Estimating cardiac filling pressure in mechanically ventilated patients with hyperinflation

Jean-Louis Teboul, MD, PhD; Michael R. Pinsky, MD, FCCM; Alain Mercat, MD; Nadia Anguel, MD; Gilles Bernardin, MD; Jean-Michel Achard, MD; Thierry Boulain, MD; Christian Richard, MD

Objective: When positive end-expiratory pressure (PEEP) is applied, the intracavitary left ventricular end-diastolic pressure (LVEDP) exceeds the LV filling pressure because pericardial pressure exceeds 0 at end-expiration. Under those conditions, the LV filling pressure itself is better reflected by the transmural LVEDP (LVEDP minus pericardial pressure). By extension, end-expiratory pulmonary artery occlusion pressure (eePAOP), as an estimate of end-expiratory LVEDP, overestimates LV filling pressure when pericardial pressure is > 0, because it occurs when PEEP is present. We hypothesized that LV filling pressure could be measured from eePAOP by also knowing the proportional transmission of alveolar pressure to pulmonary vessels calculated as index of transmission = (end-inspiratory PAOP – eePAOP)/(plateau pressure – total PEEP). We calculated transmural pulmonary artery occlusion pressure (tPAOP) with this equation: tPAOP = eePAOP – (index of transmission × total PEEP). We compared tPAOP with airway disconnection nadir PAOP measured during rapid airway disconnection in subjects undergoing PEEP with and without evidence of dynamic pulmonary hyperinflation.

Design: Prospective study.

Setting: Medical intensive care unit of a university hospital.

Patients: We studied 107 patients mechanically ventilated with PEEP for acute respiratory failure. Patients without dynamic pulmonary hyperinflation (group A; n = 58) were analyzed separately from patients with dynamic pulmonary hyperinflation (group B; n = 49).

Intervention: Transient airway disconnection.

Measurements and Main Results: In group A, tPAOP (8.5 ± 6.0 mm Hg) and nadir PAOP (8.6 ± 6.0 mm Hg) did not differ from each other but were lower than eePAOP (12.4 ± 5.6 mm Hg; p < .05). The agreement between tPAOP and nadir PAOP was good (bias, 0.15 mm Hg; limits of agreement, −1.5–1.8 mm Hg). In group B, tPAOP (9.7 ± 5.4 mm Hg) was lower than both nadir PAOP and eePAOP (12.1 ± 5.4 and 13.9 ± 5.2 mm Hg, respectively; p < .05 for both comparisons). The agreement between tPAOP and nadir PAOP was poor (bias, 2.3 mm Hg; limits of agreement, −0.2–4.8 mm Hg).

Conclusions: Indexing the transmission of proportional alveolar pressure to PAOP in the estimation of LV filling pressure is equivalent to the nadir method in patients without dynamic pulmonary hyperinflation and may be more reliable than the nadir PAOP method in patients with dynamic pulmonary hyperinflation.

Key Words: pulmonary artery occlusion pressure; left ventricular filling pressure; mechanical ventilatory support; positive end-expiratory pressure; intrinsic positive end-expiratory pressure; dynamic pulmonary hyperinflation
Thus, tPAOP was defined as transmural pulmonary artery occlusion pressure (tPAOP), the difference between stop-flow end-inspiratory and end-expiratory airway pressure. In a patient mechanically ventilated with a level of applied PEEP titrated by using disposable pressure transducers, tPAOP could then be estimated from a PAOP and Palv measurements by subtracting from the epPAOP the product of total PEEP (PEEPtot = applied PEEP + intrinsic PEEP) and 1r. We call this estimation of tLVEDP as transmural pulmonary artery occlusion pressure (tPAOP). Thus, tPAOP = epPAOP - [PEEPtot \times \text{d}PAOP/\text{d}Palv].

Our purposes were to test this hypothesis by comparing tPAOP with nadir PAOP in patients without dynamic pulmonary hyperinflation, in whom a good agreement between both pressures is expected to exist. We also sought to check that tPAOP would be lower than both nadir PAOP and epPAOP in patients with dynamic pulmonary hyperinflation, in whom nadir PAOP is expected to not be different from epPAOP.

