Combined Thermolodilution and Two-Dimensional Echocardiographic Evaluation of Right Ventricular Function during Respiratory Support with PEEP

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In ten patients requiring respiratory support for an episode of acute respiratory failure (ARF), the best therapeutic level of PEEP was determined by measurement of changes in lung and chest wall compliance (CT) during a PEEP challenge from 0 to 20 cm H2O. During this challenge, hemodynamic monitoring combined with thermodilution measurement of right ventricular (RV) ejection fraction (EF) and two-dimensional echocardiographic measurement of RV size permitted assessment of the effects of increasing levels of PEEP on RV function. RV preload, as reflected by RV end-diastolic volume (EDV) and two-dimensional RV end-diastolic area (EDA), remained unchanged and RV diastolic compliance progressively decreased. On the other hand, RV systolic function, as assessed by RVEF and two-dimensional RV fractional area contraction (FAC), was progressively depressed. Substantial deleterious effects of PEEP were noted at high levels of PEEP including reduced CT and augmented pulmonary vascular resistance. Inadequate increase in RV preload to compensate for increased RV afterload resulted in depressed RV systolic function and contributed to the reduction in cardiac output. Finally, two-dimensional echocardiography proved to be more sensitive than fast-response thermodilution to evaluate change in RV function.

Although the effect of respiratory support with PEEP on cardiac output has been studied extensively in the past 20 years, this subject remains an area of considerable debate. In a previous study, we reported that PEEP reduced left ventricular (LV) preload and in contrast to experimental studies did not alter LV contractility. Additionally, when high levels of PEEP were used, severe right ventricular (RV) pressure overload was evidenced by systolic septal flattening. This finding suggested that RV impairment in systolic function caused by PEEP might contribute to the reduction of cardiac output during this mode of respiratory support.

The aim of the present study was to assess the effects of PEEP on RV diastolic and systolic functions and to examine their relations with cardiac output changes, in a group of patients requiring mechanical ventilation with PEEP during an episode of acute respiratory failure. For this purpose, we combined two-dimensional (2-D) echocardiography and right heart catheterization using the now-available fast-response thermodilution technique. By two different approaches, both methods allow measurement of RV dimensions and monitoring their changes during the application of progressive levels of PEEP.

Material and Methods

We studied ten patients with acute respiratory failure who required continuous mechanical ventilation (controlled) with PEEP. This group consisted of six men and four women ranging in age from 20 to 75 years (mean 52 years), and previously free of cardiorespiratory disease. Respiratory failure followed bacterial or viral pneumonia in five patients, chest contusion in two patients, severe sepsis in two patients, and gastric content inhalation in one patient. At the time of the study all patients had both left and right echocardiographic ventricular size and function in a normal range, excluding previous chronic or acute cardiac dysfunction. Seven patients recovered after a mean duration of mechanical ventilation of 16 days (range 9 to 30 days). Three patients died after a mean duration of mechanical ventilation of 21 days (range, 15 to 28 days).
Hemodynamic measurements were obtained during a PEEP challenge performed under mechanical controlled ventilation with a FiO₂ at 0.6 and mild sedation (1 mg [10 mg] morphine chlorhydrate IV). This challenge consists of progressive increments of 5 cm H₂O of PEEP from 0 to 20 cm H₂O end-expiratory pressure and is usually performed in our unit to determine the best therapeutic level of PEEP in patients free of intrinsic PEEP at zero end-expiratory pressure. During PEEP challenge, respiratory flow was measured with a disposable pneumotachograph (McCaw, American Hospital Supply) connected to a differential transducer (Validyne MP 45-14). Total volume was determined by electrical integration of the flow signal (Hewlett Packard 8615 A integrator). Airway pressure was measured by a side-port of the tracheal tube. Lung and chest wall compliance (CT) were calculated at each level of PEEP, as previously described. The best therapeutic level of PEEP was determined as the level producing the highest value of CT, according to Suter's criteria. PEEP challenge was performed only in patients exhibiting a baseline level of systolic arterial pressure above 100 mm Hg. During PEEP challenge, systemic arterial pressure was continuously monitored by an indwelling radial Teflon catheter previously inserted for hemodynamic monitoring and blood gas analysis, to detect an eventual drop which would be potentially detrimental. If the application of any given level of PEEP decreased systolic arterial pressure by more than 20 percent of the baseline value, or induced cough, this PEEP level was immediately reduced. As a result, measurements could not be obtained at 15 and 20 cm H₂O in one patient and at 20 cm H₂O in two patients.

