Effect of Endotracheal Tube Size, Respiratory System Mechanics, and Ventilator Settings on Driving Pressure

Stavroula Ilia, MD, PhD1,2; Patrick D. van Schelven, BSc1; Alette A. Koopman, MSc1; Robert G. T. Blokpoel, MD3; Pauline de Jager, MD3; Johannes G. M. Burgerhof, MSc3; Dick G. Markhorst, MD, PhD4; Martin C. J. Kneyber, MD, PhD, FCCM1,5

Objectives: We sought to investigate factors that affect the difference between the peak inspiratory pressure measured at the Y-piece under dynamic flow conditions and plateau pressure measured under zero-flow conditions (resistive pressure) during pressure controlled ventilation across a range of endotracheal tube sizes, respiratory mechanics, and ventilator settings.

Design: In vitro study.

Setting: Research laboratory.

Patients: None.

Interventions: An in vitro bench model of the intubated respiratory system during pressure controlled ventilation was used to obtain the difference between peak inspiratory pressure measured at the Y-piece under dynamic flow conditions and plateau pressure measured under zero-flow conditions across a range of endotracheal tubes sizes (3.0–8.0 mm). Measurements were taken at combinations of pressure above positive end-expiratory pressure (10, 15, and 20 cm H2O), airway resistance (no, low, high), respiratory system compliance (ranging from normal to extremely severe), and inspiratory time at constant positive end-expiratory pressure (5 cm H2O). Multiple regression analysis was used to construct models predicting resistive pressure stratified by endotracheal tube size.

Measurements and Main Results: On univariate regression analysis, respiratory system compliance ($\beta$ –1.5; 95% CI, –1.7 to –1.4; $p < 0.001$), respiratory system resistance ($\beta$ 1.7; 95% CI, 1.5–2.0; $p < 0.001$), pressure above positive end-expiratory pressure ($\beta$ 1.7; 95% CI, 1.4–2.0; $p < 0.001$), and inspiratory time ($\beta$ –0.7; 95% CI, –1.0 to –0.4; $p < 0.001$) were associated with resistive pressure. Multiple linear regression analysis showed the independent association between increasing respiratory system compliance, increasing airway resistance, increasing pressure above positive end-expiratory pressure, and decreasing inspiratory time and resistive pressure across all endotracheal tube sizes. Inspiratory time was the strongest variable associated with a proportional increase in resistive pressure. The contribution of airway resistance became more prominent with increasing endotracheal tube size.

Conclusions: Peak inspiratory pressures measured during pressure controlled ventilation overestimated plateau pressure irrespective of endotracheal tube size, especially with decreased inspiratory time or increased airway resistance. (Pediatr Crit Care Med 2019; XX:00–00)

Key Words: driving pressure; in vitro techniques; mechanical ventilation; pediatric intensive care unit; pressure controlled ventilation; resistive pressure

Mechanical ventilation (MV) maintains adequate gas exchange in critically ill children without and with lung injury. Individualized optimization of MV is necessary to minimize ventilator-induced lung injury (VILI) and improve patient outcome. VILI is among others the result from the delivery of too large tidal volume ($V_t$) (known as volutrauma) and the repetitive opening and closure of alveoli (i.e., atelectrauma) (1). In adults, MV with $V_t$ of 6 mL/kg ideal body weight resulted in significantly lower mortality compared with $V_t$ of 12 mL/kg, although similar effects have yet to
be demonstrated in children (2, 3). Atelectrauma can be prevented by the application of positive end-expiratory pressure (PEEP) (4). As such, mechanically ventilated children are nowadays managed with what is supposed to be a lung-protective approach consisting of low $V_t$ and individual level of PEEP (5).

Recently, the potential importance of driving pressure ($\Delta P$) when setting MV has been proposed. $\Delta P$ reflects the functional size of the lung as it depends on $V_t$ and the amount of aerosolized lung tissue, and can be measured at the bedside by end-inspiratory plateau pressure ($P_{plat}$) minus PEEP, in the absence of spontaneous efforts and dynamic hyperinflation (6). Amato et al (7) performed a meta-analysis of data from patients enrolled into randomized controlled trials (RCTs) investigating the effect of low $V_t$ ventilation. This analysis showed that limiting $\Delta P$ by increasing PEEP was associated with significant lower mortality. It has been proposed to target $\Delta P$ less than or equal to 14 cm H$_2$O as part of a lung-protective approach albeit that at present, there are no RCT that have shown improved outcomes with this strategy (6).

