cycle. We also measured cardiac output, stroke volume index, right atrial pressure, pulmonary arterial occlusion pressure, respiratory change in pulse pressure, systolic pressure variation, and the Δdown component of SPV. Data were measured without positive end-expiratory pressure (PEEP) and after application of a PEEP of 10 cmH2O (PEEP10). When PEEP10 induced a decrease of >15% in mean arterial pressure value, then measurements were re-performed before and after volume expansion. Volume loading was done in eight patients. Right atrial pressure and pulmonary arterial occlusion pressure before volume expansion did not correlate with the change in stroke volume index after the fluid challenge. Systolic pressure variation, ΔPEP, Δdown, and change in pulse pressure before volume expansion correlated with stroke volume index change after fluid challenge (r2 = 0.52, 0.57, 0.68, and 0.83, respectively). In deeply sedated, mechanically ventilated patients after cardiac surgery, ΔPEP, a new method, can be used to predict fluid responsiveness and hemodynamic response to PEEP10.

METHODS

The respiratory change in prejection period (PEP), the time from the onset of ventricular depolarization to the beginning of left ventricular ejection, is a systolic time interval that allows assessment of ventricular function (36). More than 30 years ago, Weissler et al. (37) measured PEP with simultaneous electrocardiogram (ECG), phonocardiogram, and carotid arterial pressure tracing. Presently, PEP can be obtained by simultaneous ECG recording and arterial pressure wave tracing, which are often monitored in critically ill patients (2). Even if PEP depends slightly on afterload and cardiac contractility, it always decreases with a greater preload (36). Interestingly, in mechanically ventilated patients, we recently observed that expiratory (PEPex) and inspiratory PEP (PEPi), measured at the lower and higher systolic pressure value on arterial pressure tracing over one respiratory cycle, were of different values (3). By analogy with the concept of positive pressure ventilation-induced SVV (16), we hypothesized that the respiratory change (Δ) in PEP (ΔPEP) depends predominantly on the change in ventricular preload and is minimally influenced by contractility or afterload. Accordingly, with this hypothesis, in a preliminary study, ΔPEP was found to be a good predictor of fluid responsiveness (4). The aim of the present study was to test whether ΔPEP predicts hemodynamic changes induced by positive end-expiratory pressure (PEEP) and volume infusion in patients after coronary artery bypass graft. ΔPEP was also compared with other clinically used preload indexes [Pra, Ppao, SPV, Δdown (component of SPV)] and respiratory changes in pulse pressure (ΔPP) (20).

AFTER CARDIAC SURGERY, INTRAVENOUS fluid administration is a universally accepted treatment for hypotension occurring during positive pressure ventilation. Nevertheless, vigorous fluid resuscitation carries the risk of generating volume overload and pulmonary edema. To prevent such complications, several indexes have been used to assess preload (6). However, the accuracy of filling pressures, such as right atrial (Pra) and/or pulmonary arterial occlusion pressure (Ppao) to estimate cardiac filling, have been questioned in patients after cardiac surgery (28). Thus indexes able to unmask preload dependency and to predict increase in cardiac output with volume expansion are actively searched (14). In deeply sedated, mechanically ventilated patients after cardiac surgery, dynamic indexes, such as systolic pressure variation (SPV) and stroke volume variations (SVV), have been demonstrated to be more accurate to predict fluid responsiveness than filling pressures (23, 27, 28).

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preejection period (PEP); PEP E, expiratory
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Study protocol. All studies were performed in deeply sedated and nonspontaneously breathing patients (Ramsay 6) in the supine position. If patients were receiving vasoactive drugs, the rate of administration was not changed. The study protocol consisted of two sequential ventilatory steps of 30 min each: controlled mechanical ventilation with PEEP = 0 [zero end-expiratory pressure (ZEEP)], and controlled mechanical ventilation with PEEP = 10 cmH2O (PEEP10) without changing any other ventilatory settings. When PEEP10 induced a reduction in mean arterial pressure of >15% after the 25-min period, a hemodynamic measurement was then obtained, immediately followed by 0.9% NaCl (500 ml ± total quantity of fluid of chest drains, urine, and nasogastric output in milliliters), given over 25 min, still on PEEP10. A third set of hemodynamic measurements was then obtained.