Hemodynamic Measurements

Pulmonary artery and RV pressures were obtained from a 7.5 F quadruple lumen Swan-Ganz catheter (American Edwards Laboratories, Santa Ana, CA), equipped with a fast-response thermistor and atrial and ventricular electrodes. This catheter was previously inserted percutaneously into the pulmonary artery for hemodynamic monitoring and mixed venous blood gas analysis. Placement of a specially designed introducer (Arrow) during insertion made it possible to move the catheter during hemodynamic measurements as often as necessary. The proximal port could thus be used alternately to inject thermal indicator into the right atrium close to the tricuspid valve, or measure RV pressure by advancing the catheter 2 or 3 cm forward. All pressures were measured with Hewlett-Packard transducers, averaged during the whole respiratory cycle and expressed as transmural pressure (ie, minus esophageal pressure). Esophageal pressure was measured with an esophageal balloon advanced through the nose into the esophagus and down to 35-40 cm from the nares. Cardiac output and RV ejection fraction (EF) were measured by the fast-response thermodilution technique (Edwards REF-1 Computer), with an average of five serial determinations taken at regularly spaced intervals through the ventilatory cycle. All patients were in sinus rhythm during the study; heart rate was monitored by way of the thermodilution catheter and measurements were rejected if a premature beat occurred during the integration time. In one patient, marked RV dilatation at PEEP levels higher than 5 cm H₂O was responsible for an insufficient threshold detection of intracavitary ECG. Stroke index was calculated from cardiac output, heart rate, and body surface area. RV end-diastolic (ED) and end-systolic (ES) volume (V) indices were calculated from stroke index and RVEF.

Blood Gas Analysis

Analysis of arterial and mixed venous blood gas was determined by standard electrode techniques. Hemoglobin and hemoglobin oxygen arterial and mixed venous saturations were measured by a CO-oximeter. From these measurements, we calculated Qs/Ot and systemic oxygen transport using appropriate formulas.

Echocardiographic Measurements

Echocardiographic recordings were performed using a wide-angle mechanical sector scanner (ADR 4000, Squibb Medical). Because apical or parasternal view cannot be obtained easily during the whole respiratory cycle in ventilated patients, we used for the present study a subcostal approach. A long axis four-chamber view was obtained, with the patient in the supine position. Special attention was paid to obtain the RV cavity in its maximum dimensions, visualizing simultaneously the tricuspid valve and the apical region. Satisfactory echocardiograms showing the RV cavity during the whole respiratory cycle could thus be obtained in all patients. Echocardiographic images were recorded on videocassette, with an ECG lead, and reviewed for single frame stop-motion analysis. Using a microcomputer (Evan AT, Leancord) interfaced with the video tape player, stop motion frames at end-diastole (selected at the peak of the R wave of the ECG) and end-systole (defined as the smallest ventricular dimension during the last half of the T wave) were displayed on the microcomputer screen, and the endocardial outlines of the right ventricle digitized. RV end-diastolic (ED) and end-systolic (ES) areas (A) were automatically processed and averaged during the whole respiratory cycle to exclude respiratory changes. RV fractional area contraction (FAC) was calculated as RVEDA/RVES/A/RVEDA.

Statistical Analysis

Statistical analysis of hemodynamic changes was performed using Statgraphics package. Data are expressed as mean ± SEM. Changes
with PEEP were compared by a two-way analysis of variance completed by Scheffe’s multiple range test. A linear regression analysis was also used when appropriate. This study was reviewed and approved by the Ethical Committee of the Unité d’Enseignement et de Recherche Paris-Ouest.