To date, it is unclear if the association between $\Delta P$ and outcome also holds true for pediatric patients (8). This may in be part be explained by the fact that unlike adult critical care, there is a predominant use of ventilation modes with dynamic flow conditions in children including pressure controlled ventilation (PCV) (5, 9). During PCV, peak inspiratory pressure (PIP) is only equal to Pplat when inspiratory flow reaches zero (equilibrium with alveolar pressure) (10, 11). Normally, PCV lacks a plateau phase under zero-flow conditions as opposed to volume-controlled ventilation (VCV), making it impossible to determine $\Delta P$ during PCV unless expiration does not follow immediately end-inspiration. VCV has a zero-flow state at the end of inspiration in which the pressure equilibrates and Pplat can be measured. Because there is no zero-flow state with PCV, substituting Pplat by PIP is significantly influenced by the resistive properties of the respiratory system. On top of that, infants and children are generally ventilated with small endotracheal tube (ETT) sizes with high gas flow and high ventilation rate, all contributing to resistance (respiratory system resistance [Rrs]) (12). Also, especially young children often suffer from disease conditions characterized by increased airway resistance (Raw) such as viral bronchiolitis or pneumonia (5).

Therefore, we sought to investigate, in a bench model, factors that affect the resistive pressure (Pristive) in patients mechanically ventilated during PCV in order to better understand if PIP might be a clinically valid surrogate of Pplat in various lung conditions characterized by different degrees of reduced respiratory system compliance (Crs) and/or increased Rrs.

**MATERIALS AND METHODS**

**Bench Test Setup**

A Michigan Test Lung model 1601, composed of infant and adult lung chambers (Michigan Instruments, Grand Rapids, MI), was connected to an AVEA ventilator (Vyaire, Yorba Linda, CA) using a nonheated, nonhumidified breathing circuit and a cuffed ETT (Fig. 1). ETT sizes with internal diameter 3.0 mm to 8.0 mm, with 1.0 mm intervals, were used to match patient sizes of 5, 10, 20, 30, 50, and 70 kg modeled body weight, respectively (Table 1).

Two types of conventional breathing circuits were used, a neonatal with diameter of 10 mm (Intersurgical, Berkshire, United Kingdom) connected to ETT sizes 3.0 and 4.0 mm (Halyard Health, Alpharetta, GA) and an adult with diameter of 22 mm (Intersurgical) connected to ETT sizes 5.0 to 8.0 mm (Medtronic Covidien, Minneapolis, MN). This reflected clinical practice.

To simulate a wide range of physiologic and pathologic respiratory mechanic conditions, five levels of Crs were set, being 1 (normal), 0.8 (low), 0.6 (moderately low), 0.3 (severely low), and 0.15 mL/cm H$_2$O/kg (extremely low). The ETT size 3.0 mm extremely low Crs (< 1 mL/cm H$_2$O) scenario was not performed, as Michigan Test Infant Lung was not adjustable at this level. Raw was simulated by restricting flow with linear pneumatic resistors (Series 7100, Linear type; Hans Rudolph, Shawnee, KS) connected between ETT and lung simulator. Three levels of Raw were tested, being no, low, and high resistance. Linear flow resistors resembling low and high Raw respectively were for ETT 3.0 mm and 4.0 mm 50 and 200 cm H$_2$O/L/s, for ETT 5.0 mm and 6.0 mm 20 and 50 cm H$_2$O/L/s, and for ETT 7.0 mm and 8.0 mm 5 and 20 cm H$_2$O/L/s. Infant lung was ventilated under all aforementioned conditions with ETT sizes 3.0 mm and 4.0 mm, as well as in severely and extremely low Crs simulation with ETT 5.0 mm and extremely low with ETT 6.0 mm. The adult lung was used in all the remaining scenarios. Neonatal and adult flow sensors (Varflex, Vyaire, Yorba Linda, CA) were positioned between the ETT and Y-piece of the breathing circuit according to lung size.

**Ventilator Protocol**

PCV mode was used for all measurements. Each condition of Crs and Raw was tested setting three levels of pressure above PEEP (PAP) 10, 15, and 20 cm H$_2$O and across three levels of inspiratory time (Tinsp) (i.e., appropriate for age and ETT size, 20% below and 20% above this value) (Table 1). PEEP was kept constant at level of 5 cm H$_2$O throughout the experiment. Respiratory rate was set according to respiratory mechanics to avoid intrinsic PEEP. Flow-time scalars were visually inspected for dynamic hyperinflation. Each measurement combination setting consisted of 15 consecutive breaths. All measurements were done by changing one variable at a time, while keeping all the others constant. In total, 135 different conditions were tested per tube, resulting in 783 measurements.