Data recording. At the end of each period, all of the following variables were recorded from the bedside monitor (Agilent Technologies, M3150A): body temperature; mean dilution cardiac output; heart rate; calculated stroke volume; systolic, diastolic, and mean arterial and pulmonary arterial pressures; Pra; Ppa; SPV; and ∆PP, and ∆PEP. Mean dilution cardiac output, estimated by averaging triplicate injections, was used for statistical analysis. Arterial and mixed-venous blood gases were also simultaneously measured (Stat profile Ultra, Nova Biomedical, Waltham, MA), and standard calculated variables were obtained from hemodynamic and blood-gas data. Ventilator settings (respiratory rate, tidal volume, inspiratory-to-expiratory ratio, inspired oxygen fraction, PEEP), peak, and mean airway pressures, and auto-PEEP were recorded.

Statistical analysis. The data were analyzed by using Graph Pad Prism (Graph pad software version 3, San Diego, CA) for the personal computer. The nonparametric Mann-Whitney test was used to compare the effects of PEEP and volume expansion on hemodynamic and respiratory parameters. Additionally, the same test was used to compare the interobserver variability in measuring ∆PEP. Correlations were obtained by using regression analysis. All values are expressed as means ± SD, and P < 0.05 was considered statistically significant.

RESULTS

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender (M/F)</th>
<th>BS, m²</th>
<th>LVEF, %</th>
<th>CGB, no.</th>
<th>Pto2/FiO2</th>
<th>Vt, ml/kg</th>
<th>CT, ml/cmH2O</th>
<th>Outcome (S/D)</th>
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<td>M</td>
<td>1.93</td>
<td>60</td>
<td>4</td>
<td>285</td>
<td>7</td>
<td>34</td>
<td>S</td>
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</tbody>
</table>

Mean ± SD 64.6 ± 8.54 1.88 ± 0.17 63.4 ± 10.1 2.4 ± 0.9 350 ± 59 8 ± 1 37 ± 11 4/12 16/16

M, male; F, female; BS, body surface; LVEF, left ventricular ejection fraction; CGB, coronary grafts bypassed; Pto2/FiO2, ratio of Pto2 to inspired O2 fraction; Vt, tidal volume; CT, static compliance of the respiratory system; S/D, survived/died.

ΔPEP AND FLUID RESPONSIVENESS

ΔPEP and fluid responsiveness. The static pressures predicting the response to PEEP and the fluid responsiveness were measured in ZEEP, Pra, and Ppa and correlated with the PEEP10-induced change in cardiac index (in %) (r2 = 0.34, P = 0.02; r2 = 0.47, P = 0.003; respectively). Pra and Ppa before volume expansion did not correlate with changes in SVI after volume expansion (P = 0.7 and P = 0.3, respectively).

SPV and PP variation prediction of response to PEEP and fluid responsiveness. The SPV and PP variation prediction of response to PEEP and fluid responsiveness were measured in ZEEP, SPV, Δdown (the component of SPV), and ΔPP and one patient was hemodynamically unstable. Sixteen patients were included in the final analysis, and all of them tolerated the experimental protocol well. Demographic and preoperative characteristics are presented in Table 1. The mean cardiopulmonary bypass duration was 107 ± 42 min, and the aortic cross-clamping time was 73 ± 33 min. Catecholamine infusions were required in four patients for cardiopulmonary bypass weaning (dobutamine, n = 1; 8 µg·kg−1·min−1, and norepinephrine, n = 3). However, during the study protocol, in the intensive care unit, among these four patients, only two still required catecholamine infusions (dobutamine: n = 1; 8 µg·kg−1·min−1, and norepinephrine: n = 1; 0.1 µg·kg−1·min−1). Hemodynamic variables, respiratory, airway pressures, and gas exchange values are shown in Tables 2 and 3. In all patients, systolic arterial pressures were higher during the inspiratory than during the expiratory period. The interobserver variability in measuring ΔPEP was 8% (P = 0.89, Mann-Whitney test).

Only eight patients presented a >15% decrease in mean arterial pressure after PEEP10. Among these eight patients, one patient was under norepinephrine infusion (thick solid line in Fig. 3). Volume infusion produced an increase in stroke volume index (SVI) from 29 ± 4 to 34 ± 4 ml/m2 (P = 0.0002), and ΔPEP decreased from 11 ± 3 to 5 ± 3% (P = 0.002) (Fig. 3). No difference in response to volume infusion was seen in the patient receiving norepinephrine compared with the other patients.