**MATERIALS AND METHODS**

The protocol was approved by our institutional review board for human subjects. Written consent was obtained from the patients’ next of kin.

Patients. We studied 107 mechanically ventilated patients with the diagnosis of either acute lung injury or acute respiratory distress syndrome (ARDS) or acute cardiogenic pulmonary edema. Acute lung injury and ARDS were defined by the combination of recent bilateral infiltrates on chest radiograph, a PaO2/FIO2 ratio of <200 mm Hg (acute lung injury) or <300 mm Hg (acute lung injury) or <300 mm Hg (ARDS) (5). We studied only patients mechanically ventilated with a level of applied PEEP of >8 cm H2O who had a pulmonary artery catheter already in situ. The level of PEEP was titrated before the study by the attending physician using the best Cst,rs. All patients were ventilated in volume-controlled mode and were sedated (midazolam and fentanyl).

The population was subdivided into two groups of patients: group A, 58 patients without evidence of dynamic pulmonary hyperinflation; and group B, 49 patients with evidence of dynamic pulmonary hyperinflation. Evidence of dynamic pulmonary hyperinflation was defined as the presence of an intrinsic PEEP (PEEPI) of ≥2 cm H2O on 0 end-expiratory pressure.

**Measurements.** Airway pressures were measured by using a pressure transducer (Uniflow 43–600, Baxter Edwards Critical-Care, Irvine, CA) connected close to the proximal end of the endotracheal tube. Plateau pressure and PEEPtot were measured after end-inspiratory (2 secs) and end-expiratory (2 secs) occlusions, respectively; DPAOP was defined as the plateau pressure – PEEPtot difference. Tidal volume was measured by the means of the expiratory flow transducer of the ventilator. The static compliance of the respiratory system was calculated as follows: Cst,rs = tidal volume/(plateau pressure – PEEPtot). Pressure and flow transducers were carefully calibrated before starting the measurements. Pulmonary arterial pressure (PAP) and PAOP were measured through a pulmonary artery flotation catheter (7.5Fr, Baxter Edwards Critical Care) by using disposable pressure transducers. Patients were studied while supine, and 0 pressure was measured at atmospheric pressure at the midaxillary line. The PAOP was obtained after inflating the balloon with ≥1 mL air. Criteria for adequate wedge position of the pulmonary artery catheter tip were a phasic waveform synchronized to the electrocardiogram, a epPAOP value less than the end-expiratory diastolic PAP value, and a similar increase during inspiration of both PAP and diastolic PAP validating that the occluded pulmonary artery catheter tip was not in segments of the lung reflecting zone 1 or zone 2 conditions, according to the method described by Teboul et al (6).

Nadir PAOP was measured according to the method proposed by Pinsky et al (4). After inflation and occlusion of the pulmonary artery balloon tip, at end-expiration the patient was disconnected from the ventilator at the proximal end of the endotracheal tube for 10 secs while a continuous recording of the PAOP values was being made. Nadir PAOP was taken as the minimal PAOP value during this period. Figure 1 represents a typical tracing in a patient of group A. All vascular and airway pressures were recorded on a multichannel thermal array recorder (TA 550 Gould Instruments, Cleveland, OH, or M 1117A, Hewlett-Packard, Palo Alto, CA). From PAP, PAOP, and airway pressures measurements, we calculated ΔPAP, ΔPAOP, and tPAOP by using the following formulas:

\[ \text{ΔPAP} = \text{peak inspiratory diastolic PAP} \]
\[ - \text{end-expiratory diastolic PAP} \]
\[ \text{ΔPAOP} = \text{peak inspiratory PAOP} - \text{epPAOP} \]
\[ \text{tPAOP} = \text{epPAOP} - \left( \text{PEEPtot} \times \frac{\text{ΔPAP}}{\text{ΔPalv}} \right) \]

We also calculated the three variables I1r, I1n, and I1pa by using the following formulas:

\[ I_1r = \frac{\Delta PAOP}{\Delta Palv} \]
\[ I_1n = (\text{epPAOP} - \text{nadir PAOP})/\text{PEEPtot} \]
\[ I_1pa = \frac{\Delta PAP}{\Delta Palv} \]

Because airway pressures are expressed in cm H2O and vascular pressures are expressed in mm Hg, we used 0.74 to convert cm H2O into mm Hg, when necessary (1 mm Hg = 1 cm H2O × 0.74).