**Data Acquisition**

All data were acquired, synchronized, and analyzed using a custom-build software program (Polybench, Applied Biosignals, Weener, Germany). Figure 1 demonstrates the diagram of the experimental setup. A pressure transducer measuring the pressure at the Y-piece of the patient circuit and in the lung simulator was connected to a pulmonary function monitor (New Life Box, Applied Biosignals, Weener, Germany). Mechanical data were sampled at 200 Hz and computed offline (Polybench, Applied Biosignals GmbH, Weener, Germany). Before recording experimental measurements, all pressure and flow sensors were zeroed to ambient pressure at sea level, calibrated and absence of leak was confirmed. PIP was measured at the Y-piece of the
breathing circuit. Pplat was measured during a zero-flow state at the end of inspiration by an inspiratory hold maneuver for 4 seconds. Flow and Vt were measured using a proximally placed flow sensor (Varflex, Vyaire) that was connected to the AVEA ventilator, which in turn was connected via the analog output port to the computer using an analog to digital converter.

Outcome Measure
The primary outcome for this study was the Presistive, defined by the difference between average values of 15 breaths of PIP minus Pplat for every tested combination. Secondary outcomes included Vt and peak inspiratory flow (PIF), both normalized to bodyweight.

Statistical Analysis
Univariate linear regression analysis was used to investigate variables that are independently associated with Presistive. Multiple linear regression analysis was performed to evaluate the impact of clinically relevant variables (i.e., Crs, Raw, Tinsp, ETT size and delivered pressures) on Presistive. A p value of less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY) and graphs using Prism v7.05 (GraphPad Software, La Jolla, CA).

RESULTS
On univariate regression analysis, stratified Crs (p < 0.001), Raw (p < 0.001), level of set PAP (p < 0.001), and Tinsp were associated with Presistive for all ETT sizes. Presistive was greater with increasing resistance (β 1.7; 95% CI, 1.5–2.0) and lower with decreasing compliance (β –1.5; 95% CI, –1.7 to –1.4) across the range of all tested ETT sizes. Increasing inspiratory pressures resulted in a higher Presistive (β 1.7; 95% CI, 1.4–2.0), whereas increasing Tinsp resulted in a lower Presistive (β –0.7; 95% CI, –1.0 to –0.4).

DISCUSSION
This bench study showed that PIP during PCV cannot be used as a proxy for the Pplat, especially when there is increased Raw. Tinsp, compliance, and set inspiratory pressures also were associated with the Presistive. Our observations may have implications when interpreting ΔP in acute respiratory failure when ventilation modes are used that do not make use of end-inspiratory zero-flow conditions. We therefore propose that ΔP may not be used indiscriminately in MV without taking into consideration important issues including ventilator settings and respiratory system mechanics.

Adult studies have suggested that limiting the ΔP could be an important approach to lung-protective ventilation (7, 13, 14). Data supportive of this concept on the relevance of ΔP is lacking in pediatrics. Panico et al (15) identified an independent association between the airway pressure gradient (difference between PIP and PEEP) and mortality in 84 children with acute lung injury/acute respiratory distress syndrome after adjusting

Figure 1. Schematic diagram of the experimental setup. A flow sensor (FS) was connected to the ventilator delivering pressure control ventilation. Pressure monitoring of the Y-piece and the intrapulmonary lung were performed using tubings connected to a pressure monitor. Flow and pressure tracings were stored in the computer for further analysis. Ventilator waveforms were stored through an analog output to the computer. ETT = endotracheal tube, R = resistor.

Figure 2 and Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/PCC/B113) exemplifies the effect of the relationship between Crs and Raw on Presistive for three different levels of inspiratory PAP for ETT 4 mm in the context of severe disease (i.e., Crs 0.3 mL/kg/cm H2O). Presistive increased with increasing Raw and increasing PAP (Fig. 2), but this increase became smaller with decreasing Crs (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/PCC/B113). Concurrently, we also found that both Vt and PIF decreased with increasing resistance and increasing PAP (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/PCC/B113), explaining the decrease in Presistive with decreasing Crs. In additional analyses, we observed that PIF and inherently Presistive increased when we decreased the Tinsp and decreased when Tinsp was increased across all ETT sizes, independent of Crs, Raw, and level of set PAP. All findings were comparable when each individual ETT size was tested, suggesting no additional contribution of the ETT itself.