Innovative Methodology

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Table 2. Effects of PEEP on hemodynamic and respiratory parameters (16 patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZEEP</th>
<th>PEEP 10</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>88±12</td>
<td>86±12</td>
<td>0.08</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>69±9</td>
<td>67±9</td>
<td>0.2</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>21±4</td>
<td>23±3</td>
<td>0.004*</td>
</tr>
<tr>
<td>Pra, mmHg</td>
<td>11±3</td>
<td>13±3</td>
<td>0.004*</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>12±3</td>
<td>14±2</td>
<td>0.004*</td>
</tr>
<tr>
<td>ΔPEP, %</td>
<td>8±4</td>
<td>7±5</td>
<td>0.4</td>
</tr>
<tr>
<td>SPV, mmHg</td>
<td>10±4</td>
<td>9±4</td>
<td>0.4</td>
</tr>
<tr>
<td>ΔDown, mmHg</td>
<td>5±3</td>
<td>5±5</td>
<td>0.9</td>
</tr>
<tr>
<td>ΔPP, %</td>
<td>12±7</td>
<td>12±6</td>
<td>0.5</td>
</tr>
<tr>
<td>CI, L/min·m⁻²</td>
<td>2.9±0.3</td>
<td>2.6±0.4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>SVRI, dyne·s⁻¹·cm⁻⁵</td>
<td>1.574±246</td>
<td>1.661±282</td>
<td>0.08</td>
</tr>
<tr>
<td>PVRI, dyne·s⁻¹·cm⁻⁵</td>
<td>250±85</td>
<td>269±87</td>
<td>0.41</td>
</tr>
<tr>
<td>D O₂, ml/min</td>
<td>730±160</td>
<td>684±181</td>
<td>0.009*</td>
</tr>
<tr>
<td>PAo, Torr</td>
<td>93±22.5</td>
<td>99±15</td>
<td>0.1</td>
</tr>
<tr>
<td>PAo,c, Torr</td>
<td>39.8±5.3</td>
<td>39.9±6</td>
<td>0.9</td>
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<tr>
<td>Plateau, cmH₂O</td>
<td>18±4</td>
<td>24±3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>CT, ml/cmH₂O</td>
<td>37±11</td>
<td>45±9</td>
<td>0.013*</td>
</tr>
<tr>
<td>Auto-PEEP, cmH₂O</td>
<td>1.7±1.4</td>
<td>0.8±0.8</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are means ± SD. ZEEP, zero end-expiratory pressure; PEEP, positive end-expiratory pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; Pra, right atrial pressure; Ppa, pulmonary arterial occlusion pressure; ΔPEP, respiratory change in prejection period; SPV, systolic pressure variation; ΔDown, delta down; ΔPP, respiratory variation in pulse pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; D O₂, oxygen delivery; PAo, arterial P O₂; PAo,c, arterial P C O₂; Plateau, end-inspiratory airway pressure. *P < 0.05 (Mann-Whitney test).

correlated with the PEEP-induced change in cardiac index (in %) (r² = 0.28, P = 0.03; r² = 0.52, P = 0.002; r² = 0.63, P = 0.0002, respectively). The correlations among SPV, Δdown, and ΔPP before volume expansion correlated with changes in SVI after volume expansion (P = 0.04, P = 0.01, and P = 0.001, respectively; see Fig. 4).