As mentioned earlier, I1 was considered an index of transmission of pressure from the alveoli into the large pulmonary veins, by using ΔPAOP determination. Similarly, I1n was viewed as an index of transmission of pressures from the alveoli into the large pulmonary veins by using the airway disconnection method; whereas, I1pa was considered an index of transmission of pressures from the alveolar compartment into the large pulmonary arteries.

**Statistical Analysis.** In each group (A and B) of patients epPAOP, nadir PAOP, and tPAOP were compared by factorial analysis of variance and compared when significant by Scheffe’s test. Nadir PAOP and tPAOP were also compared by using a Bland and Altman analysis (7) to evaluate the agreement of both methods of estimation of the LV filling pressure. The bias was calculated as the mean difference ± 2 sd. I1r, I1pa, and I1n were compared by using a factorial analysis of variance. When this was significant, one variable was compared with each other by using Scheffe’s test. A statistical correlation was examined between Cst,rs, and I1r, Cst,rs, and I1n, and Cst,rs and I1n by using a linear regression test. For the whole population (n = 107), we also used a linear regression analysis for Cst,rs and I1. For all the statistical analysis, a p < .05 was considered as significant. All data are reported as mean ± sd.
RESULTS

Group A (n = 58) consisted of 20 females and 38 males. The mean age was 63 ± 13 yrs. Twenty-two patients had a diagnosis of acute lung injury, 32 patients suffered from ARDS, and four patients had a diagnosis of cardiogenic pulmonary edema. Four of these 58 patients had a previous history of chronic obstructive pulmonary disease. Thirty patients of this group recovered and were discharged from the intensive care unit.

Group B (n = 49) consisted of ten females and 39 males. The mean age was 64 ± 14 yrs. Sixteen patients had a diagnosis of acute lung injury, 26 suffered from ARDS, and seven patients had a diagnosis of cardiogenic pulmonary edema. Most of these patients (39 of 49; 80%) had a previous history of chronic bronchitis and chronic obstructive pulmonary disease. Twenty patients of this group recovered and were discharged from the intensive care unit.

Table 1 lists the main ventilatory characteristics in the two groups of patients. Table 2 gives the results of the analysis of variance for eePAOP, nadir PAOP, and tPAOP in each group. In group A, nadir PAOP and tPAOP did not differ but were significantly lower than eePAOP. In group B, tPAOP was significantly lower than both nadir PAOP and eePAOP, which were not different. A significant correlation was found between tPAOP and nadir PAOP in group A (r² = .98) (Fig. 2) and in group B (r² = .95) (Fig. 3). The Bland and Altman (7) analysis for group A (Fig. 2) showed that the agreement between tPAOP and nadir PAOP was good (bias, 0.15 mm Hg; limits of agreement, −1.5–1.8 mm Hg). The Bland and Altman (7) analysis for group B (Fig. 3) showed that the agreement between tPAOP and nadir PAOP was poor (bias, 2.3 mm Hg; limits of agreement, −0.2–4.8 mm Hg).

Table 2 gives the results of the analysis of variance for Iₜ, Iₚₐ, and Iₙ in each group. In group A, Iₜ, Iₚₐ, and Iₙ did not differ, whereas in group B, Iₙ was significantly lower than both Iₜ and Iₚₐ.

The correlations between Cst,rs and Iₜ (r² = .70), Iₚₐ (r² = .69), and Iₙ (r² = .52) in group A were significant (Fig. 4), whereas for patients in group B, strong linear correlations only exist between Cst,rs and Iₜ (r² = .77) and Iₚₐ (r² = .69) but not between Cst,rs and Iₙ (r² = .23) (Fig. 5). Importantly, Iₜ was strongly correlated with Cst,rs for the whole population of patients (n = 107; Iₜ = 0.01 Cst,rs + 0.06; r² = .72).