Multiple linear regression analysis showed the independent association between increasing Crs, increasing Raw, increasing PAP and decreasing Tinsp and Presistive across all ETT sizes (Table 2). The adjusted R2 values for all Presistive multivariable models were greater than 0.80. Based on these models, Tinsp was the variable associated with a proportional increase in Presistive. The contribution of Raw became more prominent with increasing ETT size as demonstrated by the increasing beta with increasing ETT.

Table 2

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>β Coefficient</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presistive</td>
<td>1.7</td>
<td>1.5–2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compliance</td>
<td>–1.5</td>
<td>–1.7 to –1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raw</td>
<td>1.7</td>
<td>1.4–2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tinsp</td>
<td>–0.7</td>
<td>–1.0 to –0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DISCUSSION
This bench study showed that PIP during PCV cannot be used as a proxy for the Pplat, especially when there is increased Raw. Tinsp, compliance, and set inspiratory pressures also were associated with the Presistive. Our observations may have implications when interpreting ΔP in acute respiratory failure when ventilation modes are used that do not make use of end-inspiratory zero-flow conditions. We therefore propose that ΔP may not be used indiscriminately in MV without taking into consideration important issues including ventilator settings and respiratory system mechanics.

Adult studies have suggested that limiting the ΔP could be an important approach to lung-protective ventilation (7, 13, 14). Data supportive of this concept on the relevance of ΔP is lacking in pediatrics. Panico et al (15) identified an independent association between the airway pressure gradient (difference between PIP and PEEP) and mortality in 84 children with acute lung injury/acute respiratory distress syndrome after adjusting
for disease severity and number of organ dysfunction at admission. Yehya and Thomas (16) reported that ΔP when calculated by PIP minus PEEP 24 hours after onset of n = 352 with Berlin definition defined pediatric acute respiratory distress syndrome was not associated with mortality. In both these studies, what was labeled as ΔP was measured without a zero-flow state, making it not equivalent to true ΔP. Our study confirmed that this so-called airway pressure gradient as proxy for ΔP during PCV is affected by lung mechanics and ventilator settings.

The Hagen-Poiseuille law states that the pressure gradient over a pipe is greatly dependent on the radius of that pipe (to the fourth degree). It is well-known that ETT is one of the most significant resistors in the breathing circuit (17). Previous observations have confirmed that internal tube resistance may have a great impact on pressure drop variance (12, 17). In our bench study, we observed that especially with smaller ETTs the contribution of the added Raw was lower, suggesting that smaller ETTs had a smaller radius compared to the added resistor and therefore contributed to a greater extent to the pressure drop, and that with increasing ETT size this balance shifted toward a greater contribution of the added resistor in our model. Diameter as well as length of the tube affect the pressure difference between PIP and Pplat, and this difference is not only flow-dependent but specifically influenced by a nonlinear flow state (18). The higher the inspiratory flow velocity the greater the nonlinear flow state and the magnitude of the pressure difference (12). Consequently, all factors that contribute to flow velocity may affect the Presistive.

In our bench model, we had used a constant PEEP. It might be postulated that changes in PEEP would have yielded different findings regarding Presistive. However, increasing PEEP with the same PAP would have resulted in a similar ΔP, thereby not changing the flow pattern, although with decreasing Crs the delivered Vt would be smaller. Reducing ΔP would most likely not have changed this. We propose that changes in Tinsp would have made a greater impact because decreasing Tinsp for a given PAP would lead to an increase in inspiratory flow and thus an increase in Presistive. We did some additional measurements (data not shown) that confirmed our assumptions.

During PCV, inspiratory flow decelerates as inflation proceeds and its velocity is determined by respiratory mechanics (10). As lung compliance falls, inspiratory flow declines resulting in attenuation of the Presistive. This was also observed in our study. Similarly, higher Raw causes lower inspiratory flow rates and subsequent lower Pplat, resulting in higher pressure drop, as shown in our study too (19). This is considered important, especially when it comes to infants and young children, who often suffer from lung conditions characterized by mixed increased Raw and low compliance conditions, such as viral bronchiolitis or pneumonia.