Table 3. Effects of PEEP and volume infusion on hemodynamic and respiratory parameters in eight patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZEEP</th>
<th>PEEP 10</th>
<th>VE on PEEP 10</th>
<th>PP'</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>90±10</td>
<td>87±11</td>
<td>82±9</td>
<td>0.6/0.3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>69±12</td>
<td>57±6</td>
<td>69±5</td>
<td>0.02*/0.0007†</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>19±4</td>
<td>22±3</td>
<td>23±3</td>
<td>0.11/0.5</td>
</tr>
<tr>
<td>Pra, mmHg</td>
<td>10±3</td>
<td>12±3</td>
<td>13±3</td>
<td>0.2/0.5</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>10±3</td>
<td>13±2</td>
<td>15±3</td>
<td>0.03*/0.1</td>
</tr>
<tr>
<td>ΔPEP, %</td>
<td>8±2</td>
<td>11±3</td>
<td>5±3</td>
<td>0.02*/0.002†</td>
</tr>
<tr>
<td>SPV, mmHg</td>
<td>11±3</td>
<td>10±4</td>
<td>7±2</td>
<td>0.6/0.07</td>
</tr>
<tr>
<td>ΔDown, mmHg</td>
<td>6±3</td>
<td>7±4</td>
<td>3±2</td>
<td>0.06/0.02†</td>
</tr>
<tr>
<td>ΔPP, %</td>
<td>18±4</td>
<td>14±4</td>
<td>7±3</td>
<td>0.06/0.01†</td>
</tr>
<tr>
<td>CI, L/min·m⁻²</td>
<td>2.9±0.3</td>
<td>2.5±0.4</td>
<td>2.9±0.2</td>
<td>0.04*/0.02†</td>
</tr>
<tr>
<td>SVRI, dyne·s⁻¹·cm⁻⁵</td>
<td>1.615±309</td>
<td>1.600±349</td>
<td>1.620±361</td>
<td>0.9/0.9</td>
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<tr>
<td>PVRI, dyne·s⁻¹·cm⁻⁵</td>
<td>248±73</td>
<td>305±95</td>
<td>248±99</td>
<td>0.2/0.2</td>
</tr>
<tr>
<td>D O₂, ml/min</td>
<td>691±143</td>
<td>596±159</td>
<td>611±120</td>
<td>0.2/0.8</td>
</tr>
<tr>
<td>PAo, Torr</td>
<td>96±28.6</td>
<td>98±13</td>
<td>112±15</td>
<td>0.8/0.06†</td>
</tr>
<tr>
<td>PAo,c, Torr</td>
<td>42±5.7</td>
<td>42±6</td>
<td>41±3</td>
<td>0.9/0.7</td>
</tr>
<tr>
<td>Plateau, cmH₂O</td>
<td>16±4</td>
<td>24±4</td>
<td>25±3</td>
<td>0.008*0.5</td>
</tr>
<tr>
<td>CT, ml/cmH₂O</td>
<td>41±13</td>
<td>44±5</td>
<td>43±5</td>
<td>0.5/0.7</td>
</tr>
<tr>
<td>Auto-PEEP, cmH₂O</td>
<td>1.5±0.9</td>
<td>1±1</td>
<td>0.7±0.5</td>
<td>0.3/0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. VE, volume expansion; *P < 0.05, PEEP/0-ZEEP (Mann-Whitney test); †P < 0.05, VE/PEEP10 (Mann-Whitney test).

Respiratory change in PEEP-predicting response to PEEP and fluid responsiveness. The respiratory change in PEEP-predicting response to PEEP and the fluid responsiveness were measured in ZEEP and ΔPEP and correlate with the PEEP-induced change in cardiac index (in %) (r² = 0.53, P = 0.001). ΔPEP before volume expansion correlated with change in SVI after volume expansion (P = 0.03) (see Fig. 4).

**DISCUSSION**

The present study shows a good correlation between ΔPEP value before volume expansion and SVI increase after fluid challenge in mechanically ventilated cardiac surgery patients on PEEP. In addition, ΔPEP at ZEEP predicts hemodynamic response to PEEP. However, ΔDown (the component of SPV) and ΔPP were better indexes to predict fluid responsiveness than ΔPEP.

In mechanically, deeply sedated, ventilated patients, positive pressure ventilation cyclically increases intrathoracic pressure and lung volume. Both reduce venous return, alter cardiac preload, and decrease stroke volume. Thus left ventricular stroke volume varies cyclically, being maximal during mechanical breath and minimal during expiration. During hypovolemia, the greatest mechanical breath-induced SVVs are observed (16). The respiratory change in stroke volume results in SPV and ΔPP. These two indexes have been shown to identify decreased preload hypotension and to distinguish between responders and nonresponders to fluid challenge in different patient populations (12, 20, 21, 32).