**RESULTS**

Individual changes in CT during PEEP challenge are shown in Figure 1. In all but one patient, mechanical improvement was obtained at a given level of PEEP and followed by mechanical deterioration if additional increment of PEEP was used. In terms of mechanical improvement, the best level of PEEP was $7 \pm 2$ cm H$_2$O (range 0 to 15 cm H$_2$O). Application of the best level of PEEP in each patient produced a significant improvement in average PaO$_2$ (from $59 \pm 6$ mm Hg to $104 \pm 10$ mm Hg) with a significant reduction in average $Q_s/Qt$ (from $38 \pm 5$ percent to $23 \pm 3$ percent). Systemic oxygen transport was slightly but not significantly increased (from $560 \pm 15$ to $588 \pm 17$ ml/min·m$^{-2}$).

An illustrative example of two-dimensional echocardiographic recordings is given in Figure 2. Hemodynamic and echocardiographic results are summarized in Table 1. Serial increments of PEEP produced a progressive increase in esophageal pressure and a progressive decrease in cardiac index without any significant change in heart rate. Thus, stroke index steadily decreased with increasing levels of PEEP. This decrease in cardiac performance became significant when a PEEP level of 10 cm H$_2$O was reached. RV systolic pressure did not change, whereas RV end-diastolic pressure significantly increased. Mean and diastolic pulmonary artery pressures significantly increased. RVEDV and RVEDA remained unchanged along the PEEP challenge. Despite this lack of significant change in RV diastolic dimensions in the whole group, there were large individual variations as illustrated by Figure 3. However, RVEDV and RVEDA were linearly correlated with CT values all along the PEEP challenge (Fig 4). RVEF and RVFAC were both reduced with PEEP (Table 1). The decrease in RVEF was significant only at the highest level of PEEP (20 cm H$_2$O), whereas the reduction in RVFAC became significant as soon as a PEEP level of 10 cm H$_2$O was applied. Percentage of decrease in cardiac index ($y$) significantly correlated with percentage of decrease ($x$) in both RVEF ($y = 7 + 0.5x$, $r = 0.54$, $p<0.001$) and RVFAC ($y = -0.5 \pm 0.6x$, $r = 0.78$, $p<0.001$).

**DISCUSSION**

The mechanism through which respiratory support with PEEP may induce a fall in cardiac output has long caused controversy. There is now wide assent that
PEEP decreases cardiac output by reducing LV preload. However, the mechanism through which LV preload is reduced is still disputed, particularly with respect to the relative contribution of a reduction in RV preload and an increase in RV afterload, both acting to reduce LV filling. It is likely that these two

Table 1 — Hemodynamic Changes during PEEP Challenge

<table>
<thead>
<tr>
<th>PEEP Level (cm H2O)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP (mm Hg)</td>
<td>-2.2 ± 0.5</td>
<td>-1 ± 0.05</td>
<td>0.03 ± 0.6*</td>
<td>2.1 ± 0.8*</td>
<td>3.7 ± 0.6*</td>
</tr>
<tr>
<td>CT (ml/cm H2O)</td>
<td>35.5 ± 1.7</td>
<td>40.1 ± 3.3</td>
<td>32.6 ± 3</td>
<td>30.6 ± 3.2</td>
<td>23.9 ± 2.8*</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>43 ± 3</td>
<td>41 ± 3</td>
<td>41 ± 3</td>
<td>41 ± 3</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>PAMP (mm Hg)</td>
<td>29 ± 2</td>
<td>30 ± 2</td>
<td>29 ± 2</td>
<td>31 ± 2</td>
<td>34 ± 2*</td>
</tr>
<tr>
<td>PADP (mm Hg)</td>
<td>22 ± 2</td>
<td>24 ± 2</td>
<td>25 ± 2</td>
<td>27 ± 2</td>
<td>30 ± 3*</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>12 ± 2</td>
<td>13 ± 2</td>
<td>14 ± 2*</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>101 ± 6</td>
<td>101 ± 6</td>
<td>103 ± 5</td>
<td>103 ± 5</td>
<td>105 ± 5</td>
</tr>
<tr>
<td>CI (L/min/sq m)</td>
<td>4.8 ± 0.6</td>
<td>4.4 ± 0.6</td>
<td>4.1 ± 0.5*</td>
<td>3.8 ± 0.6*</td>
<td>3.7 ± 0.8*</td>
</tr>
<tr>
<td>SI (ml/sq meter)</td>
<td>47 ± 5</td>
<td>45 ± 6</td>
<td>41 ± 6*</td>
<td>38 ± 7*</td>
<td>34 ± 9*</td>
</tr>
<tr>
<td>EDV (ml/sq meter)</td>
<td>88 ± 6</td>
<td>87 ± 7</td>
<td>94 ± 8</td>
<td>89 ± 9</td>
<td>93 ± 9</td>
</tr>
<tr>
<td>ESV (ml/sq meter)</td>
<td>40 ± 4</td>
<td>42 ± 5</td>
<td>51 ± 6</td>
<td>49 ± 5</td>
<td>56 ± 5*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>54 ± 4</td>
<td>52 ± 4</td>
<td>46 ± 5</td>
<td>44 ± 4</td>
<td>39 ± 6*</td>
</tr>
<tr>
<td>EDA (cm²/sq meter)</td>
<td>9.9 ± 1</td>
<td>10.5 ± 1.1</td>
<td>10.8 ± 0.9</td>
<td>10.7 ± 1.2</td>
<td>11.3 ± 1.3</td>
</tr>
<tr>
<td>ESA (cm²/sq meter)</td>
<td>4 ± 0.5</td>
<td>5.6 ± 0.9</td>
<td>6.2 ± 0.7</td>
<td>6.7 ± 0.8*</td>
<td>7.8 ± 1.2*</td>
</tr>
<tr>
<td>FAC (%)</td>
<td>60 ± 3</td>
<td>49 ± 5</td>
<td>43 ± 4*</td>
<td>39 ± 4*</td>
<td>31 ± 7*</td>
</tr>
</tbody>
</table>