We observed that the effect of Raw on flow varied depending on Tinsp. This is explained by the fact that a longer Tinsp (and inherently a lower inspiratory flow) is required in the presence of high Raw to complete inflation so that airway pressure equilibrates with alveolar pressure at zero flow. On the other hand, if Tinsp is short, alveolar pressure may never equal airway pressure within given time. In this situation, the flow will be higher and thus the Presistive will be higher too, as shown in our study. Based on the same concept, increase of PIP generates a greater pressure difference as a result of a more forceful inspiratory flow. However, it should be noted that

### Table 1. Values of Explanatory Variables During Pressure Control Ventilation of the Test Lung Model

<table>
<thead>
<tr>
<th>Endotracheal Tube Size (Internal Diameter)</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modeled body weight (kg)</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Pressure above positive end-expiratory pressure (cm H₂O)</td>
<td>10–15–20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspiratory time (s)</td>
<td>0.35, 0.45, 0.55</td>
<td>0.4, 0.5, 0.6</td>
<td>0.5, 0.6, 0.7</td>
<td>0.6, 0.75, 0.9</td>
<td>0.6, 0.75, 0.9</td>
<td>0.8, 1, 1.2</td>
</tr>
<tr>
<td>Compliance (mL/cm H₂O)</td>
<td>1, 3, 4, 5</td>
<td>1, 3, 5, 8, 10</td>
<td>3, 5, 10, 15, 20</td>
<td>5, 10, 20, 25, 30</td>
<td>10, 20, 30, 40, 50, 70</td>
<td></td>
</tr>
<tr>
<td>Airway resistance (cm H₂O/L/s)</td>
<td>0, 50, 200</td>
<td>0, 20, 50</td>
<td>0, 5, 20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Representative example of the mean values of the resistive pressure (Presistive) (in cm H₂O) for endotracheal tube size 4 mm and severe respiratory system compliance (i.e., 0.3 mL/kg/cm H₂O), stratified by airway resistance (Raw) at three different levels of pressure above positive end-expiratory pressure (PAP). The Presistive increased with increasing Raw, indicating that the pressure difference is affected by the degree of Raw.
TABLE 2. Multivariable Models Predicting the Resistive Pressure for a Given Endotracheal Tube Size

<table>
<thead>
<tr>
<th>Endotracheal Tube Size</th>
<th>Presistive Equation</th>
<th>Adjust R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( \text{Presistive} = -4.645 + (1.416 \times \text{Crs}) + (0.011 \times \text{Raw}) + (0.366 \times \text{PAP}) - (5.585 \times \text{Tinsp}) )</td>
<td>0.876</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Presistive} = -5.067 + (0.858 \times \text{Crs}) + (0.018 \times \text{Raw}) + (0.390 \times \text{PAP}) - (4.989 \times \text{Tinsp}) )</td>
<td>0.849</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Presistive} = -2.735 + (0.385 \times \text{Crs}) + (0.056 \times \text{Raw}) + (0.348 \times \text{PAP}) - (6.200 \times \text{Tinsp}) )</td>
<td>0.881</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Presistive} = -2.599 + (0.199 \times \text{Crs}) + (0.085 \times \text{Raw}) + (0.338 \times \text{PAP}) - (5.363 \times \text{Tinsp}) )</td>
<td>0.826</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Presistive} = -2.361 + (0.145 \times \text{Crs}) + (0.176 \times \text{Raw}) + (0.339 \times \text{PAP}) - (5.896 \times \text{Tinsp}) )</td>
<td>0.883</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Presistive} = -1.935 + (0.090 \times \text{Crs}) + (0.169 \times \text{Raw}) + (0.267 \times \text{PAP}) - (3.550 \times \text{Tinsp}) )</td>
<td>0.821</td>
</tr>
</tbody>
</table>

\( \text{Crs} = \text{respiratory system compliance}, \text{PAP} = \text{pressure above positive end-expiratory pressure}, \text{Presistive} = \text{resistive pressure}, \text{Raw} = \text{airway resistance}, \text{Tinsp} = \text{inspiratory time.} \)


To our best of knowledge, we are the first to quantify the effects of ventilator settings and respiratory system mechanics across a range of ETT sizes. To the experienced clinician-researcher with a clear interest in respiratory physiology during MV, our results may come as no surprise. On the other hand, our data may be helpful when clinicians attempt to understand the clinical observations related to ΔP and lung disease in children. Despite this, there are important limitations to our study that need to be addressed. First, our lung model did not fully represent the clinical situation, as it did not take into account the heterogeneity of the lung disease and the influence of cardiopulmonary interactions. Second, ΔP was assumed to be dissipated to the lung without simulating the pressure quota of the chest wall or the diaphragm. Last, only one ventilator was used and ETTs were all from the same manufacturer; different mechanical properties cannot be excluded (18). These limitations do not invalidate our findings; however, further (pediatric) clinical studies are necessary to investigate the clinical relevance of ΔP.

CONCLUSIONS

PIPs overestimated Pplat in the present study, challenging their suitability as surrogate for the Pplat when calculating the ΔP during MV in a mode without zero-flow conditions.

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