Because PEEP depends on preload, afterload, and contractility (36), it is related to stroke volume. Indeed, in an animal study, Wallace et al. (35) demonstrated that increasing stroke volume shortens PEP. Several human studies have also found that decreased PEP after fluid challenge is associated with increase in stroke volume (10, 13, 18). Interestingly, Brundin et al. (9) demonstrated that intermittent positive pressure ventilation increased PEP by the reduction of venous return and thus stroke volume. In the present study, ΔPEP was used as an index of preload responsiveness, with the hypothesis that, as...
for SPV and ΔPP, ΔPEP is related to positive pressure breath induces change in ventricular stroke volume related to change in ventricular preload (17). Thus the recorded lower PEP value during the mechanical inspiratory phase compared with the higher PEP during expiratory phase is in accordance with the hypothesis that ΔPEP is related to the respiratory change in left ventricular stroke volume. Indeed, early after mechanical breath, capacitance pulmonary vessels discharge into the pulmonary veins (8). This would increase left ventricular preload at that phase of the cycle. Furthermore, an inspiratory increase of left ventricular stroke volume, thus determining the minimal value of PEP, is observed secondary to the rise in left ventricular preload, which reflects the three heartbeats that were increased earlier in right ventricular preload during expiration (22). Accordingly, ΔPEP was a good predictor of hemodynamic response to PEEP_{10} (decrease in preload) and to fluid challenge (increase in preload).

The present study confirms that Pra and Ppao before volume expansion do not correlate with the volume expansion-induced change in SVI, as already demonstrated in different patient populations (20, 26, 32) and after cardiac surgery (15, 28). These results could be explained by the absence of correlation between cardiac filling pressures and cardiac volumes in patients after coronary artery bypass surgery, as demonstrated by Buhre et al. (11). However, even if ΔPEP were found to be a good predictor of hemodynamic response to fluid challenge, Δdown and ΔPP were better indexes to predict fluid responsiveness (Fig. 4). Nevertheless, Δdown data acquisitions necessitate an expiratory pause of at least 5 s, and, in the absence of automatic bedside measurements, ΔPP assessment is time consuming. In comparison, ΔPEP is easily assessed by using calipers of a central monitor, and its calculation is rapid. Moreover, in the future, ΔPEP could be measured automatically by using a personal computer (7) and/or assessed noninvasively at the bedside by the thoracic electrical bioimpedance technique (19).

As recently published (28), another message addressed by the present study is that dynamic indexes such as SPV, ΔPEP, and ΔPP could be used as predictors of fluid responsiveness after cardiac surgery, even if patients are equipped with a chest drain. Indeed, application of thoracic drainage seems to perturb minimally the physiological change in pleural pressure induced by positive pressure ventilation.

One limitation of the study is that PEP could also be minimally influenced by afterload variations induced by positive pressure ventilation. Indeed, increased pleural pressure (accompanying a positive pressure breath) may decrease left ventricular transmural pressure (afterload) and thus increase left ventricular stroke volume. In one-half of the patients, the cardiac index was not affected by PEEP. Hence, we can cautiously assume that these patients were on the flat portion of the Starling left ventricular function curve (30). In this situation, SPV, SVV, ΔPEP, and ΔPP may be due mainly to an augmentation of the stroke volume during the mechanical breath, which is related to decrease in afterload and expressed by the Δup of the systolic pressure (31). However, this positive pressure effect is rarely observed in patients with normal cardiac function after cardiopulmonary bypass (34). Indeed, Van Trigt et al. (34) have demonstrated that, in patients after coronary artery bypass surgery, PEEP_{10} or greater produces a significant fall in cardiac output, due to a decrease in preload, without a change in left ventricular contractility and afterload.

In conclusion, in patients after coronary artery bypass surgery, this study found ΔPEP to be a good predictor of hemodynamic response to PEEP and a reliable preload parameter for predicting an increase in cardiac output after volume infusion. In addition, our data confirm that Pra and Ppao are of little value in predicting the hemodynamic effects of volume expansion in cardiac surgical patients with preserved left ventricular systolic function.

Fig. 4. Linear correlation analysis of the relationship between preload parameters measured before VE and change in stroke volume after VE. A: ΔPEP; B: SPV; C: Δdown; D: ΔPP. *P < 0.05 was considered significant.
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Preliminary data have been presented as an oral communication to the VIII World Congress of Intensive and Critical Care Medicine, October 2001, Sydney, and as a poster presentation to the 31st Congress of the Society of Critical Care Medicine, 26–30 January 2002, San Diego.

REFERENCES