DISCUSSION

There were two main findings of this study performed with patients receiving mechanical ventilatory support with PEEP for acute lung injury or ARDS or acute cardiogenic pulmonary edema. First, there was an excellent agreement between values of tPAOP and nadir PAOP. Both of these estimates of the LV filling pressure differed from eePAOP in patients who did not demonstrate dynamic hyperinflation. Second, tPAOP values were lower than nadir PAOP and eePAOP in those patients with significant dynamic hyperinflation.

The application of PEEP should result in overestimation of tLVEDP or of transmural left atrial pressure (left atrial pressure minus pericardial pressure) by eePAOP because the associated increase in pericardial pressure is not accounted for. Determination of nadir PAOP has been proposed to better estimate LV filling pressure during PEEP ventilation (4, 8). By rapidly disconnecting the patient from the ventilator, the juxtacardiac pressure induced by PEEP decreases to its off-PEEP value; this causes PAOP to decline to a nadir value, which can be easily measured. In humans receiving mechanical ventilatory support with PEEP, Pinsky et al. (4) demonstrated that nadir PAOP reflected values for patients on PEEP transmural left atrial pressure better than eePAOP did. Our results in the group of patients without dynamic hyperinflation are consistent with the findings reported by Pinsky et al. (4) in thoracic surgery patients, because nadir PAOP was lower than eePAOP when PEEP was applied.

In those patients with dynamic hyperinflation evidenced on 0 end-expiratory pressure, we did not observe that nadir PAOP was significantly lower than

Table 1. Respiratory variables (mean ± SD) in the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Patients Without PEEPi on ZEEP (Group A; n = 58)</th>
<th>Patients With PEEPi on ZEEP (Group B; n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vt (mL)</td>
<td>605 ± 127</td>
<td>622 ± 104</td>
</tr>
<tr>
<td>RR (beats/min)</td>
<td>17 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Pplat (cm H₂O)</td>
<td>26 ± 5</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>PEEPi on ZEEP (cm H₂O)</td>
<td>0.6 ± 0.8</td>
<td>6.9 ± 3.1</td>
</tr>
<tr>
<td>PEEPi on total PEEP (mm Hg)</td>
<td>10.9 ± 2</td>
<td>12.4 ± 2.2</td>
</tr>
<tr>
<td>Cst,rs (mL/cm H₂O)</td>
<td>43 ± 11</td>
<td>42 ± 11</td>
</tr>
</tbody>
</table>

PEEP, positive end-expiratory pressure; PEEPi, intrinsic PEEP; ZEEP, 0 end-expiratory pressure; Vt, tidal volume; RR, respiratory rate; Pplat, plateau pressure; PEEPi on ZEEP, total PEEP (PEEPi + ZEEP); Cst,rs, static compliance of the respiratory system.

Table 2. Main results of the study (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Patients Without PEEPi on ZEEP (Group A; n = 58)</th>
<th>Patients With PEEPi on ZEEP (Group B; n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eePAOP (mm Hg)</td>
<td>12.4 ± 5.6</td>
<td>13.9 ± 5.2</td>
</tr>
<tr>
<td>nadir PAOP (mm Hg)</td>
<td>8.6 ± 6.1a</td>
<td>12.1 ± 5.4</td>
</tr>
<tr>
<td>tPAOP (mm Hg)</td>
<td>8.5 ± 6.0a</td>
<td>9.7 ± 5.4b</td>
</tr>
<tr>
<td>ΔPAOP (mm Hg)</td>
<td>5.2 ± 1.4</td>
<td>5.1 ± 1.2</td>
</tr>
<tr>
<td>ΔPAP (mm Hg)</td>
<td>5.5 ± 1.5</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>Iₜ</td>
<td>0.06 ± 0.10</td>
<td>0.98 ± 0.09</td>
</tr>
<tr>
<td>Iₚₐ</td>
<td>0.50 ± 0.14</td>
<td>0.46 ± 0.14</td>
</tr>
<tr>
<td>Iₙ</td>
<td>0.53 ± 0.15</td>
<td>0.47 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>0.48 ± 0.15</td>
<td>0.20 ± 0.11c</td>
</tr>
</tbody>
</table>