EP: esophageal pressure; CT: lung and chest wall compliance; RVSP: right ventricular systolic pressure; PAMP: pulmonary artery mean pressure; PADP: pulmonary artery diastolic pressure; RVEDP: right ventricular end-diastolic pressure; HR: heart rate; CI: cardiac index; SI: stroke index; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction; EDA: end-diastolic area; ESA: end-systolic area; FAC: fractional area contraction.

*p < 0.05 vs baseline level (0 cmH2O); values are mean ± SEM.
Evaluation of RV Function during Respiratory Support (Jardin et al.)

Factors are integrated since PEEP increases both pleural pressure and alveolar distending pressure. To assess the relative contribution of RV preload and afterload, we simultaneously measured RV pressure and dimensions during application of increasing levels of PEEP. RV size was determined by two independent techniques. Two-dimensional echocardiography has been demonstrated to provide a reliable estimate of RV size. Fast-response thermodilution has been found to be reliable in both experimental and clinical studies. Comparing this method with 2-D echocardiography in patients with adult respiratory distress syndrome (ARDS), we have reported reliable and reproducible bedside determinations of RV volumes.

In the present study, the progressive reduction in cardiac output with increasing PEEP levels primarily resulted from gradual impairment in RV systolic function. On the other hand, for the whole group, the finding of increased RV diastolic pressure associated with unchanged RV diastolic dimension would be consistent with a reduction in RV compliance. However, further analysis of the data showed that there were large individual variations. RV diastolic dimensions increased or decreased depending upon PEEP level. Of interest, a negative linear correlation was found between RV dimensions and CT. This finding thus suggests that the effects of PEEP on RV diastolic dimensions and lung mechanics are related. Indeed, in some patients a given level of PEEP improved lung mechanics and reduced RV size, while in other patients the same level of PEEP worsened lung mechanics and caused RV enlargement.

During PEEP challenge, RV systolic function was impaired as shown by a decrease in thermodilution RVEF and echocardiographic RVFAC. Such a reduction in RVFAC by PEEP has previously been documented by Mitaka et al and ascribed solely to preload reduction. In our study, however, the finding of an unchanged RV size for the whole group suggests that RV systolic dysfunction mainly resulted from an increase in RV impedance to ejection. Such an impairment in RV systolic function could be detected by 2-D echocardiography as soon as PEEP level reached 10 cm H₂O and by thermodilution at a higher PEEP level (20 cm H₂O). Moreover, RVESA and RVESV were found significantly enlarged at 15 cm H₂O and

![Figure 4: Linear relationship between individual values of CT at different PEEP levels and EDV (left panel) or EDA (right panel).](downloaded-from.http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21623/)
20 cm H₂O of PEEP respectively. Incidentally, 2-D echocardiography appeared to have a better sensitivity than fast-response thermodilution.