Iₜ, intrinsically positive end-expiratory pressure; ZEEP, zero end-expiratory pressure; PEEP, pulmonary artery occlusion pressure; eePAOP, end-expiratory pulmonary artery occlusion pressure; tPAOP, transmural pulmonary artery occlusion pressure; ΔPAOP, inspiratory peak PAOP − eePAOP; ΔPAP, peak inspiratory diastolic PAP − end-expiratory diastolic PAP; Iₜ, ΔPAOP/(plateau pressure − total PEEP); Iₚₐ, ΔPAP/plateau pressure − total PEEP; Iₙ, (eePAOP − nadir PAOP)/total PEEP.

a,b, p < .05 vs. eePAOP; c, p < .05 vs. nadir PAOP; d, p < .05 vs. Iₜ and Iₚₐ.
eePAOP when PEEP was applied. In particular, in the patients exhibiting a level of intrinsic PEEP $\geq 8$ cm H$_2$O on 0 end-expiratory pressure, values of eePAOP and nadir PAOP were almost identical. Absence of decline of PAOP after ventilator disconnection in patients with dynamic hyperinflation was already considered a limitation by Pinsky et al (4). It can be supposed that in such patients, the slow rate of alveolar gas emptying would not allow the fall of PAOP to be maximal immediately after ventilator disconnection. Thus, other events related to mechanical ventilatory support withdrawal, such as the increase in systemic venous return, may occur before the decline in PAOP is completed.

We proposed another method to estimate LV filling pressure in patients receiving PEEP. Because this method does not require any ventilator disconnection, it can be used in patients with dynamic hyperinflation, as well as in those without dynamic hyperinflation. We evaluated values of patients on PEEP tLVEDP by subtracting from eePAOP an estimated value of the fraction of PEEP transmitted to the pulmonary vessels. We evaluated airway pressure transmission to pulmonary vessels by the ratio of respiratory changes of PAOP (reflecting pressure of large pulmonary veins) and of diastolic PAP to simultaneous changes of alveolar pressure (estimated by plateau pressure – PEEPtot). Such a ratio could be a reasonable assessment of airway pressure transmission and of PEEP transmission into intrathoracic vessels, provided factors influencing transmission are unchanged over a tidal mechanical breath. By applying the level of PEEP associated with the highest $C_{st,rs}$, we can reasonably assume that lung compliance did not change significantly throughout the tidal breath administered above PEEP. In this way, airway pressure transmission to intrathoracic vessels should be unchanged from PEEP to end-inspiratory pressure.

The airway pressure transmission assessed by using PAOP ($I_T$) or diastolic PAP ($I_{pa}$) was closely correlated with lung compliance so that the higher the lung compliance, the higher the $I_T$ or $I_{pa}$. This finding is consistent with previous experimental and clinical studies.
Lung compliance was reduced by infusion of oleic acid. Similar results were found by Venus et al. (10) who observed significant decreases of fractional transmission of PEEP to the pleura and to the pericardium (from 62% ± 8% and 54% ± 19% to 34% ± 7% to 36% ± 9%, respectively) after chemically induced reduction in lung compliance.