Our results are somewhat at variance with previously published data. In fact, recent reports devoted to the study of the effects of increasing levels of PEEP on RV function have led to apparently conflicting results. Dhainaut et al 17 and Martin et al 18 concluded that increasing levels of PEEP up to 20 cm H₂O did not affect RV systolic function but progressively reduced RV preload. On the opposite, Shulman et al 19 and Biondi et al 20 evidenced a significant decrease in RV ejection fraction suggesting an increase in RV afterload or a decrease in RV contractility when a level of PEEP greater than 10 cm H₂O was applied. Three other studies 16, 81, 32 reported a reduction in RV dimensions evaluated by echocardiography during application of PEEP. In none of the above-mentioned studies were lung mechanics changes evaluated during application of PEEP. Indeed, the effects of PEEP on the pulmonary microcirculation are expected to differ depending on whether PEEP improves lung mechanics by recruiting atelectic areas or deteriorates lung mechanics by overdistending some areas. Since RV size and CT were inversely related in the present study, the apparent discrepancy in the hemodynamic effects of PEEP observed in other studies could best be explained by taking into account the simultaneous changes in lung mechanics induced by this mode of respiratory support. This concept has already been developed by Suter et al. 2

Impairment in RV function caused by PEEP became significant only when the PEEP level used was higher than the best PEEP level (7 cm H₂O in the present study). Theoretically this impairment could result from depressed RV contractility, increased RV afterload, or both. PEEP has been considered as potentially unable to depress RV contractility by reducing coronary blood flow, 26 and this effect was not addressed in the present study. However, the finding of a progressive reduction in RV diastolic compliance could suggest some impairment in RV coronary perfusion during PEEP challenge, but no shift of ST-T segment was observed on the ECG during the study. We did not attempt to evaluate RV inotropism using measurement of RV maximal elastance 24 because this method is questionable when pressure measurements are obtained from fluid-filled catheters. Even though a negative inotropic effect of PEEP on RV could not be excluded, indirect evidence suggested that PEEP essentially induced an increase in RV afterload. RV systolic dysfunction occurred simultaneously with a deterioration in lung mechanics, which indicated overinflation by PEEP. Lung overinflation has been shown to increase resistance to flow in the pulmonary circulation. 25 In our study, resistance to flow in the pulmonary circulation actually increased since pulmonary artery mean and diastolic pressures increased with PEEP while cardiac output decreased.

To a given extent, an acute increase in RV afterload does not necessarily reduce cardiac output. When RV is moderately afterloaded, the Frank-Starling mechanism becomes operative and an increased level of preload can maintain stroke output. However, this spontaneous adaptation cannot take place in the presence of RV filling impairment. Increased pleural pressure 1 or direct compression of the right heart cavities by inflated lungs 26 have been advocated to explain preload impairment caused by PEEP and reduced RV diastolic compliance could also act in the same way. In the present study, although RV end-systolic dimensions increased during PEEP challenge, no parallel increase in RV end-diastolic dimensions occurred.

Several conclusions can be drawn from our present study which further assessed the RV effects of respiratory support with PEEP in ARF patients. First, side effects were primarily observed at PEEP levels which also deteriorated lung mechanics. When PEEP level is adjusted so as to improve CT as previously suggested, 8 PEEP appears safe and does not require hemodynamic monitoring. Second, the main hemodynamic consequence of PEEP was to impair RV systolic function, apparently by increasing RV afterload, a finding consistent with our previous studies. 6, 27 Third, lack of normal preload adaptation could be interpreted as resulting from the worsening of thoracic characteristics and also a reduction in RV compliance. Such a mismatch between RV preload and afterload resulted in a fall in cardiac output. This fall could theoretically be compensated for, to some extent, by increasing extrathoracic venous pressure. 1, 28 Finally, in the present clinical setting, our study suggests that 2-D echocardiography might be more sensitive than the fast-response thermodilution technique to evaluate changes in RV function.

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