In 19 patients, ventilated for acute respiratory failure, Jardin et al. (11) found values of airway pressure transmission to the pleural space of ~37% when total lung compliance was >45 mL/cm H2O, of ~32% when compliance was between 30 and 45 mL/cm H2O, and of ~24% when compliance was below 30 mL/cm H2O. In their study, airway pressure transmission was calculated by using esophageal pressure as a reflection of intrathoracic pressure. From the data reported by Pinsky et al. (4), it is possible to evaluate fractional transmission of PEEP to the pulmonary vessels by using the eePAOP − nadir PAOP difference to PEEP ratio. Interestingly, in patients exhibiting a mean value lung compliance of 22 mL/cm H2O with 10 cm H2O of PEEP, a mean ratio of ~38% can be recalculated. These findings were near our ITn results found for relatively low levels of CST,rs in the group of patients without dynamic hyperinflation (Fig. 4). Importantly, we found that values of ITn were very close to IT and ITpa values in this latter group of patients. Moreover, a strong correlation was found between ITn and CST,rs in this group (Fig. 4). By contrast, ITn differed from IT and ITpa in the population of patients with dynamic hyperinflation. The correlation between ITn and CST,rs was strong in patients without dynamic hyperinflation (r² = .52), but was weak in the group of patients with dynamic hyperinflation (r² = .23) (Fig. 5). This is an indirect argument suggesting that the airway disconnection method has some limitations when used in patients with dynamic hyperinflation. On the other hand, the fact that we found excellent correlations between IT and CST,rs and between ITpa and CST,rs in both groups of patients suggests the method we propose for estimating airway transmission was probably valid in all patients, at least because it does not need any ventilator disconnection. IT can be approximately, but easily, obtained by using the linear regression equation between IT and CST,rs that we obtained in the whole population: IT (%) = CST,rs (mL/cm H2O) + 6.

Because we did not measure pericardial pressure, we are unable to validate that our calculated tPAOP values actually reflected tLVEDP and hence, the LV filling pressure. However, in patients without dynamic pulmonary hyperinflation, our results are very close to those of the nadir PAOP method and Pinsky et al. (4) and Carter et al. (8) found that the nadir PAOP reliably reflected the LV filling pressure in both animal models and humans without dynamic pulmonary hyperinflation. Moreover, there is no reason to believe that, in patients with dynamic pulmonary hyperinflation, transmission of end-expiratory Palv to the pericardial space is significantly different from that occurring in patients without dynamic pulmonary hyperinflation (12). Thus, it seems unlikely that our tPAOP data during hyperinflation conditions misrepresent values of patients on PEEP tLVEDP or that our assumed increase in pericardial pressure is systematically incorrect. Although we can reasonably propose our method for assessing the LV filling pressure in patients with dynamic pulmonary hyperinflation, our study did not provide an accurate measure of LV preload because the relationship between LV filling pressure and LV end-diastolic volume is both curvilinear and influenced by changes in LV diastolic compliance. However, this limitation is shared by all pressure measurements of LV preload.

In patients receiving mechanical ventilatory support with PEEP, the clinical usefulness of estimating LV filling pressure rather than accepting eePAOP without correction may be questioned. However, in 23 of our patients, the difference between eePAOP and tPAOP was >5 mm Hg. Such a difference may be large enough to have significant diagnostic and therapeutic consequences. However, our study was not designed to examine the

**Figure 5.** Relationships between static compliance of the respiratory system (CST,rs) and the indices of transmission of alveolar pressure to pulmonary vascular pressure in 49 patients with intrinsic end-expiratory pressure (PEEP) on 0 end-expiratory pressure, mechanically ventilated with PEEP (group B). Top, estimated from pulmonary artery occlusion pressure tracing on mechanical ventilatory support (IT); middle, estimated from the pulmonary arterial pressure tracing during disconnection from the ventilator (ITpa); bottom, estimated from pulmonary artery occlusion pressure tracing during disconnection from the ventilator (ITpa).

(9–12). In swine, Chapin et al. (9) reported decreases in airway pressure transmission to the intrapleural space from 52% ± 9% to 26% ± 7% after that lung compliance was reduced by infusion...
impact of this approach of LV filling pressure on clinical decision-making.

CONCLUSIONS

We conclude that our method allows a reliable estimate of LV filling pressure at the bedside in mechanically ventilated patients with PEEP. In patients without dynamic pulmonary hyperinflation, nadir PAOP and tPAOP give similar information. Because the measure of nadir PAOP is simpler than that of tPAOP, the use of nadir PAOP to estimate the LV filling pressure can still be preferred in these patients. However, because our method does not require any airway disconnection, we prefer it to the nadir PAOP method in those patients with dynamic pulmonary hyperinflation.

REFERENCES